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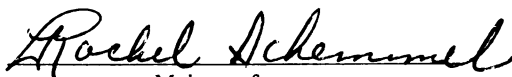
**The Influence of Zinc on Growth and Development
and on Energy Intakes of Children with Chronic
Renal Failure**

presented by

Dorothy Wermuth Hagan

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of the requirements for

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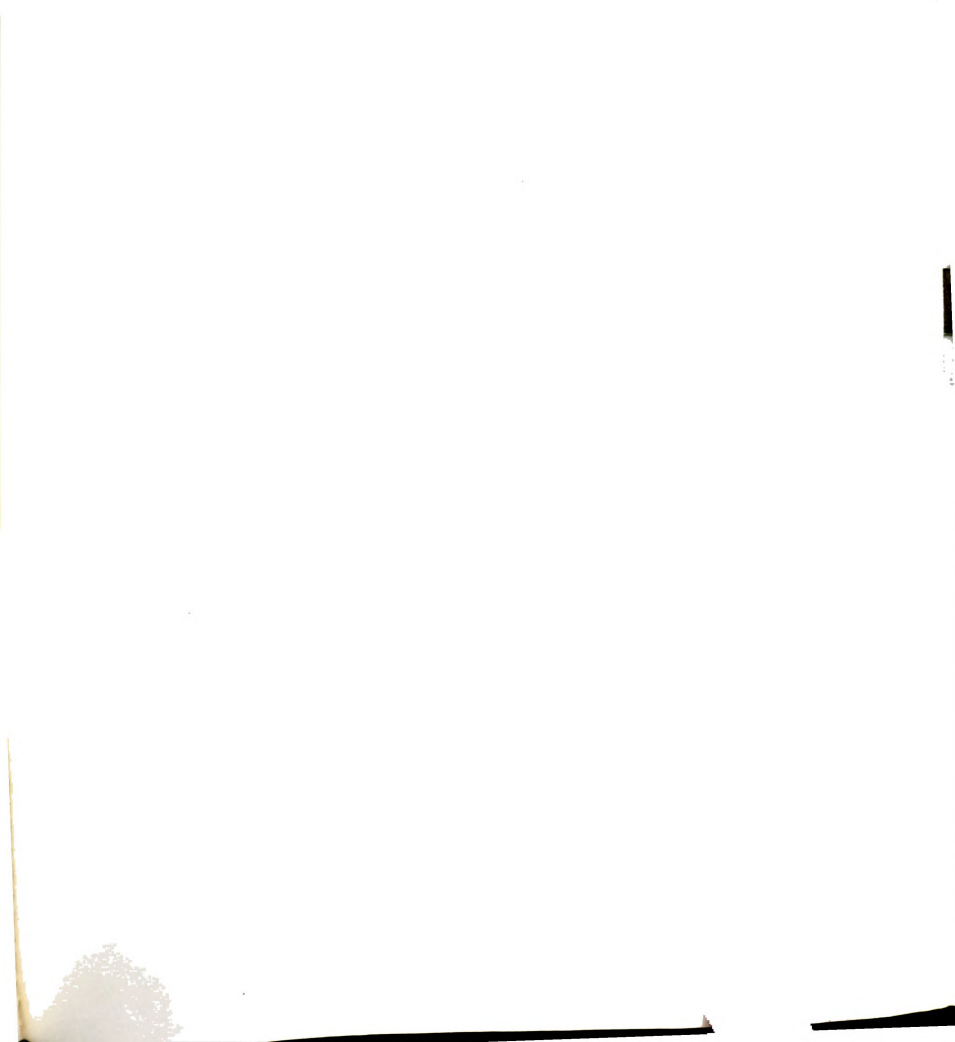

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THE INFLUENCE OF ZINC ON GROWTH
AND DEVELOPMENT AND ON ENERGY INTAKES
OF CHILDREN WITH CHRONIC RENAL FAILURE

By

Dorothy Wermuth Hagan

A DISSERTATION

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ABSTRACT

THE INFLUENCE OF ZINC ON GROWTH AND DEVELOPMENT AND ON ENERGY INTAKES OF CHILDREN WITH CHRONIC RENAL FAILURE

By

Dorothy Wermuth Hagan

This investigation assessed whether zinc acetate supplementation (2mg/kg BW, maximum 40 mg/da/child) in Children with End Stage Renal Disease, improved energy intakes and, in turn, growth and development. Twelve children completed the study. Three of the twelve did not receive zinc supplement. Seven of the 9 supplemented children, were followed for 1 year before supplementation and 1 year after supplementation. The remaining 2 subjects were followed for shorter periods of time both pre- and post-supplementation.

Height, weight, mid-arm circumference, triceps fatfold, hand wrist radiographs, and Tanner Staging measurements, were taken at the beginning of the study, prior to zinc supplementation, and at the end of the study period. Clinical analyses for serum sodium, chloride, potassium, calcium, phosphorus, magnesium, alkaline phosphatase, total protein, albumin, blood urea nitrogen, creatinine, and CO₂ were routinely completed monthly. Simultaneously, plasma zinc and copper and erythrocyte zinc and 3 day food diaries

were completed. Food diaries were then analysed for energy, protein, calcium, iron, phosphorus, sodium, potassium, and zinc intakes using the Michigan State University Nutrient Data Bank and compared to the standards resulting from HANES I and II data.

Mean growth velocity in males was 4.07 ± 2.02 cm/yr (non-supplemented), 2.98 ± 2.33 cm/yr (supplemented) and in females, 3.88 ± 0.73 cm/yr (non-supplemented), 3.28 ± 2.10 cm/yr (supplemented). There were no significant differences between the supplemented and non-zinc supplemented males or females in growth velocity. Bone maturation as determined through hand wrist radiographs, improved in 4 of 6 zinc supplemented subjects. Mean plasma zinc and copper levels before zinc supplementation were 97.1 ± 17.1 mcg/dl and 164.2 mcg/dl, and after supplementation, 101.9 mcg/dl and 172.8 mcg/dl, respectively. There were no significant differences in the plasma zinc or copper levels with or without zinc supplementation. Before zinc supplementation, 50%, 92% and 42 % of the subjects met 67% of their RDA for age and sex for energy, protein, and zinc, respectively. After zinc acetate supplementation, the percentage of subjects meeting 67% of the RDA for energy, protein, and dietary zinc were 67%, 100%, and 67%, respectively. There was a trend toward increased dietary

energy, protein, and zinc intake with zinc acetate
supplementation.

DEDICATION

This dissertation is dedicated to twenty-six children with Chronic Renal Failure at Children's Hospital of Michigan who participated in this investigation. In working with these children over more than a two year period, one is impressed with their bravery and maturity. Although like other children in most ways, they had to accept many disappointments and setbacks, additional responsibility for their future, and physical and psychological pain. Their desire to be "normal" is high, especially in males as it relates to attainment of an acceptable adult height. These children were often inconvenienced and made many sacrifices by participating in this investigation. Their contribution to increased knowledge will benefit future children with Chronic Renal Failure. This investigator and future benefactors appreciate their help and sacrifice.

ACKNOWLEDGEMENTS

The successful completion of this project took the cooperation of four major institutions in the state of Michigan: Michigan State University, Children's Hospital of Michigan, Wayne State University School of Medicine, and the Veterans Administration Hospital, Allen Park.

Michigan State University provided excellent support for the successful completion of this project. Dr. Jenny Bond, Dr. Wanda Chenoweth, and Dr. Rachel Schemmel each understood the problems associated with a human study and provided encouragement and suggestions as problems arose. Dr. John Vinsonhaler was instrumental in teaching computer literacy and systems analysis which were used in the selection and operation of computer equipment used for manuscript preparation.

The Administration of Children's Hospital of Michigan, particularly, Dr. Robert Gregg, former president, and Mr. Paul Broughton, current president, approved and supported the conducting of the research project at the hospital. Dr. Larry Fleischmann participated in guidance committee activities, and assisted in patient participation, data

collection, and clinical instruction and advice. Not only is he a brilliant physician and an excellent teacher, but he was also an advocate for utilizing allied health professionals in the care of renal patients long before it became popular and has built an effective team to provide ongoing care. This team was most helpful in collecting and coordinating data needed for this project. Special mention must be given to Nancy Gentner McDonald, Clinical Dietitian, Debbie McWilliams, Jan Sfeftick, and Mary Ann Lynch, Nursing. Information on methods and procedures used in routine laboratory analyses was provided by Mr. Abner Robinson, former, Director of Chemistry and Associate Director of Laboratories, and Dr. William Ferrel, current director. The pharmacy staff, particularly Gary Mark, consulted on the preparation of the zinc supplement.

Dr. Ananda Prasad from Wayne State University and the Veterans Administration Hospital, consulted on the research design, laboratory analysis of zinc and copper, and zinc supplementation. His laboratory staff at both the Veterans Administration Hospital and Wayne State University were most helpful in teaching the laboratory procedures for zinc and copper analysis in plasma and erythrocytes. Pat Flouriany was particularly helpful in the processing of blood samples over a time period in excess of two years.

This project was supported in part by Dietitians in Pediatric Practice, The American Dietetic Association. Dr. Larry Fleischmann supported the costs involved with zinc and copper analyses. Dr. Rachel Schemmel, Michigan State University supported computer costs through an agricultural research grant.

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I. INTRODUCTION

Chronic Renal Failure (CRF) has been associated with retarded growth in children (West and Smith, 1956; Betts and Magrath, 1974; Mehls et al, 1978; Potter and Greifer, 1978). In comparing a number of studies, Potter and Greifer (1978), report growth failure in 35 to 65 percent of all children with CRF. Growth failure in children with CRF has been associated with azotemia, acidosis, hyposthenuria, renal osteodystrophy, endocrine dysfunction, energy deficiency, abnormalities of protein metabolism, and treatment by glucocorticoid therapy (Potter and Greifer, 1978).

Reports in the literature relative to the effect of energy levels are controversial. Betts and Magrath (1974) found a significant correlation ($r=0.72$; $p<0.001$) between growth velocity, expressed as percentage of expected 50th percentile, and energy intake, expressed as percentage of kilocalories recommended for age. Normal growth would be expected in their study with an energy intake above 80 percent of kilocalories recommended for children in the United Kingdom. Likewise Simmons et al. (1971) determined that 70 percent of the Recommended Dietary Allowances (RDA) for energy must be consumed by uremic children to achieve growth. Subsequent work by Betts et al. (1977) showed that a

mean energy increase of 8.4 percent did not increase growth velocity. Betts et al. (1977) therefore concluded that decreased energy is a related factor to growth retardation in children with CRF, but not necessarily the only causal factor.

Zinc deficiency has also been associated with growth failure in children (Prasad, 1961). In 1963, Prasad (1963), determined that the failure of male Egyptian youths to grow was due to a zinc deficiency. Subsequently, Walravens and Hambridge, (Walravens and Hambridge, 1976) demonstrated low hair and blood zinc levels in infants in the United States. With zinc supplementation, the male infants demonstrated improved body length and weight.

The purpose of this investigation was to assess whether zinc acetate supplementation of children with End Stage Renal Disease (ESRD) improved energy intake and accelerated growth velocity and physical development.

II. LITERATURE REVIEW

A. Growth

Introduction

Growth and physical development of children are genetically predetermined. The normal rate of growth, however, can be influenced by such nutritional factors as undernutrition, overnutrition, or an imbalanced nutrient intake (Lowrey, 1978). Other factors influencing the growth and development of humans, both pre- and post-natally are thoroughly discussed in the treatise of Faulkner and Tanner, Human Growth, Vol. I,II,III, 1978-1979.

Humans follow a normal progression of growth and development if provided with the appropriate environmental, physical, and social factors. Growth is the process of increasing in physical size while development is the gradual unfolding of the genetic potential of the organism.

Anthropometry, radiography, and chemistry have been used to measure human growth and development. Tanner and Whitehouse (1966, 1975, 1976) used physical measurements to determine changes in height, weight, and somatic growth of children. Skeletal maturation through use of radiographs was studied by Gruelich and Pyle (1950, 1959). Macy (1942)

followed changes in the chemical composition of blood and urine in a pediatric population. Standards have been developed from these early works (Tanner and Whitehouse, 1966, 1975, 1976; Gruelich and Pyle, 1950, 1959; Macy, 1942), and from subsequent studies (Hamill et al. 1979; National Research Council, 1980). These standards are now used to assess deviation from normalcy of an individual or group of individuals.

Standards for Measuring Growth

Anthropometric

Robert's Nutrition Work With Children, (Martin, 1954) clearly summarizes the early standards developed to evaluate normal growth and development of children in America. Martin, (1954) credits Bowditch from the Harvard medical school with carrying out the first American study on height and weight in about 1872. According to Martin (1954), the Baldwin-Wood Weight-Height-Age Tables (1923) for boys and girls were the most complete and accepted tables in the early 1900's. In 1941, Dr. Norman C. Wetzel of Cleveland, Ohio developed the Wetzel Grid for evaluation of what he termed "physical fitness" (Wetzel, 1941). Wetzel (1941) viewed growth as a form of motion on three planes; quantity of growth, agents that control growth, and energetics of

growth. Martin (1954) explains that physicians found this grid an effective screening device and it was generally used by health workers both in this country and abroad. The Stuart-Meredith Growth Tables of 1946 were developed from research conducted by each investigator individually: Stuart in Boston; Meredith in Iowa (Stuart and Meredith, 1946). This collaborative effort resulted in the use of five measurements to evaluate physical growth of school children and replaced the previous standards. Height, weight, chest circumference, hip width, and leg (calf) girth were found to be reliable indicators of satisfactory growth. Percentile rankings for each measurement and each age were calculated and graphs developed. Meredith then in 1949 published the Meredith Physical Growth Record (Meredith, 1949). The Iowa Growth Charts for each sex were developed as a simplified form of the original data. They were to be used to assess the physical growth of Iowa school children.

Recognizing the regional limitations of previous studies and the apparent gradual increase in the size of the American population, the 84th Congress in 1956, authorized the National Health Survey. The studies resulting from this mandate consisted of five Health Examination Studies (HES) conducted through the National Center for Health Statistics (NCHS). Two of these health studies, HES IV and V introduced the specific focus of nutrition. These two studies are also

known as the Health and Nutrition Examination Studies (HANES I and II). The NCHS growth charts were derived from data collected in HES II, III, IV, V and information from the Fels Research Institute, Yellow Springs, Ohio (Hamill et al, 1977). Charts for both males and females, ages 0-36 months, and 2-18 years were developed as smoothed percentile curves representing almost 70 million American children (Hamill et al. 1979).

A study group consisting of the American Academy of Pediatrics, the Maternal and Child Health Program, Public Health Service, and the Department of Health, Education, and Welfare recommended that one set of data for all races would be sufficient for practical purposes (Hamill et al. 1977). The NCHS charts are commonly used today as the best standards to evaluate the growth of American children regardless of ethnic origin or regionalization.

In addition to height and weight standards, other anthropometric measurements have been developed to evaluate body composition (Falkner and Tanner, 1978-1979). Among these are the triceps skinfold (TSF) to estimate body fat and the upper arm muscle circumference (AMC) to estimate lean body mass. Seltzer et al. developed a reasonably precise method ($r=0.795$) for estimating the degree of obesity in obese female adolescents using the TSF measurement (Seltzer et al. 1965). Durnin and Rahaman (1967) achieved

approximately a 0.80 correlation coefficient between skinfold thickness and body density in a study on British adults and adolescents. Regression equations were calculated to predict body fat from the skinfold measurements with an error of about $\pm 3.5\%$. Durnin's formulas (Durnin and Womersley, 1974) are widely used today in the evaluation of skinfold data.

The Ten-State Nutrition Survey (TSNS), was approved by congress in 1967 (USDHEW, 1972). It provided the first comprehensive, single-source, life span data on body composition through the use of anthropometrics in the United States or any other country (Garn and Clark, 1975). HES cycle II data provided information on skinfold thickness of children in the United States (Johnston et al. 1972; Johnston et al. 1974).

Visweswara et al. (1970) studied the relationship of anthropometric measurements to nutritional status. Results of their study indicated that anthropometric measurements, especially the weight/height index were influenced by protein-calorie malnutrition. Forbes and Amirhakimi's (1970) work confirmed the data of other investigators showing that there is a linear relationship between skinfold thickness and body fat in normal children. Their data show that the average of six fatfold measurements obtained a higher correlation coefficient than the use of only one fatfold

measurement (Forbes and Amirhakimi, 1970).

Radiographs

Roche (1978) credits Howard in 1928 with presenting the first radiographic data on the evaluation of growth through skeletal maturation. Baldwin et al. (1928), studied the bones of the hand, wrist, and lower forearm of children by means of roentgenograms to evaluate their anatomic growth. Gruelich and Pyle (1959) credit Todd who was director of The Brush Foundation, Cleveland, with gathering information on x-rays of the hand and publishing these data in 1937 in Todd's Atlas for Skeletal Maturity: I The Hand. This atlas was the predecessor to the standard atlas used today, Radiographic Atlas of Skeletal Development of the Hand and Wrist by Gruelich and Pyle (Gruelich and Pyle, 1959). Tanner and Whitehouse (1975) developed the TW2 (Tanner and Whitehouse 2) method to assess skeletal maturity. Depending on the level of nine maturity indicators or stages for each bone, numerical scores are assigned to 20 bones of the hand and wrist (Tanner and Whitehouse, 1975).

Tanner et al. (1975) also developed a method for predicting adult height based on the TW2 method. Bayley's Bone Age (Bayley and Pinneau, 1952) was developed earlier to predict adult height and was based on the work of Gruelich and Pyle.

The TSNS of 1967 also provided valuable normative data on the effects of nutritional status on ossification timing, bone remodeling, bone lengths, and bone proportions during growth (Garn and Clark, 1975). At the request of NCHS, Dr. S. Idell Pyle was asked to "assemble a standard of skeletal maturity from the Gruelich and Pyle Atlas for assessment of HES, cycle II radiographic data on children, aged 6-11 and 12-17 years" (Abraham et al, 1979). NCHS publications refer to this as the HES Standards (USDHEW, Series 11, no. 140, 1974 and no. 160, 1976).

Dietary

It is generally accepted by many authors that growth is influenced by the nutritional status of the individual (Falkner and Tanner, 1978-1979; Martin, 1954; Lowrey, 1978;). Therefore, methodology relating to the collection and evaluation of nutrient intakes becomes important in the evaluation of growth.

Burk and Pao (1976) summarized the evaluation of four quantitative dietary collection methods used in surveys of food intakes of individuals. The weighed record, estimated record, 24-hour recall, and the dietary history are compared using the following criteria: reliability relating to sampling and repeatability of data; validity; respondent burden; field survey costs; and data processing costs.

Validity is further subdivided in terms of being accurate (absence of systematic error), concurrent (two measures of same concept), construct (degree to which variability in concept is measured), and representative (measure on level taken as an indicator on more general level). The results of this comparison indicate that no one method was consistently advantageous. Therefore, Burk and Pao (1976) recommend that researchers decide which trade-offs are most relevant to their objectives.

The TSNS was the first and most comprehensive attempt to survey the dietary intakes of Americans at all age levels (Garn and Clark, 1975). Approximately 16,000 children participated in the pediatric age group. A one day recall was the method used in this survey. Results showed that "the absolute intakes of energy (calories) and of all the nutrients examined reflected socioeconomic status", (American Academy of Pediatrics, 1975) and that the quantity of food was the major dietary problem disclosed (Garn and Clark, 1975).

HANES I was conducted between April, 1971 and June, 1974. This was the first program to collect measures of nutritional status for a scientifically designed sample representative of the U.S. civilian, noninstitutionalized population in a broad range of ages, 1-74 years (Abraham et al. 1979). HANES II was started in February, 1976 and ended

in December, 1979. The focus of HANES II was to examine population subsets within the ages of 6 months to 74 years (Carroll et al. 1983).

The Recommended Dietary Allowances (RDA) were first published in 1943 to "provide standards serving as a goal for good nutrition" (National Research Council, 1980). The RDA's were published in 1943 to determine how much manpower to direct to growing food to provide the necessary nutrients through food for a nation at war. The RDA's are now in their ninth revision and are based on the best scientific information available. RDA's are nutrient consumption recommendations for healthy population groups. The RDA's are recommendations that cover 95% of the nutrient needs for 95% of healthy people (National Research Council, 1980).

Standards established to evaluate the HANES I dietary intake data were from a variety of sources. Iron, thiamine, and riboflavin were evaluated using standards from the 1968 recommendations of the Food and Nutrition Board, National Research Council while calcium and vitamin A standards were closer to Food and Agriculture Organization/World Health Organization recommendations (Abraham et al. 1979). HANES data can now be used to compare intakes of subpopulation groups to the normative data for the total U.S. population (Abraham et al. 1979).

B. Growth and Chronic Renal Failure

Introduction

The etiology of Chronic Renal Failure (CRF) in children is discussed by Boyer (1984). Broad categories presented by Boyer (1984) include: glomerulonephritis, pyelonephritis and urinary tract malformations, renal dysplasia/hypoplasia, hereditary diseases, systemic diseases, vascular diseases, and miscellaneous other diseases (Boyer, 1984). The primary diseases leading to End Stage Renal Disease (ESRD) vary with age. Treatment for CRF varies somewhat with the primary diagnosis, the degree of renal insufficiency, and individual variation (Boyer, 1984).

Holliday outlines the progression of renal insufficiency (Holliday, 1976). Uremia occurs when the glomerular filtration rate (GFR) reaches a severity of 15-25 percent of normal functioning mass (Holliday, 1976). With the onset of ESRD, artificial means of removing the waste products of metabolism become mandatory. Methods commonly used include hemodialysis (HD), intermittent peritoneal dialysis (IPD), and continuous ambulatory peritoneal dialysis (CAPD). The method of choice will depend upon dialysis center objectives and individual patient variation (Tenckhoff, 1974). Dialysis is indicated when the blood urea levels are greater than 150

mg/dl and serum creatinine reaches 6-8 mg/dl.

Blood values of patients with CRF are normally monitored to determine the extent of uremia and asymptomatic changes. Normal ranges of commonly monitored blood values as used at Children's Hospital of Michigan are given in Table 1.

Medications and purpose of each medication commonly used to treat children with ESRD are listed in Table 2. Three of these medications, multivitamin preparation, folic acid, and Rocaltrol (vitamin D₃), are nutrient supplements necessary for either replacement of dialysate losses or replacement of products normally metabolized in the kidney (Nelson and Stover, 1984; Holliday et al. 1979). Amphojel and Dialume are trade names for aluminum hydroxide which is used in renal patients for its phosphate binding properties. Side effects include a decreased absorption of vitamin A, possible osteomalacia, constipation, anorexia, decreased weight, gastrointestinal cramps, a chalky taste and the inactivation of thiamin. Aldomet and Apresolene are both trade names for antihypertensives. Aldomet can result in drowsiness, dry mouth, diarrhea, edema, depression, nausea, and increased weight. Hemolytic anemia can occur with an increased need for vitamin B₁₂ and folic acid. An increase in serum alkaline phosphatase and creatinine, transaminase enzymes, and bilirubin are also seen with the use of Aldomet. Apresoline, can result in anorexia, gastrointestinal

distress, dizziness, tremors, constipation, blood dyscrasias and an increased need for pyridoxine. Phenobarbital, an anticonvulsant, can increase the turnover of vitamin D and K in children resulting in rickets, decreased bone density, or osteomalacia. Other side effects of phenobarbital may also include increased appetite, nausea, vomiting, and anorexia. Calcium carbonate, or Tums, is an antacid which can also be used as a calcium supplement. Calcium carbonate can result in infrequent hypercalcemia with alkalosis and decreased absorption of magnesium. Side effects of calcium carbonate include chalky taste, belching, nausea, constipation, and steatorrhea (Powers and Moore, 1983).

The aims of appropriate dietary and pharmacological management are to (1) improve or stabilize renal function, (2) promote growth, and (3) permit the child to continue a normal life (Hollerman, 1979). Various reviews, (Fine and Gruskin, 1984; Pediatric Clinics of North America, 1979) are available on the nutritional and medical management of children with CRF.

In evaluating the growth in children with CRF, growth velocity (cm/yr) and standard deviation score (SDS), (Falkner, 1962), also known as the Z-score (Snedecor and Cochran, 1968), are usually used. Potter et al. (1978) recommend the use of the SDS because "normal" growth velocity is not known. These two methods of reporting results make

comparison of data difficult. References on growth in children with CRF differ in the populations studied. Growth velocity of children differs according to whether they have renal insufficiency, ESRD requiring dialysis, or kidney transplant.

Growth Implications

Children with CRF often have impaired statural growth (Potter and Greifer, 1978). West and Smith, (1956) in an attempt to elucidate the cause of growth retardation in renal disease, categorized the various factors into calorie insufficiency, chronic acidosis, or primary endocrine abnormality.

Nash et al. (1972), studied a group of nine children with the presenting complaint of growth failure. Evaluation of these children revealed an alkaline urine and renal tubular acidosis of the proximal or distal type. In this sample population, with alkali therapy, growth improved from below the third percentile for height age to the third to tenth percentile. Three patients achieved the twenty-fifth to fiftieth percentile for height. These patients were not azotemic. Metabolic acidosis may impair the biological activation of 1,25-dihydroxyvitamin D₃ (Norman, 1982). Ten children with type I renal tubular acidosis, were studied for growth by McSherry (1978). Results of this study showed that

correction of the acidosis could be achieved with alkali therapy. The alkali requirement was sometimes in excess of 5 mEq of bicarbonate per kg of body weight per day. She concluded that with sustained correction, children will attain normal stature (McSerry, 1978). The oldest child in this study was 3.5 years with 7 of the ten children aged less than 4.5 months. Kohaut (1983), in a study on eleven patients undergoing CAPD for at least one year, showed a 0.274 positive, but weak, correlation between serum CO_2 plotted against growth. However, the level of significance is not noted in the article. Patients in this study had a mean height growth velocity of 0.69 cm/month as compared with an expected velocity of 0.73 cm/month.

Malnutrition will cause growth failure in otherwise normal children as well as children with CRF (Potter and Greifer, 1978). Malnutrition can be the result of inadequate energy, vitamins, and or minerals. Current dietary treatment for patients in renal failure is to decrease the dietary protein and maintain an adequate mineral intake based on measuring the blood mineral levels. Energy requirements are met by increasing carbohydrate and fat intake. Multivitamin supplementation, 1 tablet per day, plus 1 mg of folic acid is normally given (Holliday, 1979; Wassner, 1982; Nelson et al. 1984).

Simmons et al. (1971), and Betts and Magrath (1974)

established that adequate energy intake must be provided to achieve normal growth in uremic children. Simmons et al. (1971) determined that approximately 70 percent or more of the RDA for energy was compatible with growth in their patient population while Betts and Magrath (1974) determined that an energy intake of 80 percent of the United Kingdom's recommended allowances was required for normal growth to occur in their uremic patients.

Work done by Boyer et al. (1974) demonstrated that a caloric intake meeting the RDA did not guarantee normal growth. In subsequent work done by Betts et al. (1977), 80 percent of the energy recommendation for children in the United Kingdom, plus an additional 8.4% mean energy supplementation, did not increase growth velocity even though some patients reported "improved well-being". These studies suggest that decreased energy intake in children with CRF is a related factor but not necessarily the only factor in their growth retardation.

CAPD patients obtain additional energy through the absorption of glucose from the dialysis solution. An investigation by Brown et al. (1973) demonstrated that 10 to 60 grams of glucose (40-240 kilocalories) per liter of dialysate may be absorbed during peritoneal dialysis. Likewise, De Santo et al. (1982) found that up to 140 gm/day (560 kilocalories) of glucose could be absorbed by children

during CAPD therapy while Moncrief et al. (1985) cites higher amounts depending upon the number of exchanges and the concentration of each exchange daily. The amount of glucose absorbed is related to glucose concentration, absorption being almost complete within the first thirty minutes (Brown et al. 1973, Moncrief and Popovich, 1985).

Both Arnold et al. (1983) and Takala (1982) used aggressive nutrition therapy to improve the nutritional status and growth in renal patients. Arnold et al. (1983) worked with 12 children aged 2.5-11 years (9 males, 3 females) and demonstrated a 5.68 ± 0.26 cm/yr growth velocity with glucose polymer supplementation versus 3.90 ± 0.58 cm/yr without supplementation. Each child served as his/her own control and was followed for one year both pre- and post-supplementation. All children were at least two years prepubertal prior to initiation of the study. Arnold et al. (1983) concluded, however, that the nutritional deficit was small, but improved growth was seen when supplementation was given to patients ingesting less than 75 percent of RDA calories for height. Serum albumin concentrations also increased significantly ($p < 0.05$) which provided additional evidence that a dietary deficiency was corrected. It has recently been reported (Kelley et al. 1984) that glucose polymers enhance the intestinal absorption of calcium in a liquid formula diet or in an aqueous

solution. Takala (1982) used total parenteral nutrition or continuous enteral nutrition to supplement three young renal patients (2 infants, one 4 year old). These patients had cessation of growth or deteriorating growth prior to the aggressive nutritional therapy. Results demonstrated a restoration of growth without an unreasonable urea production.

Kleinknecht et al. (1980) followed 76 children with ESRD for more than one year to evaluate growth velocity and the relationship between bone length gain and bone maturation. Forty-five boys and 35 girls, aged 16 months to 16 years were followed for a mean of 29.6 months (boys) and 30.7 months (girls). A mean annual loss of length for age, compared to French national standards, was 0.4 SD/year for boys and 0.38 SD/year for girls. With dialysis, approximately one third of the patients showed a satisfactory growth rate (but no catch-up growth), one third had a moderately reduced growth rate and one third had severely impaired statural growth. The diet for this population was calculated to provide 75 percent of protein of RDA for children of similar height. Increased calories were provided using lipid and carbohydrate supplements. Kleinknecht et al. (1980) also demonstrated that the level of bone maturity was retarded for chronological age thus increasing the time span for statural growth to occur. In boys the level of bone maturity for

puberty (a bone maturation score between 138-158) occurred at ages 15-18 years. In girls a bone maturation score of 134-142 was reached between the ages of 14-16 years. Onset of puberty for normal children occurs at a bone maturation score of 130. This equates with a bone age of 13 for boys and 11 for girls. Therefore, it appears that the potential for growth is maintained throughout childhood and until pubertal growth and bone maturation occur.

Kleinknecht et al. (1980) also concluded that growth velocity remained constant over several years of dialysis treatment and that children with the most retarded statural growth at the beginning of dialysis showed the best growth rate under dialysis treatment. Lowered serum creatinine levels were significantly related to improved growth. The techniques and schedules of dialysis have not previously been related to growth but Kleinknecht et al. (1980) state that the efficiency of dialysis and the accumulation of waste products, as demonstrated by serum creatinine, may play a role. Seventeen children aged 0.4-18.5 years receiving CAPD treatment, were studied by Stefanidis et al. (1983) for at least 5 months and compared to 18 children undergoing HD and 20 children who had received a renal transplant. Stefanidis et al. (1983) concluded that significantly ($p < 0.001$) better growth was seen in patients treated by CAPD than in those receiving HD and that the treatment with CAPD did not show

significantly different growth rates from those of children who have kidney transplants.

Other studies dealing specifically with CAPD provide additional information. Williams et al. (1983) concluded that patients on CAPD may be in longterm negative nitrogen balance if their protein intake is maintained at 1.0 g/kg/day or less. Balfe et al. (1981) studied 10 patients less than 6 years old and 9 patients older than 6 years for 6 months. These investigators demonstrated a growth rate of 0.31 cm per month with a range of 0 to 110 percent of absolute growth compared to predicted. Children less than 6 years of age also appear to lose greater amounts of protein (gm/kg/day), but absorb greater amounts of glucose (mg/dl) through the dialysate than children over 6 years.

Salusky et al. (1982) evaluated the effect of CAPD therapy on children with CRF who had previously been treated by either HD or IPD. They found a mean growth velocity of 0.35 cm/month as compared to a normal growth rate of 0.5 cm/month in 9 patients, ages 1.5 to 11.4, on CAPD therapy for more than 6 months. They reported a significant decrease ($p < .002$) in mean serum total protein levels and a trend toward a decrease in serum albumin levels with the CAPD treatment. Energy intake was evaluated in twelve patients, including the 9 patients evaluated for growth velocity. Three of the 12 averaged less than 75 percent of the RDA

while the remaining 9 each had an average energy intake of 82 percent of the RDA for children of the same height and sex. They reported that the amount of energy absorbed through the dialysate was 7.8 kilocalories per kg per day. Data for a comparison of growth and energy intake for each subject were not presented.

A more comprehensive evaluation on the nutritional status of 24 children undergoing CAPD was presented by Salusky et al. (1983). The patient population was divided into children less than 10 years (9 patients) and those 10 years and older (12 patients). Four younger children and 6 older children had a total energy intake (diet plus dialysate) of less than 75% of the prescribed intake (the RDA for energy and a minimum of 3.0g/kg/day of protein for children less than 5 yrs old, 2.5g/kg/day for 5 yrs to puberty, 2.0g/kg/day during puberty and 1.5g/kg/day thereafter). Growth, as determined by TSF, mid-arm circumference (MAC), height, and weight for chronological age and sex, was significantly reduced in the younger group, while the same was true for height and weight and MAC in the older age group. The MAC, however, was normal when evaluated against height per age. The TSF for the older group of subjects was normal. Serum total protein, albumin and transferrin were low and the amino acid concentrations were altered and similar to the pattern seen in children with

chronic uremia and malnutrition. A significant direct correlation was found between the TSF, expressed as Z-scores for chronological age ($r=0.60, p<0.01$) and height/age ($r=0.70, p<0.001$), and the duration of CAPD therapy. The authors conclude that these positive correlations indicate CAPD can promote "catch-up" accrual of body fat probably related to glucose absorbed from dialysate and that a weak correlation between Z-scores for MAC and duration of CAPD ($r=0.43, P<0.05$), supports the possibility that CAPD improves the nutritional status of pediatric ESRD patients.

Continuous cycling peritoneal dialysis (CCPD) is a variation of CAPD (Brem and Toscano, 1984). CCPD is a combination of CAPD and IPD. Dialysis exchanges are made during the nighttime hours and a prolonged dwell is left in the abdomen during the day. Brem and Toscano (1984), compared growth in six patients on HD with 7 children maintained on CCPD. In the three patients on HD who had not reached puberty, linear growth averaged 3.5 ± 1.1 cm/year, while in 6 of the pre-pubertal children maintained on CCPD, the growth velocity was 3.2 ± 1.7 cm/year. Both groups ingested approximately two-thirds of the recommended age adjusted caloric intakes. Brem and Toscano (1984), concluded that no form of dialysis treatment holds any advantage over another in terms of growth in children with CRF.

Delayed sexual maturation has also been shown to occur

in children with ESRD. Hutchings et al. (1966) describe a 15 year old girl, treated by hemodialysis, who had decreased growth and sexual maturation. Menstruation had not begun and there was no breast development or axillary hair. Likewise, Lirenman et al. (1968) present a case history of a boy maintained on dialysis from 16 months to 16 years. Growth was below normal and puberty was delayed for age.

C. Growth, Renal Disease and Zinc

Introduction

Since the excretion of minerals in renal disease is altered, much attention has been given to monitoring the Na, K, Cl, Ca, and P levels. Little attention has been given to monitoring Zn levels.

Prasad et al. (1963) established the relationship between zinc deficiency and decreased growth in an adolescent Egyptian male population. Walravens and Hambridge (1976), and Hambridge et al. (1972), likewise, established that zinc deficiency was present in infants in the United States and was associated with decreased growth.

When there is a zinc deficiency, depressed taste acuity has been correlated with plasma levels of zinc in adults with CRF (Mahajan et al. 1980). Anorexia is commonly observed in patients with CRF and leads to diminished energy intake (Blendis et al. 1981; Wassner, 1982; Holliday et al. 1979; Scharer and Gilli, 1984). Whether or not this anorexia is the result of changes in taste acuity has not been demonstrated.

The factors affecting the absorption of zinc have not been completely elucidated. Dietary phytates and fiber decrease the availability of zinc for absorption (Kelsay et

al. 1979), while the presence of dietary calcium enhances the binding of zinc with phytates (Prasad, 1978). Ronaghy et al. (1974) found increased growth in an adolescent male population who were supplemented with zinc carbonate as compared to a control non-supplemented group. The diets of both groups were the same and contained unleavened wholemeal wheat bread rich in phytates.

The location of zinc absorption is presumed to be the upper jejunum (Matseshe et al. 1980). The absorption of zinc is thought to be aided by a zinc binding ligand (ZBL) (Evans et al. 1975). Zinc appears to be secreted into the jejunum after stimulation from the pancreas by a meal (Matseshe et al. 1980) and therefore must be reabsorbed to maintain positive zinc balance.

Once absorbed, zinc is transported by a transport protein (Solomons, 1982). This transport protein is thought to be either albumin (Cousins, 1979) or transferrin (Evans, 1976). Solomons (1982) presents an excellent review of the intrinsic and extrinsic factors regulating zinc absorption. Aamodt et al. (1981) found a $65 \pm 11\%$ mean absorption in normal adult subjects using 10 micro Ci of carrier-free ^{65}Zn administered orally after a 14 hour overnight fast. Istfan et al. (1983) studied the absorption of ^{70}Zn in 4 healthy young men and determined that the fractional absorption of zinc varied directly with the stable isotope dosage given and

that this fractional absorption increased after restricted dietary zinc.

Using ^{65}Zn , Aamodt et al. (1982) studied the distribution, retention and excretion of zinc in 50 patients with taste and smell dysfunction. Results of this investigation revealed that 70% of the injected ^{65}Zn activity was in the liver within five to seven days and was retained with a final biological half time ($T_{1/2}$) of about 75 days. The total distribution of zinc in the body was 60%-62% in skeletal muscle, 20%-28% in bone, and 2%-4% in liver. The same group of investigators (Babcock et al. 1982) evaluated the kinetics of oral zinc loading in this same group of subjects. They determined that 10% of the total body zinc (2.1-2.5 g in normal subjects) was in a pool rapidly exchanging with plasma and the remaining 90% was postulated to be in a single slow turnover pool which was probably skeletal muscle. The kinetic curves which occur following administration of oral zinc loading could be accounted for by changes in gastrointestinal absorption and renal excretion.

In a study performed in rats by Jackson et al. (1982), zinc depletion was associated with a low plasma zinc level and an elevated plasma copper concentration. In these zinc deficient animals, bone zinc levels fell to 1/3 the normal level with zinc deficiency and remained significantly ($p < 0.001$) below the normal values upon zinc repletion while

hair and skin zinc levels remained unchanged (Jackson et al. 1982). Jackson et al. (1982) also determined that the level of zinc in the testes of zinc-depleted animals was approximately half that of normal rats. McClain et al. (1984), working with rats, determined that both zinc deficiency and energy restriction produced hypogonadism and suggest that the hypogonadism in zinc-deficient animals is principally attributable to Leydig cell failure. In order to examine the relevance of the animal studies to man, Jackson et al. (1982) also measured zinc levels in a variety of tissues from three patients with disturbed zinc metabolism. The results of the investigation revealed decreased plasma, but normal hair, skin and muscle zinc levels. Post mortem zinc levels were analyzed on tissues from one patient. Results showed low zinc levels in bone, liver, and testes.

Zinc is excreted from the body primarily via the feces. Secondary routes include urine and sweat (Underwood, 1977). In a balance study on humans performed by Milne et al. (1983), it was determined that 0.4-0.5 mg of zinc per day could be lost through sweat. The zinc lost via sweat was reduced by 50 percent or more when the amount of zinc given was reduced from a mean of 8.3 mg/day to 3.6 mg/day. Research on zinc has also determined that renal tubular disease leads to the failure of tubular reabsorption of zinc (Beisel et al. 1978). During catabolic states, the excretion

of zinc in the urine has been related to loss of muscle tissue (Kirchgeßner et al. 1978).

Zinc is a component of hundreds of enzymes and other proteins. In animals, the alkaline phosphatase activity in serum declines rapidly as a result of zinc deficiency. Bone and kidney alkaline phosphatase activity may also decline with zinc depletion (Kirchgeßner et al. 1978).

Growth and Zinc

Studies with rats demonstrated that zinc is essential for normal fetal growth (Hurley et al. 1966; Warkany et al. 1972), tissue development (McKenzie et al. 1975), and maternal weight gain (Fosmire et al. 1977).

Prasad et al. (1963) published a classic study associating zinc deficiency with growth in a male Egyptian adolescent population. Hambridge et al. (1972) later reported poor growth, hypogeusia, and zinc deficiency in an otherwise normal child population in Denver, Colorado. Walravens and Hambridge (1976) measured weight, height, and head circumference in a healthy zinc supplemented and control infant population. Results of this investigation indicated a significant increase in the supplemented group for all three parameters in male infants. During clinic visits, parents of all subjects were asked if their infants experienced constipation, diarrhea, or vomiting. The zinc supplemented

group reported significantly decreased gastrointestinal problems ($p < 0.005$). Energy intake was the same in both groups of infants studied.

In 1983, Walravens et al. (1983), supplemented a group of low income children from Denver with zinc and compared their linear growth with controls from the same population pair-matched, for sex, age, and initial height for age percentiles. These children had low growth profiles and were presumed to be zinc deficient. During the first 6 months of the study there was no significant difference between test and control subjects although a trend for a greater height increment was seen in the zinc supplemented boys compared to their pair-matched controls. However, at the end of 12 months there was a significant difference in height growth velocity between test and control groups and these differences were primarily due to the increase in height gain of zinc supplemented males. It was also noted in this study that energy and protein intakes did not differ significantly between the groups upon entry into the study, but were significantly greater in the zinc-supplemented group at the end of the study period.

Zinc and Renal Disease

Growth retardation is documented in zinc deficient children (Prasad et al. 1963; Hambridge et al. 1972) and in

children with CRF (West and Smith. 1956; Potter and Greifer, 1978). Low plasma zinc levels and significantly depressed RBC zinc ($p < 0.05$) have also been documented in children with CRF (Siegler et al. 1981). In a comparison of three adult hospital dialysis programs in Toronto, Canada (Blendis et al. 1981), there was a significant difference in plasma zinc levels between patients in hospital A and hospitals B and C patients. The estimated zinc and protein intakes were significantly greater from patients from hospital A than from patients from the other two hospitals. These authors concluded that the zinc deficiency seen in hospitals B and C was due to a low protein diet in their chronic dialysis patients. Hypogeusia was implied as a possible cause of the decreased protein intake. Slight leaching of the dialysis equipment was noted as a possible reason for combating the development of zinc deficiency in hospital A patients. Likewise, Mansouri et al. (1970) noted that undialysed children with CRF on a low protein diet had lower plasma zinc levels than dialysed uremic subjects on a normal protein intake. Although not discussed by Mansouri et al. (1970), the lower plasma zinc in the nondialyzed subjects may well be due to the dilution effect caused by the edema of CRF.

Fourteen patients with CRF were evaluated by Siegler et al. (1981) for zinc deficiency. Results of this study indicated a strong correlation ($r = 0.96$, $p < 0.01$) between both



energy and zinc intake and protein and zinc intake. A similar correlation was found between erythrocyte zinc and both percent ideal body weight ($r=0.56$, $p<0.05$) and height percentile ($r=0.61$, $p<0.01$).

D. Analysis of Zinc

Zinc can be analyzed in biological fluids by various techniques. According to Henry et al. (1974), Clinical Chemistry: Principles and Techniques, the method of choice is based upon many factors. These factors include the sensitivity of the method, reproducibility, precision or accuracy, analytical recovery, sample size required, simplicity or convenience of the method, and repeatability.

The conventional method for the analysis of zinc in blood is atomic absorption spectrophotometry (Walsh, 1955). Prasad et al. (1965), described a technique for the determination of zinc in plasma, red blood cells and urine using a commercially available spectrophotometer. Prasad et al. (1965), used this technique to determine the red blood cell, and urine zinc levels in patients with cirrhosis of the liver and compared their results with the dithizone method. Comparable results were obtained. In addition, atomic absorption spectrophotometry, was much simpler, less time consuming, and more sensitive than the dithizone method.

Curtis and Roth (1978) define atomic absorption as the determination of "the type and amount of an element by measuring wavelength and intensity of the light absorption of its mono-atomic vapor". Conversion of the element to atomic

vapor from a solution or solid is generally carried out using a flame. The heat from the flame nebulizes the liquid, evaporates the solvent and the dissolved particles, and causes atomic dissociation of the molecules of salts in the vapor phase. Atomization occurs.

In atomization, heat excites the electrons to raise from their ground state or orbital rings. When under low temperature, heat is released, but when using a higher temperature, light, which can be measured by absorbance, is released. Even a higher temperature will ionize the substance and remove it from the medium. Therefore, an optimal temperature for each element is required.

Various modified techniques of the atomic absorption method are noted in the literature. Matsuura (1982) compares flame and flameless atomic absorption techniques and concludes that the flameless as compared to the flame requires a smaller specimen and has much higher sensitivity, but requires much more elaborate preparation and does not have good reproducibility. Sekiya et al. (1981) and Whitehouse et al (1982) concur. Foote and Delves (1982) obtained a 0.94 correlation coefficient between flame atomic absorption and electrothermal atomization techniques. The primary advantage of electrothermal atomization over flame atomic absorption is the much smaller sample required. This is particularly useful in measurements made on biological

fluids or tissues of neonates and newborns. Taylor and Bryant (1981) compared sample pretreatment methods using water, butan-1-ol or propan-1-ol, trichloroacetic acid, and electrothermal atomization. None of these methods showed superior between-batch precision. The inclusion of sodium and potassium ions was also examined by these authors. Ionization interference was found to occur. Flow injection analysis was shown by Rocks et al. (1982) to offer fast, direct analysis of copper and zinc in small volumes of serum. Discrete nebulization of a sample as compared to conventional nebulization was reported by Makino et al. (1981) to have slightly poorer precision.

III. METHODS AND PROCEDURES

A. Research Site

Children's Hospital of Michigan is a 290 bed teaching hospital located in Detroit, Michigan. The hospital is affiliated with Wayne State University School of Medicine. Children between the ages of birth and 18 years are routinely treated for renal diseases, including ESRD. Dialysis facilities exist for both hospital based HD and IPD therapy, and CAPD treatment for outpatients. Hospital support services include laboratory facilities for routine chemical analyses, radiology services for obtaining and reading hand wrist radiographs, and a professional nephrology staff who commonly participate in research projects. Dr. Larry Fleischmann who is Director of Nephrology and all dialysis programs at Children's Hospital of Michigan, actively participated in this study.

B. Subjects

All patients, aged 6 to 18 years, who regularly undergo treatment for ESRD at Children's Hospital of Michigan, Detroit, Michigan, were invited to participate in the study.

The project was approved by the Research Grants and Investigation Committee at Children's Hospital of Michigan and the University Committee on Research Involving Human Subjects (UCRIHS) at Michigan State University and subsequently has been renewed annually. Signed consent forms (Appendix A) were obtained from all legal guardians prior to initiation of the study and/or assent obtained from patients 12 years and older. All analyses not done at the hospital for clinical purposes were completed using the medical record number to assure confidentiality of the subject. Subjects were able to withdraw from the study at any time.

All patients were diagnosed as having ESRD and were being treated for their renal failure by hemodialysis (HD), intermittent peritoneal dialysis (IPD), or continuous ambulatory peritoneal dialysis (CAPD). Patients were changed from one method of treatment to another as determined by the clinical judgment of the attending physician. During the course of the study, 26 patients participated. Of the 26 subjects, 17 were male and 9 female, while 11 were Black, 14 White and 1 Asian. The characteristics of the study participants are given in Table 3.

Patients treated for their ESRD by CAPD or their caretaker, received an extensive 2 to 3 week in house training course. Each member of the nephology team provided training in their area of specialization and was

required to sign off as to the competency of the patient before home care was approved. The dietary training was given by a masters prepared registered dietitian. Therefore, the participants in this study were well prepared to provide dietary intake data, and comply with all medical instructions as well as zinc supplementation instructions.

C. Dialysis Fluids

Hemodialysis patients were dialyzed for approximately 3 hours, 3 times each week. Eri-lyte 8306 hemodialysis concentrate (Erika Inc., Rockleigh, N.J. 07647) was used in a Drakes Willock Dialyzer (Portland, Oregon) to ultrafiltrate patients' blood. The composition of the dialysis fluid is given in Table 4. Children maintained on CAPD used Dianial PD-2 manufactured by Baxter Travenol Laboratories, Inc (Deerfield, Il.) to complete 4 to 5 exchanges daily. In CAPD, dialysate is gravity fed into the peritoneal cavity where it dwells for two or more hours depending upon the individual patient's schedule. The composition of Dianial PD-2 dialysate is listed in Table 4. Dianial PD-2 is Potassium free as are solutions used in IPD and HD. However, the dextrose concentration can be 1.50, 2.50, 4.25 gm dextrose per 100 ml. Higher dextrose concentrations increase the osmolarity of the dialysate thus removing larger

quantities of water from the patient. Patients are evaluated monthly by the attending physician and dialysis staff and the appropriate solutions and schedules are prescribed. A combination of different solutions could be used for separate exchanges during the course of the day. CAPD patients are home trained on the maintenance dialysis treatment and provide their own care or the care is provided by a trained caretaker, usually a parent. Patients maintained on IPD are dialyzed for approximately 12 hours, 3 times per week using a AMP 80/2 Peritoneal Dialysis System (Freehold, N.J. 07728). Hemodialysis and IPD patients receive dialysis treatment at the hospital where specialized equipment and staff are available.

D. Anthropometric Measurements

Anthropometric measurements included height, weight, MAC, and TSF. Measurements were usually obtained monthly at regularly scheduled clinic visits according to the method described by Foman (1976). Height was measured on each subject undergoing hemodialysis using a non-stretchable tape affixed to a true vertical surface in the dialysis suite. A manual headboard was constructed by the maintenance staff at Children's Hospital of Michigan. This headboard was placed on the head of each subject while standing against the

vertical metal tape with their heels, buttocks, shoulders and head against the wall and with the head held parallel to the floor, facing forward (Foman, 1976). Markings were made at the base of the headboard and the measurement was read in cm directly from the tape. Height measurements on subjects undergoing CAPD treatment were obtained at the beginning, the initiation of zinc supplementation, and end of the study by the principal investigator using a calibrated digital counter stadometer (Holtain Limited, Crymmych, England). Monthly heights were taken by nursing personnel regularly assigned to outpatient duty. A stadometer (Continental Scale Corporation, Bridgeview, Ill. or Detecto Scales Inc, Brooklyn, N.Y.) was used.

The prediction of adult height was determined by calculating the midparent stature and by using the method of Bayley and Pinneau (1952). Calculations based on the work of Garn and Rohmann (1966) were also completed to determine the current extent of growth necessary to achieve midparent height.

Body weights were measured to 0.1 kg on either a Continental or Detecto beam balance (Continental Scale Corporation, Bridgeview, Il.; Detecto Scales Inc, Brooklyn, N.Y.). Beam balances were commercially calibrated several times per year. The Detecto beam balance in the dialysis suite was documented as being calibrated 4 times in 1984.

Nursing personnel were responsible for collecting weights on all CAPD children and patients when hospitalized. Hemodialysis and IPD patients were taught to obtain their own weight pre- and post-dialysis treatment. Post-dialysis weights were used in the study for hemodialysis subjects. Weights on CAPD subjects were obtained after subjects had emptied their dialysis bags.

MAC and TSF measurements were taken by the principal investigator. MAC was obtained using an Inset-Tape, compliments of Ross Laboratories (Ross Laboratories, Columbus, Ohio 43216). The midpoint was determined using a Dritz (John Dritz & Sons, Inc. N.Y., N.Y.) non-stretchable tape. Lange calipers (Cambridge Scientific Industries, Inc., Cambridge, Maryland 21613) were used to measure TSF. The Lange caliper was calibrated frequently using the metal calibration standard supplied with the instrument.

E. Radiographs

Radiographs of the hand and wrist were taken as part of a regular skeletal survey prior to zinc supplementation by radiology technicians at Children's Hospital of Michigan. At the completion of the zinc supplemented period, a second hand-wrist x-ray was taken. Additional baseline radiographs were available on 5 subjects so that change over time was

compared between pre-zinc bone age and post-zinc bone age. All radiographs were assessed for bone age according to the method of Gruelich and Pyle (1959), by Thomas Slovis, M.D., pediatric radiologist at Children's Hospital of Michigan.

F. Physical Examination

A physical examination was obtained by the attending physician and/or the clinical nurse specialist at least monthly throughout the study. The purpose was to provide ongoing medical care. CAPD patients were examined approximately every month as outpatients, unless hospitalized, in which case more frequent examinations were noted in the medical record. Physical examination data were used by the principal investigator to track medical and/or social events, such as infections, changes in treatments, compliance to medical instructions, and other disease conditions which might influence the results.

Tanner staging (Tanner and Whitehouse, 1976), to determine the degree of sexual maturation, was completed during the physical examination both before and after zinc supplementation by the attending physician or the clinical nurse specialist. Developmental changes in the male genitalia and pubic hair growth in males, and breast and pubic hair growth in girls, provided an index to evaluate the

influence of puberty on statural growth.

G. Laboratory Analyses

Laboratory data commonly obtained for routine care of renal patients included blood determinations for calcium, phosphorus, sodium, potassium, chloride, magnesium, urea nitrogen, creatinine, alkaline phosphatase, total protein, hemoglobin, hematocrit, CO_2 . Blood samples were collected monthly, either at the time of the clinic appointment or prior to the initiation of HD, which was usually in the morning after breakfast.

The Centrif-Chem analyzer (Union Carbide Corporation, Rye, N.Y. 10580) was used to measure alkaline phosphatase by a modified Bessey, Lowry, and Brock technique (Bessey et al, 1946), and serum creatinine using alkaline picrate. The Centrif-Chem is an automated instrument and is also used to measure magnesium (Grindler and Heth, 1971). Eastman Kodak's Ectachem equipment (Rochester, N.Y.) was used to determine blood urea nitrogen using a urease reaction; serum chloride, sodium, potassium and CO_2 using an ion specific electrode; serum phosphorus using a Fiske Subbarow molydate reduction reaction; serum calcium using an arsenazo-3 dye complex; total protein using the biuret reaction; and serum albumin using bromocresol green color reaction (Eastman Kodak,

1985). A manual method using ammonium hydroxide was used to determine hemoglobin, while the hematocrit was measured manually by centrifugation.

These values were recorded in the patients medical record and were used to evaluate the severity of renal failure and to monitor dietary compliance. The diet prescription was readjusted by the attending physician when necessary as indicated by the laboratory values.

H. Zinc and Copper Analysis

Erythrocyte and plasma zinc and copper levels were determined by atomic absorption spectrophotometry (AAS), both pre- and post-supplementation, in the laboratory of Dr. Prasad, Veterans Administration Hospital, Allen Park, Michigan. This method has previously been published by Prasad et al. (1965).

Blood samples were collected both pre- and post-supplementation by nursing or laboratory personnel at Children's Hospital of Michigan. A 5-10 ml sample of whole blood was drawn with a needle and syringe and put into a Nalge (Nalgene Labware, Rochester, N.Y.) test tube containing 4 drops of zinc free heparin. Extra care was taken to prevent contamination of the sample. The sample was capped, mixed, and refrigerated. After 2 to 4 hours, the blood

sample was centrifuged (Sorvall RC2-B) at 3000 rpm for 20 min at 4° C. The supernatant (plasma) was transferred to a second Nalge tube, the buffy coat discarded by pipetting, and the precipitate (RBC) washed with 0.9% cold saline (NaCl + deionized H₂O). The erythrocytes were centrifuged again at 3000 rpm for 20 minutes at 4° C. The supernatant was removed by pipetting and discarded. This washing of the erythrocytes was repeated 3 times.

One ml of 10% trichloroacetic acid (TCA) was added to 1 ml of plasma to precipitate the plasma proteins. The plasma sample was vortexed, then heated for 10 min in a 110° water bath, and centrifuged for 15 min (3000 rpm) at 15-20° C. The supernatant was then poured into a clean Nalge test tube and the process repeated two more times on the precipitate. The supernatant each time was added to the previous collection. The total collection was brought to 3 ml with deionized H₂O and was analyzed for zinc and copper concentration.

Erythrocyte zinc was determined by pipetting 0.5 ml of packed RBC's using a plastic serological pipette into an 18 ml Nalge test tube. One ml of deionized H₂O were added using an automatic pipetter, the sample vortexed, and 1 ml of concentrated HNO₃ added using a repipettor attached to a HNO₃ bottle. The sample was lightly capped, placed under a fume hood in a 110° hot water bath, uncapped, and heated for 2 to 2 1/2 hours. The volume of the sample was brought to 4 ml

with deionized H_2O by pouring the sample into a graduated glass test tube, rinsing the Nalge test tube with deionized H_2O , adding this rinse to the sample, and finally adding more deionized H_2O to 4 ml. The sample was then decanted back into the original Nalge test tube and zinc and copper concentrations measured.

Standard solutions were made using zinc oxide (Fisher Scientific, Pittsburgh, Pa 15219) and copper nitrate (Fisher Scientific, Pittsburgh, Pa 15219) in dilute nitric acid. The concentrated standard of 100 mcg/ml was made fresh each month by diluting 3 times with deionized H_2O to obtain the final concentration range of 0.2ug/ml to 1.0 ug/ml. A Perkin Elmer 306 Atomic Absorption Spectrophotometer was used to measure the concentration of zinc and copper in standard solutions, and plasma and erythrocyte preparations. The spectrophotometer wavelength was set at 214 nm and 325 nm for zinc and copper analyses, respectively.

I. Food Intakes

A dietary history and a 24-hour dietary recall were * obtained on each subject at the beginning of the study using dietary department forms (Appendix A). Each participant or his/her caretaker was requested to keep a 3 day (2 weekdays and 1 weekend day) food diary of all food ingested at the

initiation of the study and for each month throughout the study. These records were then reviewed with the subject or caretaker by the clinical dietitian to expand and clarify information. Frequently, during periods of hospitalization, food records were collected by hospital staff to monitor energy, protein, sodium, potassium, and fluid intake.

Using standard references (Pennington et al, 1980; USDA, 1975), calculations for energy, protein, sodium, and potassium intakes were made of the 3 day food record, 24-hour recall, and food intakes, to determine the diet prescription for each participant. Energy and protein levels were prescribed according to those recommended for age. Specialized supplements such as Polycose (Ross Laboratories, Columbus, Ohio), Propac (Biosearch, Somerville, N.J.), and Amin-Aid (American McGraw, Irvine, Ca) were prescribed and encouraged if the manually derived calculations indicated a need for additional energy or protein. The 3 day food records, 24-hour recalls, and hospital food records were then coded for nutrient analyses using the Michigan State University computerized nutrient data base (Morgan and Zabik, 1983). Each subject's daily intake was evaluated as percent of RDA for age and per weight for energy and protein, and the RDA per age for calcium, phosphorus, sodium, chloride, potassium, magnesium, zinc, copper, and iron.

Since subjects were not consistent in bringing in the 3

day food records, the intake data (24-hr recall, 3 day record, or hospital food intake) from the one date closest to the end of each month were used for statistical evaluation of each subject's dietary intake. The mean values were compared to the HANES I data for children of the same age and sex for energy, protein, calcium, and iron. HANES II standards were used to compare each subject's mean data for energy, protein, calcium, phosphorus, iron, sodium, and potassium with American children of the same age and sex. Information provided in the HANES I data allowed for Z-score analysis of each subject's data. However, the information provided in HANES I was limited to only energy, protein, calcium, and iron. HANES II data contained a more complete listing of nutrients, but did not provide standard deviations for the American population thus negating Z-score calculations. Therefore, each subject's intake for energy, protein, calcium, phosphorus, iron, sodium, and potassium was calculated as a percent of the 50th percent of HANES II data, to see if there were significant changes in intake between the non-zinc supplemented and zinc supplemented periods.

J. Zinc Supplement

A liquid form of zinc acetate (USP Reagent) was prepared in the pharmacy at Children's Hospital of Michigan by the investigator. Using a Mettler balance, 56.1 gms of USP Reagent grade zinc acetate (Frank W. Kerr Chemical Co., Novi, Michigan) was weighed. The powder was then added to 1000 ml of sterile water (Travenol Laboratories, Deerfield, Il.) and mixed by shaking in the original container. The final concentration of the mixture was calculated to be 20 mg of elemental zinc per ml. The zinc acetate solution was poured into a 2 or 3 oz amber bottle and labelled. Each bottle contained sufficient zinc acetate solution to last one month. Therefore, zinc acetate was provided on a monthly basis to each subject.

The amount of zinc supplementation for each subject was calculated based on the recommendations of Walravens (1979) and through personal communications with Dr. Prasad. The quantity was determined by multiplying the patient's body weight in kilograms by 2 mg/kg. The total amount prescribed was the result of this calculation, but in no instance exceeded a total of 40 mg of elemental zinc per day. Bottles of liquid zinc acetate were labelled with the patient's name, the name and telephone numbers of Dr. L. Fleischmann and

Dorothy Hagan, the concentration of the solution (5.6 gm/100 ml), the amount delivered per ml (20 mg elemental zinc per ml), the prescribed prescription for the subject, administering instructions (Take ____ml daily, 1 hr. before breakfast) and the current date. Participants and/or caretakers were verbally instructed and shown how to measure the zinc acetate liquid using an oral syringe (Baxa, Denver, Co) with adaptor. The prescribed dosage level was marked on the syringe for the convenience of the subject or caretaker.

Zinc supplementation was started after collecting one year of baseline data on all except 2 subjects. At least 3 months of data were collected on these 2 exceptions. The subjects were maintained on zinc supplementation for one year (April, 1984 to April, 1985).

K. Statistical Procedures

Statistical procedures used to evaluate the data included calculations of means, standard deviations, Z-scores, correlation coefficient, and the student t test (Snedecor and Cochran, 1968). Ages for the study population were converted to decimal age (Buckler, 1979) to simplify mathematical manipulation of data.

Growth was evaluated using a variety of procedures. A

correlation coefficient between height and decimal age was determined for each subject both before and after zinc acetate supplementation. The student t test was then used to determine the level of significance. Mean and standard deviations were calculated on growth velocity (cm/yr) data for male and female subjects. Growth was further evaluated as height per age and weight per age. Calculations of Z-scores were made to show change between the beginning of the study, the initiation of zinc supplementation, and the end of the study. Correlation coefficients for each subject were calculated between the height per age, weight per age, and weight per height both before and after zinc acetate supplementation. The student t test was again used to determine if the correlation coefficients were significant. Percent medians and Z-scores were calculated on AMC, and TSF, MAC, respectively, using HANES I data (Johnson et al, 1981; Johnston et al, 1974) as the standard. Bone maturation was compared to HANES I standards (Roche et al, 1974; Roche et al, 1976) and Z-scores determined. The deviation from the predicted adult height for each subject was evaluated using a Z-score.

Mean and standard deviations were calculated for each subject for all biochemical parameters both before and after zinc acetate supplementation. Statistical significance between the pre- and post-supplemented values was determined.



Mean and standard deviations were calculated for each subject for dietary intakes both before and after zinc acetate supplementation. Using HANES I and II data for age and sex (Abraham et al. 1979; Carroll et al. 1983), these dietary intake data were then evaluated using Z-scores and percent median, respectively, for each subject. The student t test was used to test for significance between mean values on each subject.

IV. RESULTS

A. Introduction

Of the 26 participants in this investigation, 9 completed the study, 4 males and 5 females. Three additional male subjects completed the study, but refused the zinc supplement and could only be evaluated for the non-zinc supplemented phase of the study. Thus a total of 12 subjects 7 males and 5 females, were followed before zinc acetate supplementation and 4 males and 5 females after supplementation. The remaining subjects were lost to the study for the following reasons: 7 transplant, 2 death, 2 moved from the area or transferred to another health facility, 2 withdrew, and 1 could not be followed (Table 3).

The primary diagnosis and daily urine output for each participant are listed in Table 5. Six of the 12 participants were anephric, 4 produced 0-50 cc of urine per day, and the remaining 3 had urine outputs of less than 1000 cc per day.

The initial heights and weights of the 12 subjects who completed the study are shown in Table 6. Ages of the subjects were quite varied. Male ages ranged from 5.7 to 15.5 decimal years at the initiation of the study. For the 5

females the decimal age range was 5.2 to 19.6 years.

The prediction of adult height based on two methods, midparent stature and the method of Bayley and Pinneau (1952), are presented in Table 7. Predictions are given for children completing the study and are based on height measurements obtained at the end of the study period. Z-scores calculated from the predicted adult height and HANES I (Johnson et al. 1981; Johnston et al. 1974) mean adult height show all subjects will be below the mean adult height. Predicted height for 2 older subjects, nos. 14 and 26, were less than 1 standard deviation below the adult mean height of 25 year olds and 5 other subjects (nos. 17, 15, 18, 19, 24) varied from the adult mean by more than 1 standard deviation. Predicted heights for 2 subjects, nos. 10 and 9 varied from the adult mean by more than 2 standard deviations. Based on final height measurements, the height the child should have achieved per chronological age to ultimately reach the midparent height (Garn and Rohmann, 1966) are listed in Column 6, Table 7.

B. Growth Measurements

Growth velocity calculations expressed in centimeters per year (cm/yr) for each subject when non-zinc supplemented and zinc supplemented are shown in Tables 8 and 9. Subjects

numbered 10, 1, 18, and 23 were followed for less than the research design of one year pre- and post-supplementation. Data on these four subjects were extrapolated to one year to present comparable results.

There were no significant differences between the zinc supplemented and non-zinc supplemented males or females in growth velocity (Figure 1). Male subject no. 17 and female subject no. 24 demonstrated increased growth velocity, while male subjects no. 10, 15 and female subjects no. 19, 23, and 26 showed a decrease in growth velocity post- versus pre-zinc supplementation. Patients no. 18, and 5 remained at essentially the same growth velocity level with or without zinc supplementation. Significant individual correlation coefficients were found between decimal age and height in 8 of 12 subjects (nos. 5, 17, 15, 1, 14, 18, 19, 23), in the non-zinc supplemented period and only 3 of 9 subjects (nos. 5, 17, and 24), in the zinc supplemented group.

Height per age, expressed as Z-scores for the 12 subjects, is shown in Table 10. Results show that this population varied from the mean for their age and sex by 2 to over 6 standard deviations, regardless of zinc supplementation. Only two subjects (nos. 18, 26) demonstrated deviations less than 2 from the mean for height for their age and sex. Five subjects moved closer to the mean with zinc supplementation, 5 moved farther from the mean

with zinc supplementation, and 2 remained essentially at the same distance from the mean for their age and sex.

Weight per age for both male and female subjects is shown in Table 10 as Z-scores. Distance from the mean weights of the American population show all subjects, except subject no. 18, were below the mean for their age group and sex. Individual data show equal movement of the number of subjects to and from the mean pre- versus post-zinc supplementation.

Weight for height comparisons are an indicator of malnutrition. Scharer and Gilli (1984) recommend standard deviation score comparisons for height and weight be used so that height, weight, and age can be included in the evaluation. However, reference data were not available to calculate weight per height Z-scores. Therefore, a comparison of the Z-scores for height per age and weight per age is presented together in Table 10. In most subjects, the Z-score for weight is approximately half the Z-score for height. This indicates that weight was closer to the mean of the American population than was height, and that the weight per height was adequate.

Significant correlation coefficients for height per age, weight per age, and weight per height, based on individual patient data, are presented in Table 11. Nineteen significant correlations were found prior to zinc supplementation while only 6 were found after zinc

supplementation. Height per age was significant for subjects no. 5, 17, 15, 1, 14, 18, 19, and 23 before zinc supplementation, and only subjects no. 5, 17, and 24 after supplementation. Significant correlation coefficients for weight per age, were found for patients 5, 17, 18, 23, 24, and 26 prior to zinc supplementation, and subjects no. 5, 17, and 24 after zinc supplementation. A significant correlation coefficient for weight per height was found for subjects no. 5, 17, 15, 18, and 23 in the non-zinc supplemented group and only subject no. 5 in the zinc supplemented group.

Weight per height, when standards were available for calculation, are presented as percent median in Table 12. All subjects for whom reference data were available demonstrated adequate weight for their height. Missing calculations indicate that the height per age value per subject was below the available HANES I reference standards for height-weight-age tables.

C. Anthropometric Measurements

Mid-arm circumference, TSF, and AMC data for each subject are presented in Appendix B. Arm muscle circumference is presented as percent median while MAC and TSF are calculated as Z-scores (Table 13). These data indicate AMC values close to the median for age and sex while

MAC and TSF values show a negative deviation from the mean in all but 2 cases during both period I (before zinc supplementation) and period II (after zinc supplementation of 9 of 12 subjects). However, the TSF hovered around the mean in all cases except 3 subjects in period I, and 3 subjects in period II. Only 1 of these 3 subjects (no.24) in period II received zinc supplement and showed a negative standard deviation of 1.04. Subject no. 14 who did not receive zinc supplement had a higher negative standard deviation of 1.33 while the other zinc supplemented subject (no. 18) showed a positive standard deviation of 1.98. MAC varied from the mean by more than 1 standard deviation in 7 cases in period I and 7 cases in period II. Zinc supplemented subjects nos. 5, 10, 17, 18, and 24 moved closer to the mean for MAC while subjects nos. 5, 18, 19, and 23 showed a more positive TSF, period I versus period II. This positive movement in 4 subjects (nos. 5, 18, 19, 23) for TSF may indicate an increase in fat stores when zinc supplemented, but is countered by the fact that 2 of 3 non-zinc supplemented children also showed improved Z-scores during period II. In 7 out of 9 children supplemented with zinc, there was an increase in the percent median for AMC, while 1 of 3 non-zinc supplemented subjects improved his percent median for AMC.

D. Chronological Age and Bone Age Comparisons

The chronological decimal age at the time radiographs of the hand and wrist were taken for males and females and bone age readings are presented in Tables 14 and 15. Bone age percentage of chronological age and Z-scores are given for male and female subjects at the beginning of the study, at the initiation of supplementation and at the end of the zinc supplemented period.

The bone age of the 7 male subjects, prior to zinc supplementation ranged from 0.2 - 5.3 years less than the chronological age or from 40 - 95% of chronological age. For the child 4.2 decimal years, the age was only 0.2 years behind. This subject, no.1, was the youngest subject and was 95 percent of chronological age.

In 3 of the 4 male and 2 of the 3 female subjects (nos. 5, 17, 15, 18, 9), who were zinc supplemented and for whom data were available, there was a positive change in the percent median with zinc acetate supplementation. One of the 3 non-supplemented male subjects also showed a positive change in percent median during similar time periods, while one subject remained unchanged and one showed a negative change. Similar changes were seen in the Z-score calculations. Three of the 4 male subjects (nos. 5, 10, 15)

and 1 of the female subjects (no.18) showed a positive movement toward the mean with zinc supplementation. However, 2 non-zinc supplemented male subjects (nos. 9, 14) also showed positive movement toward the mean and 2 supplemented female subjects (nos. 19, 24) showed negative movement from the mean. The change in percent median and Z-score evaluations were not always in the same direction for each subject as is shown in subject no. 17. Subject no. 26 was excluded from evaluation because she had already reached maturity. Change in chronological age and bone age for each subject is graphically represented in Figure 2.

A comparison of the slopes for growth velocity and bone maturation are presented in Table 16. These calculations show an increase in the slope in growth velocity (GV) in only 2 subjects (no. 17, 24) with zinc acetate supplementation, but an increase in bone maturation (BM) in 4 of the 6 zinc supplemented subjects (nos. 5, 17, 15, 19) for whom data were available

E. Tanner Staging

Tanner sexual maturity scores for male subjects per chronological decimal age and the percent of normal are presented in Table 17. Identical information is given for females in Table 18. All subjects remained at their same

level of sexual maturity regardless of zinc supplementation although the percentile of the reference population changed in some cases. Subject 5 appeared to be advanced for his age, while male subjects 9 and 14 appeared to have a delay in sexual maturity for their age. Female patients maintained their same level of sexual maturity for decimal age. A dash in Table 17 indicates that the sexual maturity rating per age fell outside the parameters of the reference data. Consequently, a percentile comparison could not be noted.

F. Biochemical Measurements

The normal range of blood chemistry values used at Children's Hospital of Michigan are presented in Table 1. Individual mean chemistries for male and female subjects are presented in a series of Tables (19-29). As would be expected in children with ESRD, mean blood urea nitrogen (BUN) and serum creatinine concentration (Table 19) were above the normal range for each subject. However, the range of values for BUN and serum creatinine appeared to increase in males during the zinc supplemented period (period II). In females, the range for BUN seemed to decrease during the supplemented period, while serum creatinine values also appeared to rise. Mean total CO_2 (Table 20), which is an indicator of acidosis, was maintained within the normal range



in all cases except subjects no. 15 and 26. Both patients 15 and 26 were being treated for their ESRD using HD. The low mean CO_2 values occurred during the zinc supplemented period. Alkaline phosphatase (Table 20) values were consistently above the normal range in most subjects both pre- and post-supplementation. The exceptions were subjects no. 18, 23, 10 in whom normal values occurred both pre- and post-zinc supplementation, and in subjects no. 14 and 26 pre-supplementation and subject no. 19 post-supplementation. Therefore, of the 12 subjects studied, 5 males and 2 females had high mean alkaline phosphatase values when not supplemented with zinc and, of the 9 zinc supplemented subjects, 3 males and 2 females had high mean alkaline phosphatase values. However, with zinc acetate supplementation, mean alkaline phosphatase values increased in 3 out of 4 male subjects and 4 out of 5 female subjects.

Since alkaline phosphatase is a zinc dependent enzyme, correlation coefficients were calculated between alkaline phosphatase and plasma zinc levels (Table 21). Limited number of values were available for testing of significance. However, one male and one female subject were found to have significant correlations between their plasma zinc values and their alkaline phosphatase levels when non-zinc supplemented.

Mean serum sodium and chloride levels were maintained within the normal range for all subjects when supplemented

and when non-supplemented with zinc (Table 22). Mean serum calcium and magnesium values hovered around the normal range, while mean serum phosphorus levels were high in 5 out of 7 males, 2 out of 5 females pre-supplementation and 3 out of 4 males, 4 out of 5 females post-supplementation (Tables 23 and 24). Although mean serum calcium values were in the normal range, mean serum calcium values increased in 5 out of 9 subjects and remained the same in 2 subjects when zinc supplemented. Mean serum phosphorus levels usually show an inverse relationship with calcium, but this was only true for half (4/9) of the zinc supplemented subjects. High mean serum magnesium levels were noted in subjects' no. 1, 19, 26. These high magnesium levels may have been due to recent blood transfusions. High mean serum potassium values were found in 1 male and 2 female subjects before zinc supplementation, and 2 different male, but the same two female subjects after supplementation with zinc.

Mean hemoglobin and hematocrit values were below the normal range for children in all cases (Table 25). Total serum protein mean values were within the normal range for all subjects except no. 17 (Table 26). Mean albumin levels, however, were below the normal range in all cases except subject nos. 10 and 15 post-supplementation and subject nos. 19 and 26, both pre and post-supplementation (Table 26).

Plasma zinc and copper and erythrocyte zinc levels are presented as mean values for male subjects (Table 27), female subjects (Table 28), and as a composite of all subjects (Table 29) both before and after zinc supplementation. Significant differences between the zinc supplemented and the non-zinc supplemented mean plasma values were not found. Comparisons of individual mean plasma zinc values and group mean values with a normal level of 120 ± 10 mcg/dl [1] indicate that all except one male subject had low zinc levels before supplementation and all subjects had low zinc levels after zinc supplementation. The situation is similar in the female population with only two subjects, nos. 18 and 19, showing adequate mean plasma zinc levels pre-supplementation and one subject, no. 19, within the normal range post-supplementation. Erythrocyte zinc was measured in a small number of samples. Compared to a normal adult value of 45-47 mcg/dl/gm hemoglobin/ml [1], the RBC zinc was low both before and after zinc acetate supplementation. Mean plasma copper values, however, did not change in an inverse relationship to mean plasma zinc levels. Male subject no. 5 had an elevated mean plasma copper level, and male subject no. 14 presented slightly depressed mean plasma copper. Likewise, female subject no. 19 had elevated mean plasma copper levels both before and after zinc supplementation, and subject no. 23

presented a mean plasma copper level slightly above the normal range of 130 - 200 mcg/dl [1].

Blood values for BUN, serum creatinine calcium, phosphorus, sodium, potassium, magnesium, hemoglobin, hematocrit, alkaline phosphatase, CO_2 , zinc and copper were typical of children with ESRD.

G. Dietary Measurements

The evaluation of individual subject dietary intake data, as shown in Appendix B, demonstrates a significant change in sodium ($P < 0.05$), and magnesium, zinc, and iron intakes ($p < 0.01$) between the zinc supplemented and non-supplemented periods for male subject no. 5 and for sodium ($p < 0.01$) in male subject no. 15. Female subject no. 18 showed a significant, pre- versus post-zinc supplement, increase in sodium ($p < 0.05$), and subject no. 23 a significant decrease in calcium ($p < 0.05$), and phosphorus ($p < 0.01$) in the non zinc supplemented versus the zinc supplemented period.

Percent medians, using HANES II reference data for age and sex, are given in Tables 30 and 31, for kilocalories, Protein, calcium, iron, sodium, and potassium for males and females, respectively. HANES II reference data rather than

the RDA's were used to evaluate individual mean dietary intake data because HANES II data are representative of intakes of the American population. Approximately three quarters of the subjects had dietary intakes that were 67% or greater of the reference median intake for energy and protein before zinc supplementation and 78 percent and 89 percent, respectively, after zinc supplementation. Fifty percent of the subjects had calcium and iron dietary intakes which met 67 percent the reference median intake when non-zinc supplemented, while there was no change with supplementation for calcium, but an increase to 78 percent of the subjects meeting the 67 percent guideline for iron.

HANES I reference standards (Abraham et al. 1979) for the United States population were used to calculate Z-scores for kilocalories, protein, calcium, and iron for each subject. HANES I was used to evaluate dietary intakes not only because it is representative of the American population, but also because it provides standard deviations data from which Z-scores can be calculated. Z-scores for individual subjects and nutrients are presented in Table 32. Results indicate adequate dietary intakes of these four nutrients in all cases. However, subject no. 5 demonstrated a negative variation from the mean by more than 1 standard deviation for kilocalories, protein, and iron when non-zinc supplemented and protein during zinc supplementation. Likewise, subject

no. 10 varied from the mean by 1 standard deviation for kilocalories and calcium regardless of zinc supplementation status and male subject no. 15 had a Z-score of -1.01 for calcium when zinc supplemented. Only female subject no. 23 showed a negative standard deviation of greater than 1 for calcium while zinc supplemented.

Dietary intake records show Z-scores that are less than 2 standard deviations from the mean for all subjects for kilocalories, protein, calcium, iron. A comparison of the dietary intake for each subject for energy and protein with the recommendations of Holliday et al. (1979) and Wassner (1982), for children with CRF are presented in Table 33. During the non-zinc supplemented period, fifty percent of the subjects (6 out of 12) had energy intakes meeting at least 67 percent of their respective RDA for kilocalories, while 92 percent (11 out of 12) of the study population exceeded 67 percent of their RDA for protein. The percentage of the study population meeting 67 percent of the RDA's increased to 67 percent (6 out of 9) for energy and 100 percent for protein with zinc acetate supplementation. However, subject no. 14 who had low protein intakes in the non-supplemented period was not included in the study period after zinc supplementation so protein intake was similar before and after zinc supplementation. Dietary zinc intake was at 67 percent of the RDA in 42 percent (5 out of 12) of the study



population before zinc supplementation and increased to 67 percent (6 out of 9) of the subjects during the zinc supplemented period.

H. Growth Evaluation

The onset of puberty can effect growth velocity. Decimal ages shown in Tables 8 and 9, indicate that 5 of 7 males in this study were older than 9 and therefore possibly in their adolescent growth spurt during one or both phases of the study. Subject No. 5, aged 7-9 during the study, maintained his same growth velocity regardless of zinc acetate supplementation. Subject 17, aged 9-11 during the two years of the study, increased his growth velocity from 1.6 cm/yr when non-zinc supplemented to 4.1 cm/yr while zinc acetate supplemented. The growth velocity of subject no. 10, aged 10-11 years throughout the study, decreased. However, Tanner staging and bone maturation remained at essentially the same level of maturity. Subject no. 15, aged 12-14 years throughout the study, demonstrated a decrease in growth velocity during the second year. Radiographs of the hand and wrist show an increase of 1.5 years in bone age in 0.8 chronological years during the first year before zinc supplement was given.

For females, the data are similar. Four out of 5

subjects were greater than 7 years of age and therefore their growth velocity could possibly be affected by the pubertal growth spurt. Subjects no. 18 and 19, aged 14-15 and 14-16, respectively, during the study, maintained their growth velocity. The physical examination records revealed that subject no. 24, aged 11-13 during the study, began menstruation at the age of 12. This subject also grew 6.1 cm during the second year compared to 2.8 cm the first year of the study. Female subjects no. 23 and 26, aged respectively 5 to 7 and 19 to 21 years, demonstrated decreased growth velocity with zinc supplementation. Bone maturation data on subject no. 26 shows a bone maturation of 17 at the initiation of the study.

All subjects, except subject no. 26, were well below the mean height for their age as compared to the normal American population. The age of onset of ESRD, the duration of the time the children had been treated for ESRD calculated from the time dialysis was initiated through the end of the study period and the Z-scores for height at the end of the study are given in Table 34. The two children who have the greatest negative standard deviations from the mean for height (subjects no. 5 and 17) are also the two subjects who developed ESRD at a young age and had been under treatment for their renal failure for a number of years.

Comparisons of bone age to the age of onset of ESRD

and the duration of dialysis treatment show a similar relationship. Subjects no. 10, 1, and 18 were recent entries into the dialysis program at Children's Hospital of Michigan. Their bone ages were 2.2, 0.2, 1.4 years, respectively, below chronological age before zinc supplementation, and 2.4, 1.0, and 0.6 years, respectively, below chronological age after zinc acetate supplementation. In contrast, subjects no. 5, 17, and 19, who were longer term patients, presented bone ages 5.2, 5.4, 6.5 years, respectively, below chronological age before zinc supplementation, and 5.2, 5.3, 5.4 years, respectively, after zinc supplementation.

Table 1. Normal Ranges of Blood Chemistries for
Children at Children's Hospital of Michigan

Constituent	Range	Units
Blood Urea Nitrogen (BUN)	<20	mg/dl
Serum Creatinine	0.4-1.3	mg/dl
Total Protein	5.1-8.6	gm/dl
Albumin	3.8-5.4	gm/dl
Globulin	1.28-3.16	gm/dl
Alkaline Phosphatase	60-230	IU/L
Ferritin	10-300	ng/ml
Hemoglobin (Hb)	11.6-15.1	gm/dl
Hematocrit (Hct)	34.2-44.6	%
Cholesterol	80-180	mg/dl
Triglycerides	47-155	mg/dl
Sodium (Na)	134-142	mEq/L
Potassium (K)	3.5-5.0	mEq/L
Chloride (Cl)	90-110	mEq/L
Calcium (Ca)	9.0-11.0	mg/dl
Phosphorous (P)	3.4-5.4	mg/dl
Magnesium (Mg)	1.6-2.7	mg/dl
Glucose	60-100	mg/dl
Carbon Dioxide (CO ₂)	20.0-29.0	mmol/L

Table 2. Common Medications Used in Treatment of ESRD
at Children's Hospital of Michigan

Medication	Purpose*
Poly-Vi-Sol	Multivitamin preparation used to replace vitamins removed by the dialysis process
Folic Acid	A vitamin that is necessary for blood formation which is removed in the dialysis process
Dialume (Aluminum Hydroxide)	Phosphate binder designed to decrease the blood phosphorus level
Amphojel (Aluminum Hydroxide)	Phosphate binder designed to decrease the blood phosphorus level
Rocaltrol	Active form of vitamin D ₃ used to replace this kidney function
Tums (Calcium Carbonate)	Replacement calcium required to maintain normal blood calcium levels and counteract bone calcium losses
Phenobarbitol	Medication designed to prevent seizures
Aldomet	Antihypertensive
Apresoline	Antihypertensive

* From Physician's Desk Reference



Table 3. CHARACTERISTICS OF STUDY POPULATION

Subject No.	Sex	Ethnic Origin	Dialysis Method ¹	Study Disposition
(1) ²	M	Asian	CAPD	No Zn-completed 6 mo.
2	M	White	HD	Transplant
3	M	White	HD	Transplant
4	M	Black	HD	Transplant
<u>5</u> ³	M	Black	IPD/CAPD	Completed study
6	M	Black	HD	Death
7	M	White	IPD	Moved from area
8	M	Black	HD	Transferred
(9)	M	White	HD/CAPD	No Zn-completed study
<u>10</u>	M	White	HD/CAPD	Completed 5 mo.
<u>11</u>	M	White	IPD	Unable to follow
12	M	Black	HD	Withdrew
13	M	Black	HD	Transplant
(14)	M	White	HD/CAPD	No Zn-completed study
<u>15</u>	M	Black	HD	Completed study
<u>16</u>	M	White	HD/CAPD	Withdrew
<u>17</u>	M	White	HD	Completed study
<u>18</u>	F	White	CAPD	Completed 6 mo.
<u>19</u>	F	Black	HD/CAPD	Completed study
20	F	White	CAPD	Transplant
21	F	Black	HD	Transplant
22	F	White	HD	Transplant
<u>23</u>	F	Black	IPD/CAPD/Completed study IPD	
<u>24</u>	F	White	HD/CAPD	Completed study
25	F	White	IPD	Death
<u>26</u>	F	Black	HD	Completed study

1. HD - Hemodialysis

CAPD - Continuous Peritoneal Dialysis

IPD - Intermittant Peritoneal Dialysis

2. Subjects in parenthesis completed the study but were not supplemented with zinc

3. Subjects underlined in the first column completed the study



Table 4. Composition of Dialysate Solutions Used
at Children's Hospital of Michigan*

Chemical	Eri-lyte 8306 Solvent	Dianial PD-2 Solvent
Sodium (mEq/L)	134	132
Calcium (mEq/L)	2.5	3.5
Magnesium (mEq/L)	1.5	0.5
Chloride (mEq/L)	101	96
Acetate (mEq/L)	37.0	Lactate 40
Dextrose (gm/L)	2.5	45

* Manufacturers' data

Table 5. Disease Characteristics of Participants

Subject No.	Primary Diagnosis	Daily Urine Output

Males, Zinc Supplemented		

5	Hypoplastic dysplastic kidneys	500-700 cc
10	Henoch Schoelin Purpura	< 50 cc
17	Focal Segmented Glomerulonephritis	Anephric
15	Chronic Sclerosing Glomerulonephritis	0 cc
Males, Non-Zinc Supplemented		

1	Focal Sclerosing Nephrotic Syndrome	300-700 cc
9	Obstructive Uropathy Secondary to Posterior Urethral Valves at Birth	Anephric
14	Acute Glomerulonephritis	Anephric
Females, Zinc Supplemented		

18	Chronic Pylonephritis	1000 cc
19	Focal Segmented Glomerulonephritis	0 cc
23	Focal Segmented Glomerulonephritis	< 50 cc
24	Hypoplastic Kidneys	Anephric
26	Membranoproliferative Glomerulo- nephritis	Anephric

Table 6. Ages, Heights and Weights of
Subjects at Initiation of Study*

Subject No.	Decimal Age(yrs)	Height (cm)	Weight (kg)

Males, Zinc Supplemented			

5	7.6	90.0	12.0
10	10.7	126.0	27.8
17	9.3	109.5	17.7
15	12.1	129.5	32.2
Males, Non-zinc Supplemented			

1	5.7	100.0	16.8
9	13.6	131.4	32.6
14	15.5	149.0	38.1
Females, Zinc Supplemented			

18	14.8	149.0	49.7
19	14.3	135.0	29.1
23	5.2	96.0	14.2
24	11.8	127.0	20.5
26	19.6	154.9	57.6

* Subjects started at various times for different time periods.

Table 7. Prediction of Adult Height By Various Methods for Male and Female Subjects

Subj. No.	CA ^a (yr)	BA ^b (yr)	HT (in)	Midparent Stature (in)	PMH ^c Garn Rohmann (in)	PMH ^d Bayley & Pinneau (in)	Z-score ^e
Males							
5	9.6	4.5	40	67.5	53.9	-	-
10	11.4	9.0	50	64.3	54.5	63.6	-2.35
17	11.3	6.0	45	65.0	56.7	66.2	-1.41
15	13.9	11.0	54	-	-	65.6	-1.63
1	6.6	4.5	41	44.7	59.0	-	-
9	14.6	10.0	53	68.5	67.0	65.3	-2.18
14	16.6	12.0	59	66.0	69.0	69.8	-0.10
Females							
18	15.6	15.0	60	65.0	64.0	60.6	-1.48
19	16.4	11.0	56	-	-	61.0	-1.31
23	6.4	4.2	40	68.5	66.0	-	-
24	13.7	10.0	53	66.8	62.5	60.6	-1.48
26	20.9	17.0	62	-	-	62.0	-0.87

a CA-Chronological Age

b BA-Bone Age

c PMH-Predicted Mature Height, Garn and Rohmann, 1966

d PMH-Predicted Mature Height, Bayley and Pinneau, 1952

e Denotes predicted standard deviation from mean adult height based on Bayley and Pinneau method

Table 8. Growth Velocity - Males

Subject No.	Age yrs	Non-Zinc cm/yr	Supplemented r^*	slope	Zinc cm/yr	Supplemented r^*	slope
5	7	5.9	0.98 ^b	5.32	5.7	0.95 ^b	5.17
10 ^a	10	3.9	0.70	3.17	1.4	0.11	0.53
17	9	1.6	0.70 ^c	2.04	4.1	0.76 ^c	2.67
15	12	6.6	0.89 ^b	5.55	0.7	-0.03	-0.09
1	5	5.3	0.48 ^d	0.55	-	-	-
9	13	3.8	0.05	0.35	-	-	-
14	15	1.4	0.60 ^d	2.24	-	-	-
Mean		4.07		2.75	2.98		2.31
SD		2.02		2.08	2.33		1.88

* Correlation between height and decimal age

a 5 months growth extrapolated to 1 yr.

b Statistical significance $P < 0.01$

c Statistical significance $P < 0.02$

d Statistical significance $P < 0.05$

Table 9. Growth Velocity - Females

Subject No.	Age yrs	Non-Zinc Supplemented			Zinc Supplemented		
		cm/yr	r*	slope	cm/yr	r*	slope
18	14	4.5	0.92 ^b	3.81	4.4	0.27	2.75
19	14	3.8	0.88 ^b	3.29	2.4	-0.15	0.55
23	5	4.6	0.94 ^b	5.12	3.0	0.59	1.91
24	11	2.8	0.50	3.88	6.1	0.70 ^c	6.11
26	19	3.7	0.76	3.47	0.5	0.43	2.05
Mean		3.88		3.91	3.28		2.67
SD		0.73		0.72	2.10		2.07

* Correlation between height and decimal age

a 6 month growth data extrapolated to 1 yr

b Statistical significance $P < 0.01$

c Statistical significance $P < 0.02$

d 13 months growth post-supplementation reduced to 1 year

Table 10. Height per Age, Weight per Age^a of Male and Female Subjects Expressed as Z-scores (Z)

Subject No.	Beginning of Study		Crossover Point		End of Study	
	Ht/Age Z	Wt/Age Z	Ht/Age Z	Wt/Age Z	Ht/Age Z	Wt/Age Z
Males						
5	-6.63	-3.11	-6.68	-3.47	-6.05	-1.92
10	-2.30	-0.93	-2.60	-1.25	-2.68	-1.38
17	-4.59	-2.03	-4.41	-1.82	-4.56	-2.03
15	-2.64	-0.85	-3.00	-1.05	-2.39	-1.61
1 ^b	-	-	-3.02	-1.16	-2.13	-0.85
9 ^b	-	-	-3.26	-1.82	-4.32	-2.28
14 ^b	-	-	-3.13	-2.04	-3.32	-2.78
Females						
18	-1.74	+0.55	-2.06	+0.17	-1.84	+0.25
19	-4.11	-2.24	-4.00	-2.24	-3.08	-1.83
23	-2.43	-1.62	-2.80	-1.04	-3.40	-1.97
24	-3.11	-2.22	-3.98	-2.19	-4.50	-2.07
26	-1.42	-0.19	-0.80	-0.81	-0.65	-0.68

^a Reference standards from HANES I (Hamill et al. 1977; Hamill et al. 1973)

^b No zinc supplement

Table 11. Correlation Coefficients for Height per Age, Weight per Age, and Weight per Height for Male and Female Subjects

Subject No.	r values					
	Non-Zinc Supplemented			Zinc Supplemented		
	Ht/Age	Wt/Age	Wt/Ht	Ht/Age	Wt/Age	Wt/Ht
Males						
5	0.98 ^a	0.93 ^a	0.60 ^c	0.95 ^a	0.95 ^a	0.95
10	0.70	-1.00	-1.00	0.11	-0.29 ^c	-0.52
17	0.70 ^b	0.92 ^a	0.63 ^c	0.76 ^b	0.73	0.78
15	0.89 ^a	0.69	0.89 ^b	-0.03	0.36	0.16
1	0.48 ^c	0.73	0.52	-	-	-
9	0.05	-0.23	0.19	-	-	-
14	0.60 ^c	-0.37	-0.26	-	-	-
Females						
18	0.92 ^a	0.94 ^a	0.79 ^c	0.27	0.39	-0.03
19	0.88 ^a	0.23	0.60	-0.15	0.58	-0.09
23	0.94 ^a	0.90 ^a	0.76 ^c	0.59	0.35	-0.41
24	0.50	0.87 ^b	0.27	0.70 ^b	0.77 ^a	0.34
26	0.76	-0.88 ^a	-0.64	0.43	0.60	0.68

a Statistical Significance $P < 0.01$

b Statistical Significance $P < 0.02$

c Statistical Significance $P < 0.05$

Table 12. Weight per Height of Male and Female
Subjects Expressed as % Median*

Subject No.	Beginning of Study	Crossover Point	End of Study
5	-	-	-
10	109	108	108
17	098	104	113
15	-	108	113
1	-	-	-
9	-	-	-
18	117	132	134
19	-	-	-
23	-	-	-
24	-	-	-
26	-	-	-

*Reference standards from HANES I (Hamill et al. 1973).
Missing calculations indicate that individual data was
outside the range of reference standards.



Table 13. Arm Muscle Circumference (AMC) Expressed as Percent Median, Mid-Arm Circumference (MAC), and Triceps Fatfold (TSF) Expressed as Z-scores (Z) for Male and Female Subjects^a

Subject No.	Period I			Period II		
	MAC	AMC	TSF	MAC	AMC	TSF
	---	---	---	---	---	---
	Z	% med.	Z	Z	% med.	Z
Males						
5	-1.93	96	-1.04	-0.65	106	-0.84
10	-0.70	92	+0.23	-0.58	101	-0.43
17	-1.83	84	-0.73	-1.58	85	-0.81
15	-0.42	105	-0.23	-0.79	106	-0.60
1 ^b	-1.57	88	-0.39	-0.20	97	+0.71
9 ^b	-1.48	94	-0.69	-1.43	91	-0.63
14 ^b	-1.59	88	-0.53	-2.82	80	-1.33
Females						
18	+1.53	126	+0.92	+1.21	109	+1.98
19	-0.92	87	-2.39	-1.33	92	-0.75
23	-0.71	106	-1.02	-1.21	98	-0.95
24	-1.67	92	-0.95	-1.42	94	-1.04
26	-	103	-	-	114	-

^a Reference standards HANES I (Johnson et al. 1981; Johnston et al. 1974)

^b No zinc supplement



Table 14. Chronological Age (CA) and Bone Age (BA) for Male Subjects^a

Subj.	Non-Zinc Supplemented					Crossover Point ^b					Zinc Supplemented				
	CA yrs	BA yrs	SD mo	%CA	Z-score	CA yrs	BA yrs	SD mo	%CA	Z-score	CA yrs	BA yrs	SD mo	%CA	Z-score
Males - Zinc															
5	6.9	2.5	5.8	36	-4.05	8.7	3.5	7.0	40	-5.36	9.7	4.5	8.4	46	-5.63
10	-	-	-	-	-	10.7	8.5	11.9	79	-1.35	11.4	9.0	11.3	79	-1.27
17	9.1	5.0	9.0	55	-3.80	10.4	5.0	9.0	48	-4.15	11.3	6.0	9.8	53	-4.59
15	11.2	8.0	11.2	71	-1.69	13.2	9.5	11.0	72	-2.40	14.0	11.0	10.5	79	-2.92
Males - No Zinc															
1	4.2	4.0	7.5	-	-	4.2	4.0	7.5	95	-	5.2	4.5	8.4	82	-
9	12.0	7.0	10.5	58	-6.40	13.8	8.5	11.9	62	-3.31	14.7	10.0	11.6	68	-4.34
14	14.6	11.5	11.0	78	-2.03	15.8	11.5	11.0	73	-4.08	16.5	12.0	10.4	73	-4.38

^a Reference standards from HANES I (Roche et al. 1974; Roche et al. 1976)^b Beginning of zinc supplementation^c Standard Deviation of Bone Age (Greulich and Pyle, 1959)

Table 15. Chronological Age (CA) and Bone Age (BA) for Female Subjects^a

Subj.	Non-Zinc Supplemented					Crossover Point ^b					Zinc Supplemented				
	CA yrs	BA yrs	SD ^c mo	%CA	Z- score	CA yrs	BA yrs	SD mo	%CA	Z- score	CA yrs	BA yrs	SD mo	%CA	Z- score
18	-	-	-	-	-	14.9	13.5	14.8	91	-0.86	15.6	15.0	13.2	96	+0.60
19	14.0	8.0	9.0	57	-8.61	15.5	9.0	9.5	58	-9.22	16.4	11.0	12.3	67	-6.44
23	-	-	-	-	-	6.4	4.2	7.8	66	-2.85	-	-	-	-	-
24	12.0	8.8	9.3	73	-1.26	12.8	10.0	10.9	78	-1.57	13.7	10.0	10.9	73	-3.46
26	19.2	17.0	-	-	-	20.9	17.0	-	-	-	-	-	-	-	-

^a Reference standards from HANES I (Roche et al. 1974; Roche et al. 1976)

^b Beginning of zinc supplementation

^c Standard Deviation of Bone Age (Greulich and Pyle, 1959)

Table 16. Comparison of Slope for Growth Velocity (GV) and Bone Maturation (BM) for Male and Female Subjects

Subject No.	Slope			
	Non-Zinc Supplemented		Zinc Supplemented	
	GV	BM	GV	BM

Males				

5	5.32	0.56	5.17	1.00
10	3.17	-	0.53	0.71
17	2.04	0.00	2.67	1.11
15	5.55	0.75	-0.09	1.88
Females				

18	3.81	-	2.75	2.14
19	3.29	0.67	0.55	2.22
23	5.12	-	1.91	-
24	3.88	1.50	6.11	0.00
26	3.47	0.00	2.05	-

Table 17. Sexual Maturity Ratings for Males
Expressed as Tanner Score and Centile

Subject No.	Non-Zinc Supplemented			Zinc Supplemented		
	Age yrs	Tanner Score	Tanner ^a Centile	Age yrs	Tanner Score	Tanner ^a Centile
5	9.2	I	-	9.6	I-II	97
10	10.8	I	-	11.4	I	-
17	10.2	I	-	11.2	I	-
15	11.7	II-III	90	-	-	-
1 ^b	5.1	I	-	6.6	I	-
9 ^b	13.6	II	10-25	14.6	II	3
14 ^b	15.5	II	< 3	16.6	II	< 3

a Centile reference from Buckler, 1979. Missing data indicates that readings were not taken.

b No zinc supplement

Table 18. Sexual Maturity Ratings for Females
Expressed as Tanner Score and Centile

Subject No.	Non-Zinc Supplemented			Zinc Supplemented		
	Age yrs	Tanner Score	Tanner Centile ^a	Age yrs	Tanner Score	Tanner Centile ^a
18 ^b	15.2	B5,P5 ^c	-	15.6	B4,P4	10
19	15.2	B2,P3	<3, 3	16.4	B2,P3	<3, <3
23	5.7	B2	>97	7.1	B2	>97
24	12.7	B1,P2	<3,50	13.7	B1/2,P2	-
26	20.6	B4,P5	<3	-	-	-

a Centile reference from Buckler, 1979. Missing data indicates that readings were not taken.

b Incorrect scoring on this subject

c B=breast, P=pubic hair

Table 19. Individual Means for BUN and Serum Creatinine
for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
	BUN mg/dl			Creatinine mg/dl			BUN mg/dl			Creatinine mg/dl		
No.	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	11	43	15.4	11	7.0	0.73	12	61	12.06	11	8.9	1.27
10	5	29	3.27	5	9.5	0.59	5	47	11.57	4	8.9	0.52
17	3	67	29.5	3	9.1	1.25	9	75	13.67	9	9.9	0.89
15	7	99	16.96	7	12.0	2.60	11	90	7.27	10	13.6	0.77
Males - No Zinc												
1	10	51	13.8	10	4.7	0.53	-	-	-	-	-	-
9	12	72	12.60	11	8.4	0.57	-	-	-	-	-	-
14	12	56	5.16	12	11.5	0.69	-	-	-	-	-	-
Females												
18	4	59	5.45	4	9.3	0.41	4	56	9.46	4	9.8	0.67
19	9	64	9.88	8	14.4	1.88	12	43	11.14	12	10.5	3.50
23	12	75	15.14	12	8.6	0.69	9	68	18.13	9	8.9	1.12
24	11	67	13.67	10	10.7	1.74	12	58	8.97	12	11.2	1.11
26	12	66	9.65	9	14.5	0.84	10	83	12.45	9	15.0	1.02

* N-number of observations; X-mean; SD-standard deviation

Table 20. Individual Means for Serum CO₂ and Alkaline Phosphatase (Alk Phos) for male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
No.	CO ₂ mmol/L			Alk Phos IU/L			CO ₂ mmol/L			Alk Phos IU/L		
	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	11	23.1	2.16	10	283	95	12	27.2	2.82	11	452	132
10	5	26.2	2.22	5	86	17	4	24.5	2.22	3	114	18
17	3	28.6	1.64	2	689	276	7	26.5	2.57	9	686	337
15	7	22.5	8.07	6	294	95	10	18.3	2.02	11	605	171
Males - No Zinc												
1	11	24.3	2.85	10	255	41	-	-	-	-	-	-
9	11	28.9	2.04	11	342	149	-	-	-	-	-	-
14	12	26.6	1.71	12	151	47	-	-	-	-	-	-
Females												
18	4	24.0	1.46	4	95	30	4	22.5	2.71	4	180	34
19	8	24.3	3.13	8	284	73	10	23.5	2.35	10	197	56
23	11	22.0	2.43	12	130	44	7	25.0	1.59	7	141	84
24	7	27.0	4.83	9	635	149	10	25.1	2.97	12	896	259
26	1	20.9	-	12	210	36	7	17.6	2.76	10	417	56

* N-number of observations; X-mean; SD-standard deviation

Table 21. Comparison of Alkaline Phosphatase (A/P) and Plasma Zinc Levels for Individual Male and Female Subjects

Subject	Non-Zinc Supplemented					Zinc Supplemented				
No.	N	A/P	Pl Zn	r*		N	A/P	Pl Zn	r	
		-----	-----				-----	-----		
		IU/L	mcg/dl				IU/L	mcg/dl		

Males										

5	-	283	127	-		6	452	111	-0.32	
10	3	86	91	-1.00		-	114	-	-	
17	1	689	93	-		3	686	71	0.38	
15	2	294	113	-1.00		5	605	108	0.09	
Males - No Zinc										

1	4	255	83	-0.94 ^a		-	-	-	-	
9	5	342	89	0.71		-	-	-	-	
14	8	151	98	-0.33		-	-	-	-	
Females										

18	3	95	126	0.92 ^b		3	180	105	-0.48	
19	1	284	112	-		4	197	151	-0.42	
23	1	130	78	-		5	141	86	0.26	
24	2	635	88	1.00		5	896	86	0.32	
26	1	210	83	-		7	397	94	0.30	

* r-correlation coefficients

a Statistical significance $P < 0.01$

b Statistical significance $P < 0.05$

Table 22. Individual Means for Serum Sodium and
Serum Chloride for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
No.	Sodium mEq/L			Chloride mEq/L			Sodium mEq/L			Chloride mEq/L		
	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	11	138	2.21	11	101	3.14	12	135	2.43	12	95	3.23
10	5	143	2.41	5	95	4.04	5	133	3.65	5	93	5.40
17	3	136	2.52	3	97	3.21	9	137	1.87	9	98	2.49
15	7	135	4.90	7	100	3.64	10	136	1.45	11	99	1.76
Males - No Zinc												
1	11	132	1.86	11	96	2.60	-	-	-	-	-	-
9	11	137	2.36	11	96	2.37	-	-	-	-	-	-
14	12	139	2.39	12	100	1.86	-	-	-	-	-	-
Females												
18	4	140	1.71	4	104	2.00	4	141	1.50	4	105	2.06
19	9	135	2.99	9	97	4.56	12	133	2.70	12	95	3.70
23	12	137	2.81	12	100	2.64	9	138	3.39	9	99	3.35
24	8	138	2.00	8	99	3.25	12	137	1.88	12	98	2.97
26	9	137	2.86	9	105	2.98	9	137	1.92	9	102	1.79

* N-number of observations; X-mean; SD-standard deviation

Table 23. Individual Means for Serum Calcium and
Serum Phosphorus for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
No.	Calcium mg/dl			Phosphorus mg/dl			Calcium mg/dl			Phosphorus mg/dl		
	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	11	9.9	0.80	11	5.3	1.88	12	10.3	0.62	12	3.6	1.36
10	5	10.2	0.40	5	6.0	0.95	4	10.8	0.45	4	7.3	2.72
17	2	8.2	0.42	2	7.0	0.99	9	8.7	0.43	9	5.5	1.56
15	7	9.8	0.46	7	7.1	2.15	11	9.8	0.40	11	8.5	1.67
Males - No Zinc												
1	11	11.2	1.49	11	3.9	1.06	-	-	-	-	-	-
9	12	9.5	0.39	12	6.0	1.09	-	-	-	-	-	-
14	12	9.6	0.22	12	5.8	1.26	-	-	-	-	-	-
Females												
18	4	10.8	0.46	4	3.7	0.40	4	10.0	0.24	4	4.2	1.0
19	9	9.4	0.80	9	7.1	2.27	11	10.2	0.41	10	5.8	1.59
23	12	9.4	0.30	12	7.1	1.42	9	9.5	0.85	8	5.9	1.39
24	11	9.3	0.53	11	4.9	0.96	12	9.3	0.46	12	6.2	1.65
26	11	8.6	0.41	10	4.6	1.14	9	7.9	0.96	9	5.4	1.01

* N-number of observations; X-mean; SD-standard deviation

Table 24. Individual Means for Serum Potassium and Serum Magnesium for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
	Potassium mEq/L			Magnesium mg/dl			Potassium mEq/L			Magnesium mg/dl		
No.	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	11	4.0	0.46	11	2.0	0.26	12	4.1	0.41	11	2.8	0.88
10	5	4.5	0.48	5	1.8	0.22	5	4.5	0.38	4	2.9	2.32
17	3	4.5	0.90	2	1.8	0.42	10	5.3	0.59	8	1.9	0.15
15	7	4.6	0.71	-	-	-	11	5.3	0.43	8	2.0	0.39
Males - No Zinc												
1	11	3.6	0.23	9	3.4	1.53	-	-	-	-	-	-
9	11	5.5	0.31	12	1.9	0.17	-	-	-	-	-	-
14	12	4.2	0.44	11	2.3	0.22	-	-	-	-	-	-
Females												
18	4	4.1	0.42	4	2.1	0.29	4	3.6	0.18	4	2.0	0.29
19	9	4.3	0.94	6	3.5	0.51	12	3.7	0.81	6	2.7	0.31
23	12	4.5	0.56	11	3.0	0.29	9	4.6	0.59	7	2.2	0.23
24	11	5.9	0.49	6	2.2	0.39	12	5.5	0.74	12	2.2	0.33
26	12	5.1	0.52	1	3.7	-	10	5.4	0.44	-	-	-

* N-number of observations; X-mean; SD-standard deviation

Table 25. Individual Means for Hemoglobin and Hematocrit for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
No.	Hemoglobin gm/dl			Hematocrit %			Hemoglobin gm/dl			Hematocrit %		
	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	12	8.43	0.57	11	25.8	1.04	11	7.37	0.47	11	22.6	1.40
10	5	9.50	0.91	5	28.4	3.00	5	8.90	1.22	5	26.4	3.53
17	2	6.80	0.42	2	21.1	1.70	9	7.23	1.03	9	21.7	2.44
15	3	7.17	1.17	7	20.8	4.29	7	7.07	1.51	12	22.5	3.91
Males - No Zinc												
1	10	9.93	1.32	10	29.7	3.93	-	-	-	-	-	-
9	12	7.40	0.96	12	20.9	4.89	-	-	-	-	-	-
14	12	6.94	1.63	12	20.9	4.99	-	-	-	-	-	-
Females												
18	4	10.6	0.84	4	31.1	2.57	4	10.5	0.85	4	31.4	2.11
19	8	7.28	1.85	8	22.6	6.84	13	7.02	1.31	13	21.0	3.93
23	11	7.26	1.62	11	22.3	5.73	9	6.73	0.67	9	20.7	1.98
24	9	7.00	1.44	10	21.4	4.55	12	6.40	1.14	12	19.9	3.54
26	10	7.70	1.11	12	23.2	3.54	12	7.60	1.25	12	23.1	4.03

* N-number of observations; X-mean; SD-standard deviation

Table 26. Individual Means for Total Serum Protein and Serum Albumin for Male and Female Subjects

Subj.	Non-Zinc Supplemented						Zinc Supplemented					
	Total Protein gm/dl			Albumin gm/dl			Total Protein gm/dl			Albumin gm/dl		
No.	N*	X	SD	N	X	SD	N	X	SD	N	X	SD
Males												
5	12	5.57	0.40	12	3.29	0.39	12	5.65	0.37	12	3.18	0.41
10	4	6.13	0.17	4	3.55	0.38	4	6.73	0.17	4	4.00	0.16
17	2	4.20	0.28	2	2.33	0.16	8	4.45	0.51	8	2.52	0.36
15	-	-	-	-	-	-	6	7.10	0.32	6	4.59	0.23
Males - No Zinc												
1	11	5.26	0.36	11	2.53	0.19	-	-	-	-	-	-
9	12	5.36	0.30	12	3.07	0.39	-	-	-	-	-	-
14	12	5.29	0.37	12	3.47	0.43	-	-	-	-	-	-
Females												
18	4	6.28	0.22	4	3.59	0.33	4	6.00	0.36	4	3.64	0.35
19	7	6.54	0.90	7	4.16	0.72	12	6.65	0.65	11	3.93	0.61
23	12	5.31	0.47	12	3.10	0.60	7	5.23	0.28	7	2.72	0.31
24	7	5.39	0.56	7	3.39	0.67	11	5.85	0.34	11	3.50	0.77
26	5	6.14	0.27	6	4.07	0.20	7	6.66	0.38	8	4.20	0.26

* N-number of observation; X-mean; SD-standard deviation

Table 27. Individual Mean Plasma and RBC Zinc and Plasma Copper Levels for Male Subjects

Subj.	Non-Zinc Supplemented			Zinc Supplemented		
No.	Zinc		Copper	Zinc		Copper
	Plasma	RBC	Plasma	Plasma	RBC	Plasma
	mcg/dl	mcg/dl	mcg/dl	mcg/dl	mcg/dl	mcg/dl
5	127(3)*	44(2)	218(3)	111(6)	33(5)	153(8)
10	91(3)	-	189(3)	107(3)	40(1)	200(3)
17	93(2)	-	133(2)	71(5)	42(4)	137(5)
15	113(3)	52(1)	192(2)	108(6)	40(4)	173(6)
1	83(4)	32(2)	175(4)	-	-	-
9	89(5)	34(2)	163(5)	-	-	-
14	98(8)	44(4)	127(8)	-	-	-

* Number of samples

Table 28. Individual Mean Plasma and RBC Zinc and Plasma Copper Levels for Female Subjects

Subj. No.	Non-Zinc Supplemented			Zinc Supplemented		
	Zinc		Copper	Zinc		Copper
	Plasma	RBC	Plasma	Plasma	RBC	Plasma
	mcg/dl	mcg/dl	mcg/dl	mcg/dl	mcg/dl	mcg/dl
18	126(3)*	-	192(3)	105(3)	41(2)	188(3)
19	112(1)	-	225(1)	151(6)	49(2)	226(6)
23	78(1)	-	142(1)	86(7)	34(3)	202(7)
24	88(2)	27(1)	169(2)	86(5)	36(2)	172(5)
26	83(1)	-	133(1)	94(7)	39(4)	129(7)

* number of samples



Table 29. Group Mean Zinc and Copper Blood Levels for
Male and Female and Males and Females Combined

Blood Component	No. ^a	Non-Zinc Supplemented		Zinc Supplemented	
		mean	standard dev.	mean	standard dev.
Males (7) ^b					
plasma Zinc	34	98.6	17.6	99.2	26.7
RBC Zinc	14	40.6	6.8	38.5	5.6
plasma Copper	33	160.8	42.5	161.2	45.2
Females (5)					
plasma Zinc	9	91.3	14.1	103.9	33.0
RBC Zinc	1	27.4	0	38.9	6.1
plasma Copper	9	176.4	42.2	182.0	44.9
Males and Females (12)					
plasma Zinc	43	97.1	17.1	101.9	30.3
RBC Zinc	15	39.9	7.4	38.8	5.7
plasma Copper	42	164.2	42.4	172.8	45.8

a Number of samples before zinc supplementation includes more than 1 years data

b Number of subjects in parenthesis includes both zinc supplemented and non-supplemented

Table 30. Individual Mean Dietary Intakes for Males
Evaluated as Percent Median of HANES II*

Subject No.	No. of Food Diaries	% Median						
		Kcal	Pro	Ca	P	Fe	Na	K
Non-Zinc Supplemented								
5	13	67	61	58	76	36	79	38
10	5	62	76	62	65	57	51	88
17	11	76	82	96	79	80	99	81
15	2	68	108	51	68	83	57	74
1	7	53	49	57	49	49	44	51
9	9	83	94	148	112	53	82	118
14	9	50	41	43	35	45	58	41
Zinc Supplemented								
5	10	69	53	53	51	60	40	35
10	4	74	93	42	73	97	58	88
17	8	85	96	97	85	96	103	81
15	2	63	71	42	51	67	40	75

* Reference standards from HANES II (Carroll et al. 1983)

Table 31. Individual Means for Dietary Intakes for Females
Evaluated as Percent Median of HANES II*

Subject No.	No. of Food Diaries	% Median						
		Kcal	Pro	Ca	P	Fe	Na	K
Non-Zinc Supplemented								
18	4	94	113	144	116	124	83	137
19	9	115	117	74	100	132	124	126
23	12	68	92	53	79	64	63	80
24	7	71	75	80	76	83	70	72
26	5	86	98	92	83	99	74	102
Zinc Supplemented								
18	4	118	102	127	109	124	165	83
19	8	133	148	123	126	210	173	138
23	4	63	77	27	33	60	59	52
24	8	85	82	75	77	83	81	86
26	5	86	98	92	83	99	74	102

* Reference standards from HANES II (Carroll et al. 1983)

Table 32. Dietary Intakes for Kilocalories (Kcal), Protein (Pro), Calcium (Ca), Iron (Fe) for Male and Female Subjects Expressed as Z-scores (Z)

Subj.	No. of Food Diaries	Non-Zinc Supplemented				Zinc Supplemented			
		Kcal	Pro	Ca	Fe	Kcal	Pro	Ca	Fe
		Z	Z	Z	Z	Z	Z	Z	Z

Males									

5	13/10	-1.02	-1.13	-0.67	-1.74	-0.96	-1.25	-0.77	-0.81
10	5/4	-1.34	-0.91	-1.01	-0.80	-1.01	-0.50	-1.36	-0.00
17	11/8	-0.90	-0.75	-0.41	-0.35	-0.69	-0.47	-0.38	-0.02
15	2/2	-0.84	-0.33	-0.81	-0.18	-0.98	-0.61	-1.01	-0.40
Females									

18	4/4	-0.31	+0.10	+0.11	+0.48	+0.26	-0.14	-0.09	+0.47
19	9/8	+0.09	+0.08	-0.53	+0.43	+0.44	+0.59	+0.18	+1.72
23	12/4	-0.76	-0.28	-0.79	-0.67	-0.89	-0.64	-1.51	-0.76
24	7/8	-0.93	-0.88	-0.60	-0.46	-0.59	-0.75	-0.66	-0.47
26	5/5	-0.24	-0.16	-0.04	-0.11	+0.40	+0.28	+0.05	+0.32

* Slash separates non-zinc supplemented and zinc supplemented number of food diaries

Table 33. Recommended Nutrient Levels and Percentage of Recommended for Male and Female Subjects

Subject No.	Recommended ^a				% Recommended non-supplemented			% Recommended Zn-supplemented		
	1		2		Kcal %	Pro gm%	Zn mg%	Kcal %	Pro gm%	Zn mg%
	Kcal	Pro gm	Pro gm	Zn mg						
5	1300	24	29	10	98	175	49	102	134	124
10	2400	56	55	10	54	100	50	64	125	94
17	1700	35	40	10	95	174	71	104	175	73
15	2400	64	68	10	66	140	121	61	87	73
1 ^b	1700	34		10	48	79	44			
9 ^b	2400	67		10	80	116	90			
14 ^b	2700	76		15	49	52	27			
18 ^c	2200	50	60	15	70	136	68	88	102	51
19	2400	58	62	10	78	121	77	90	144	116
23	1300	28	34	10	92	200	63	85	134	55
24	2400	41	54	10	53	91	59	63	91	69
26 ^c	2200	58	53	15	62	100	50	86	136	64

- a Reference for Kcal from Recommended Dietary Allowances, National Research Council (RDA,NRC); protein calculated at 2 gm protein per kg body weight (Holliday et al. 1979), 1) protein calculation based on weight at initiation of study, 2) protein calculation based on weight at beginning of supplemented period
- b No zinc supplement
- c Protein calculated at adult recommendation of 1 gm protein per kg body weight (Holliday et al. 1979)

Table 34. Relationship of Z-scores for Height,
Age of Onset of ESRD, and Duration of
Dialysis for Males and Females

Subject No.	Age of Onset ESRD(yrs)	Duration of Dialysis(yrs)	Height Z-score

Males			

5	birth	7.9	-6.05
10	11	0.8	-2.68
17	5	5.9	-4.56
15	8	6.3	-2.39
1	6	0.7	-2.13
9	11	4.3	-4.32
14	10	7.7	-3.32
Females			

18	15	0.7	-1.84
19	10	5.9	-3.08
23	3	4.1	-3.40
24	10	4.6	-4.50
26	8	14.6	-0.65

Figure 1: Growth Velocity of Subjects With and Without
Zinc Acetate Supplementation

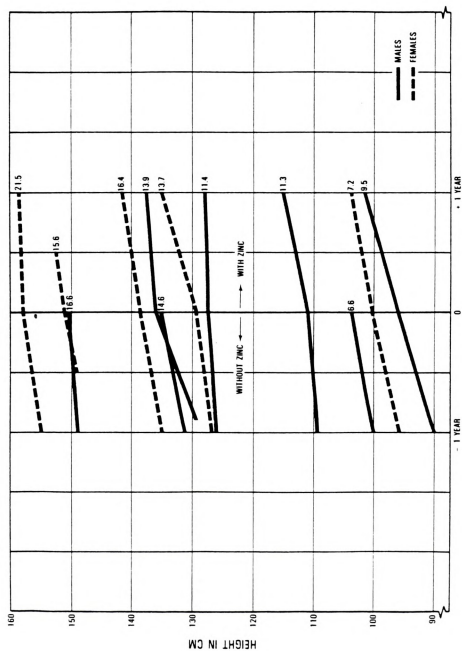


Figure 1.

Figure 2: Mean Skeletal Age at Each Chronological Age
(Diagonal Line) From Greulich and Pyle.
Radiographic Atlas of Skeletal Development of the
Hand and Wrist, 1959. Subjects Before ZN - *.
Crossover Point - 0, After ZN - []

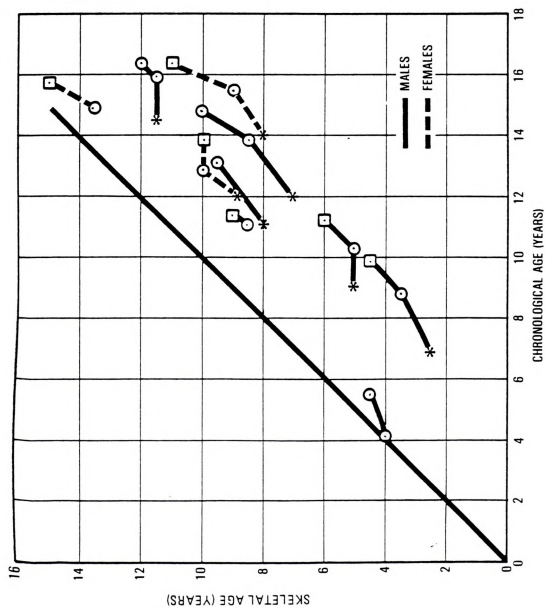


Figure 2.

V. DISCUSSION OF RESULTS

A. Introduction

Growth retardation in children with CRF was evident in this study as has been reported by other investigators (West and Smith, 1956; Potter and Greifer, 1978; Boyer et al. 1974; Kleinknecht et al. 1980; Salusky et al. 1983). This investigation also demonstrated that this growth failure is associated with decreased growth velocity, decreased bone maturation per chronological age, decreased sexual maturation for age, decreased AMC and TSF measurements for age and sex, increased BUN, serum creatinine, and alkaline phosphatase values, low hemoglobin, hematocrit, albumin, and plasma zinc levels, and in some cases inadequate nutrient intake.

As in other studies (Boyer et al. 1974; Betts and Magrath, 1977; Simmons et al. 1971; Balfe et al. 1981; Salusky et al. 1982), population numbers are low and the characteristics of the population varied. Seven males and 5 females completed this study. Since this was a longitudinal study encompassing two years, it was difficult to keep subjects for the entire time. Subjects were lost to the study primarily due to the normal course of CRF and prudent medical care (Table 1). At the initiation of the study, 4 of the 7 males were prepubertal the other 3 either in or

entering the pubertal phase (Tanner and Whitehouse, 1976) of development (Table 8). Likewise, three females were entering or in the pubertal growth phase, one beyond this physical developmental period and one prepubertal (Table 9). Salusky et al. (1983) split their study population into children less than 10 years of age and children greater than 10 years to account for the effect of puberty on growth. However, the population characteristics in this study limited such global evaluation of data. Therefore, in addition to discussing the results collectively, data on each subject is presented separately in Appendix B as individual cases.

With all clinical studies, the investigator is dependent upon the cooperation of the study population, in this case children, to obtain reliable data from which conclusions can be drawn. In a long-term study, such as the two year time period in this study, the risks of facility, personnel and environmental changes, which affect the research design, are increased. Likewise, in a population where dysgeusia, anorexia, social and psychological problems, and medical complications are common, the risks of non compliance and lack of cooperation are increased. Also, in clinical investigations, the cooperation of many health professionals is required for the collection and processing of information. Inherent in this process is the possibility of error.

B. Growth Measurements

Stefanidis et al. (1983) reported improved growth velocity in children treated with CAPD compared to those treated with HD and IPD. Salusky et al. (1983) found a significant positive correlation between TSF and duration on CAPD. Brem and Toscano (1984), however, conclude that no form of dialysis treatment holds any advantage over another in terms of growth in children with CRF. In our study population, 1 male and 1 female were treated with HD and the remaining 10 subjects were treated using CAPD. One patient was treated with CAPD and periodic HD due to a decrease in ultra-filtration of the peritoneum. Due to the small numbers and ages of the two patients in our study who were treated with HD, it is impossible to draw conclusions from our data on the effect of treatment method on growth velocity, and bone maturation.

A number of authors (Betts and Magrath, 1974; Mehls et al. 1978; Boyer et al. 1974; Scharer and Gilli, 1984) note that there appears to be a relationship between the extent of the growth retardation, the age of onset ESRD, and the duration of dialysis. This is evident in this study also. Two children who have the greatest negative standard deviations from the mean for height (Table 34) are also the

two subjects who developed ESRD at a young age and have been under treatment for their renal failure for a number of years.

In addition to statural growth retardation, Kleinknecht et al. (1980) determined that the level of bone maturity was retarded for chronological age and that this increased the time span for statural growth to occur. This is evident in subject no. 26 who continued to grow through the age of 20. Roche and Davila (1976) evaluated the reliability of assessments of maturity of hand wrist radiographs using the Gruelich and Pyle atlas. They concluded that bones of the hand-wrist should be assessed in a random order, that a single age should be given to groups of bones and that carpals should be excluded from the assessment. Hand-wrist radiographs for subjects in this study were read in this manner.

Anthropometric measurements provide a rough estimate of body composition. Arm muscle circumference estimates the amount of muscle and TSF is an estimate of body fat (Frisancho, 1974). Therefore, according to the percent median for AMC (Table 13) there appears to be a trend toward an increase in muscle in the zinc supplemented group. Salusky et al. (1983) reported a significant direct correlation between Z-scores for TSF and months of treatment with CAPD and a weak correlation between Z-scores for MAC and

duration of CAPD. These authors suggest that this improvement with CAPD treatment "could be due to the glucose absorbed from the dialysate and, possibly, the periodic surges of hyperinsulinemia which occur after each exchange with hypertonic glucose". In our study (Table 13), 4 out of 8 subjects who demonstrated improved Z-scores for TSF, and the 4 out of 8 subjects who showed improved Z-scores for MAC, were all treated with CAPD and received zinc acetate supplementation. However, 2 of the 3 subjects followed who did not receive zinc supplementation but were treated with CAPD, also had improved Z-scores for MAC and TSF. Although Salusky et al. (1983) did not report an improvement in AMC with CAPD treatment, our data show an improved percent median for AMC in 5 of 7 subjects treated with CAPD and zinc supplement (71%), and 1 of 3 subjects treated with CAPD without zinc supplement (33%). This suggests that zinc may have a positive effect on muscle mass and may enhance the positive effect of CAPD therapy on TSF and AMC. However, CAPD appears to be more beneficial than does zinc supplementation on improvement in TSF and AMC.

Increased energy and protein intake could also be responsible for the improvement seen in MAC, AMC, TSF (Tables 13 and 32). In 2 of 4 subjects with improved Z-scores for MAC and TSF after zinc supplementation, there was also an improvement in the energy intake. The kilocalorie Z-score in

these 2 subjects (nos. 17 and 24) increased from -0.90 and -0.93 to -0.69 and -0.59, respectively, with zinc acetate supplementation. Both of these subjects were on CAPD, were beginning puberty during the second year of the study, and were also the 2 subjects that demonstrated increased growth velocity with zinc supplementation. In 5 out of 7 subjects who demonstrated improved percent median for AMC with zinc acetate supplementation, the energy intake was also improved and 3 were being treated with CAPD and 2 by HD. The protein intake Z-scores were also improved in 5 of the 7 subjects with improved AMC percent median during zinc acetate supplementation. All these 5 subjects were on CAPD therapy. Therefore, it would appear that adequate energy intake may have spared protein as an energy source in some subjects, thus allowing for increased muscle mass. Adequate zinc may have also been beneficial to this anabolic process. It is also known that DNA and RNA polymerases, required for protein biosynthesis, are zinc dependent enzymes (Coleman, 1983). Consistent with the observation of increased protein intake and metabolism and the improved AMC after zinc acetate supplementation was the increase in mean BUN in 4 of 7, and serum creatinine in 5 of 7 subjects. However, it is clear that the improvement seen in MAC, AMC, and TSF, is related to many factors. Zinc may be only one of these factors.

Using Bayley and Pinneau's (1952) method (Table 7), one

can predict that under optimum conditions, this child population will be 1 to 2 standard deviations less than the mean adult height in all cases except subjects no. 14 and 26. These predictions are based on normal growth rates occurring at the time of the height observation and calculation. The Bayley and Pinneau, (1952) method was used because it is geared to the reading of radiographs using the Greulich and Pyle Atlas. Other methods presented in Table 7, give conflicting predictions. However, all methods were developed to evaluate normal children, not children compromised with a chronic disease condition. Therefore, these predictions are of limited value. Height per age Z-scores present an even more dismal prediction of adult stature. Z-scores for height per age range from a low of -2.13 standard deviations to a high of -6.05 standard deviations from the mean for males, and -0.65 to -4.50 standard deviations from the mean for females. These predictions, however, support the goal of early transplantation of children with CRF.

C. Biochemical Measurements

It is common that children with ESRD have high levels of BUN, serum creatinine, phosphorus, and alkaline phosphatase and low hemoglobin, and hematocrits. These

abnormal blood values were observed in this investigation also. Dialysis reduced BUN and serum creatinine chemistries to tolerable levels. Transfusions were given, when required, to increase hemoglobin and hematocrit levels, and aluminum hydroxide given to reduce phosphorus levels. Acidosis was uncommon as demonstrated by mean CO_2 values and therefore was probably not related to the nausea and vomiting associated with ESRD. Mean mineral levels for calcium, magnesium, sodium, potassium, and chloride, were also within the normal range both pre and post-zinc supplementation and thus appear not to be related to zinc metabolism.

Alkaline phosphatase is monitored to determine the dosage of calcium and vitamin D sterols (Paunier et al. 1984). Calcium and Vitamin D_3 are used in the treatment of renal osteodystrophy. Alkaline phosphatase is also a zinc dependent enzyme (Galdes and Vallee, 1983) with most of the enzyme in normal serum being derived from bone (Isselbacher and Tisdale, 1971). Of the approximately 2.5 gms of zinc in a hypothetical 70 kg male, thirty percent is in the bone. Bone tissue is exceeded only by eyes and male reproductive organs in concentration of zinc (Walravens, 1979). Serum alkaline phosphatase levels are commonly used in clinical medicine as a clinical index of osteoblastic activity (Rabinowitz and Bledsoe, 1972). According to Galdes and Vallee (1983), the zinc in alkaline phosphatase is not

directly involved in catalysis nor is it essential for the maintenance of the tertiary structure of the enzyme.

However, it may stabilize the enzyme's structure. Therefore the precise function of zinc in alkaline phosphatase is as yet unknown.

Several investigators (Prasad et al. 1978; Kasarskis and Schuna, 1980; Weismann and Hoyer, 1985; Rothbaum et al. 1982) have reported increased alkaline phosphatase activity after supplementation with zinc. In studying children with chronic renal failure and concomitant renal osteodystrophy, Paunier et al. (1984) separated the subjects into two groups according to the changes in serum alkaline phosphatase activity. Subjects in group I had alkaline phosphatase levels that decreased or were relatively stable while undergoing continuous ambulatory peritoneal dialysis. Bone radiographs showed adequate control of renal osteodystrophy. Subjects in group II, however, who had rising alkaline phosphatase levels, showed no improvement or a worsening of their bone disease upon radiographic examinations. Betts and White (1976), and Boyer et al. (1974) report delayed bone maturation in relation to chronological age in children with CRF, but no mention was made of alkaline phosphatase activity in their studies. In agreement with the work of Paunier et al. (1984), our subjects had elevated alkaline phosphatase levels (7 of 12 subjects) and decreased bone maturation per

chronological age (all subjects) during the non-zinc supplemented period. However, when supplemented with zinc acetate, the mean alkaline phosphatase levels continued to be elevated in 5 of the 9 zinc supplemented subjects, but bone maturation increased in 4 of the 5 zinc supplemented subjects for whom complete data were available. All subjects still demonstrated depressed bone maturation per chronological age, but not to the same extent as prior to supplementation. Thus there appeared to be an acceleration in bone maturation with zinc acetate supplementation which could possibly account for the increased serum alkaline phosphatase levels. This improved bone maturation, however, may be an unwanted effect since Kleinknecht et al. (1980) note that the retarded bone maturation per chronological age increases the time span for statural growth to occur. Since the majority of the subjects in this study received Vitamin D₃ throughout both study periods, the change in the alkaline phosphatase values or the change in the bone maturation values would not appear to be due to the activity of Vitamin D₃.

Some medications such as Aldomet, Keflex, Valporic Acid, and Inderol, which were prescribed for some subjects, can also increase serum alkaline phosphatase levels (Powers and Moore, 1983). These medications could account for an increased alkaline phosphatase level in subject nos. 17, 15, 19, and 24, but probably not in subjects nos. 5 and 26. The

level of elevated serum alkaline phosphatase was also higher during the zinc supplemented period than the non-supplemented period in subject nos. 15, 24, and 26. Medications were prescribed and changed by the attending physician as the medical condition of a subject indicated. Since these medication changes and their immediate affect on alkaline phosphatase levels were not tracked by the principal investigator, the effect of medications on alkaline phosphatase levels in this population is unknown. Interaction of zinc with drugs commonly used to treat CRF is also unknown (Mahajan et al. 1982).

Hypoalbuminemia of long term duration is a sign of malnutrition (Blackburn et al. 1977). Albumin is also a carrier of zinc in the blood (Cousins, 1979). Plasma zinc levels were low for 10 out of 12 subjects pre-zinc supplementation, and 8 out of 9 post-zinc supplementation. Mean serum albumin and plasma zinc correlation coefficients were $r=0.37$, ($p<0.50$, -Zn) and $r=0.73$, ($p<0.10$, +Zn) for males; $r=0.34$, $r=0.45$, ($p<0.50$, -Zn and +Zn), respectively, for females; and $r=0.29$, ($p<0.05$, -Zn), $r=0.53$, ($p<0.10$, +Zn) for males and females combined. Subject nos. 19 and 26 had mean serum albumin values within the normal range before zinc supplementation, but only subject 19 had a concurrent mean normal plasma zinc value. However, after zinc acetate supplementation, subjects nos. 10, 19, and 26 demonstrated



normal mean serum albumin values. Mean plasma zinc levels remained in the normal range for subject 19, but improved from 91.0 to 106.5 mcg/dl in subject no. 10 and from 82.8 to 94.0 mcg/dl in subject no. 26 with zinc acetate supplementation. Dietary intake of protein and kilocalories was adequate as compared to HANES I and II reference standards. However, these reference data as well as the RDA's, were not designed to evaluate the special needs of the compromised child (Holliday, 1979). Therefore, the kilocalorie and protein intake of the population studied may actually be inadequate.

It is possible that the failure of serum zinc to increase during supplementation was due to subjects' non-compliance in taking zinc acetate as instructed and not informing the primary investigator. However, compliance in taking medications, as demonstrated through recorded Home Peritoneal Dialysis Medication Records and patient interviews, is high among these children. Two children objected to the taste of the liquid form of the product and refused supplementation at the beginning of the supplemented period. Therefore, one can postulate that the low plasma zinc levels were due to the decreased level of the carrier protein albumin. If this theory is correct, one must then question the disappearance of the increased zinc load. Turnover rate and the 24-hour exchangeable pool for zinc have

been studied by Prasad et al. (1963) using ^{65}Zn . The quantity of zinc in an exchangeable pool is dependent upon the amount entering the pool, the amount leaving the pool, and possible recycling of zinc. Therefore, it is possible that the low plasma zinc levels could be the result of zinc leaving the exchangeable pool due to the low level of albumin and becoming deposited in bone tissue. This theory would explain the increased alkaline phosphatase levels seen in 5 of 9 zinc supplemented subjects and the increased bone maturation observed in 4 of 5 zinc supplemented subjects. However, one cannot preclude the possibility that the additional zinc load was not absorbed and therefore, was excreted in the feces.

Mahajan et al. (1982) report the significant increase in serum testosterone and sperm count in adult hemodialyzed men who were given zinc acetate supplementation. This was a double blind study (Mahajan et al. 1982) which suggested that zinc deficiency was a cause of gonadal dysfunction in uremic men. Hormone changes were not measured in our study population. However, one can postulate that the low plasma zinc levels and the increased bone maturation after zinc acetate supplementation were related to zinc stimulation of testosterone. However, the Tanner staging data does not support an improvement in sexual maturation with zinc supplementation (Table 17, 18).

Excretion of zinc through normal excretory routes or through dialysate was not measured in this investigation. Lindeman et al. (1977) report that already low levels of plasma zinc were further depressed in patients undergoing hemodialysis. With decreasing urine output, one should see an increase in plasma zinc levels (Lindeman et al. 1976). Six of the 9 zinc supplemented patients (67%) demonstrated lower plasma zinc levels during the zinc supplemented period than during the non-supplemented period. This could be accounted for through non-compliance in taking the zinc supplement, through increased losses through the dialysate, through increased excretion of zinc via other normal excretory routes such as the feces, by the depositing or replenishing of zinc into body zinc stores (bone, muscle, testes, eyes), through a decrease in serum albumin, or through an inadequate amount of zinc acetate given to counter increased losses, decreased absorption, or increases in body zinc stores.

Normal plasma zinc levels in the laboratory of Prasad are 120 mcg/dl (+/- 10) [2]. In adults, Walravens et al. (1983), have established 65 mcg/dl as the lower limit for normal plasma zinc; Blendis uses 70-120 as the normal range; Rose et al. (1972) report normal plasma zinc levels in mcg/dl of 50-118 for males, 43-123 for females, and 94-163 for pregnant females. Siegler et al. (1981) uses 112 +/- 12

mcg/dl as their normal value in children while Bhandari et al. (1980) report a normal range in children of 66-194 mcg/dl. Plasma zincs for this study were analyzed in the laboratory of Dr. Prasad. Therefore the normal range used in this study was higher than used by some other investigators. These differences in normal values appear to be due to the variations in laboratory methods [2], (Walravens, 1979).

Hemoglobin and hematocrit levels were low in all patients as were the plasma zinc levels in the majority of children regardless of zinc acetate supplementation. Solomons and Jacob, (1981), studied the bioavailability of zinc in humans and the effects of heme and nonheme iron on zinc absorption. Their study demonstrated a competitive interaction between nonheme iron and inorganic zinc. Zinc acetate supplementation in our study was given one hour before breakfast daily to avoid the inhibition of zinc absorption by other metals and foodstuffs. Some subjects would take the zinc supplement with juice or at bedtime due to time constraints in the morning. It is unlikely that zinc had an effect on the iron status of the body since the mean levels for each subject are similar both pre- and post-zinc acetate supplementation. However the reverse could be true if the subjects did not follow instructions for taking

2. personal communication Dr. A.S. Prasad

the supplement. Children were given blood transfusions as indicated by the hemoglobin and hematocrit value. Whole blood contains 438 ug/dl of zinc, 96 ug/dl of copper, 53,604 ug/dl of iron, and 5.4 ug/dl of manganese (Askari et al. 1983). Therefore, in addition to providing iron to depleted patients, zinc, copper and manganese were also given with each transfusion. Records of blood transfusions on each subject were not maintained.

D. Dietary Measurements

Dietary intake records show Z-scores that are less than 2 standard deviations from the mean for all subjects for kilocalories, protein, calcium, and iron. Two standard deviations fall within the 5th to 95th percentile for the American population (Falkner, 1962) and represent normal dietary intakes for children in the United States. Therefore, if this were a normal sample of the American population, the dietary intake of the subjects studied would be adequate. However, all subjects who participated in this study had CRF and were regularly undergoing treatment for their disease. Infections, which increase the energy requirement, are a typical side effect of treatment in patients undergoing dialysis. Reference standards for dietary requirements for children with CRF are not available

to evaluate individual dietary intakes. Holliday et al. (1979) recommend that the RDA's for sex and height be applied. Wassner (1982) recommends the RDA's as a starting point from which upward adjustments can be made for children with growth failure. Protein recommendations by Wassner (1982) follow the RDA guidelines for height age. Holliday et al. (1979), however, recommend that 1.5-2.0 gm/kg/day of protein be supplied to children over 2 years old. Salusky et al. (1983) gave even larger amounts of protein to their CAPD children: 3.0g/kg/day to children less than 5 years of age, 2.5g/kg/day from 5 years to puberty, 2.0g/kg/day during puberty, and 1.5g/kg/day thereafter. Protein of a high biological value should be given. In Appendix B, a listing of each subjects dietary intake for kilocalories and protein as well as other nutrients is presented.

According to Simmons et al. (1971), 70 percent of the RDA's must be consumed to achieve growth in children with CRF. Betts and Magrath (1974) determined that 80 percent of the British recommended allowances must be provided to achieve normal growth. One can see in Table 33, that 50 percent of the subjects failed to consume adequate energy through dietary intake before zinc supplementation and 33 percent after zinc supplementation. However, the amount of additional kilocalories absorbed through the dialysate may have brought energy intake to acceptable levels for all

subjects except subjects no. 10, 1, 14, 24. Protein intake was adequate in all subjects except no. 1, 14, 24, pre-supplementation, and subjects no. 15 and 24, post-supplementation. Dietary zinc intake, however, was below the RDA's for all children except one, subject no. 15, before zinc acetate supplementation. Krebs et al. (1984) also reported dietary zinc intakes at 52 percent of the RDA in children with evidence of mild zinc deficiency. Since good food sources of zinc are protein foods of high biological value, these results lead one to believe that children in this study chose protein foods of low biological value. Observations of food records confirm this suspicions, but quantitative analyses of food choices have not been done. Zinc deficiency has also been associated with decreased taste acuity in uremic adults (Mahajan et al. 1980; Burge et al. 1979). With zinc supplementation the percentage of subjects meeting their RDA's for energy increased from 50 percent to 66 percent (Table 33) which may be the result of improved taste acuity.

Kelly et al. 1984) reported the enhanced intestinal absorption of calcium with the ingestion of glucose polymers in a liquid formula diet or in an aqueous solution. Polycose, a glucose polymer, was supplied, compliments of Ross Laboratories, to subjects who had low energy intakes throughout the entire study. One could postulate that the

Polydose increased calcium absorption and resulted in increased calcium deposited in the bone. The increased bone calcium could account for the increased alkaline phosphatase levels and the increase in bone maturation observed in zinc supplemented subjects. However, Polydose was given both pre and post-supplementation and dietary records show that compliance with the inclusion of the supplement in the diet, was low, but varied among subjects. A quantitative analysis of Polydose consumption before and after zinc acetate supplementation has not been made. According to dietary records, Polydose was mixed with food items such as mashed potatoes, jello, or milk and usually taken with other foods in a mixed diet. Thus the effect of the glucose polymer on the absorption of calcium in this population is unknown.

VI. SUMMARY AND CONCLUSIONS

Catch up growth did not occur with zinc acetate supplementation in this population within the study period. In fact, the data suggest that zinc acetate supplementation had limited, if any, effect on linear growth. However, TSF and AMC data suggest a trend toward an improvement in body fat and muscle with zinc acetate supplementation. Subjects also tended to eat a higher percentage of the RDA's for energy following zinc supplementation. This trend to increased energy intake after zinc supplementation appeared to result in improved nutritional status as evidenced by increased muscle mass. This improved nutritional status could be due to either the increased energy intake, the zinc supplementation itself, or an effect of zinc on increasing food intake.

While this investigation did not demonstrate increased linear growth with zinc acetate supplementation, there was a trend toward a positive change in the rate of bone maturation. The zinc supplementation appeared to affect bone maturation more positively than it did growth velocity. The improved bone maturation per chronological age could be the result of depositing of calcium and/or zinc into bone tissue. Increased alkaline phosphatase levels would support this hypothesis. However, improved bone maturation may be an unwanted

effect in children with CRF since a decreased bone maturation per chronological age allows linear growth to continue for a longer period of time.

Low levels of plasma zinc were observed in this investigation even though up to 40 mg of zinc acetate was given daily. Possible explanations for low plasma zinc levels include decreased absorption of zinc, lack of adequate carrier protein for zinc, depositing of zinc into body tissues such as testes, bone, muscle, and eyes, and utilization of zinc for wound healing and infections.

Although the current recommendation for zinc intake in children with CRF is the RDA value (Holliday et al. 1979), this study demonstrates that children with CRF do not meet their RDA for zinc through their food intake. Therefore, with the positive influence of zinc supplementation on the nutritional status and bone maturation suggested in this study, further investigation is recommended to identify the specific effect, if any, of zinc on energy intake, nutritional status, bone maturation, and possibly growth. Children with CRF should also be evaluated for zinc deficiency, counselled on good food sources of zinc, and more serious consideration be given to zinc supplementation.

VII. SUGGESTIONS FOR FURTHER RESEARCH

The disappearance of zinc in the body of patients with CRF has not been determined. Urinary losses of zinc are diminished with increasing renal insufficiency. Low plasma zinc concentrations are documented in patients with CRF which are further reduced with dialysis treatment. Balance studies to determine decreased absorption of zinc in humans or isotope tracers to determine the redistribution and to ascertain the deposition of zinc in the uremic animal model is necessary to demonstrate the safe level of zinc supplementation.

The effect of zinc on bone maturation observed during zinc supplementation deserves further investigation. The elevated alkaline phosphatase levels and the depressed plasma zinc values with zinc supplementation and their interrelationship with bone maturation, if any, must be explained. Since glucose polymers have recently been reported to influence calcium absorption and since Polycose is a common energy supplement given to patients with ESRD, the influence of glucose polymers on calcium absorption before and after zinc supplementation should be evaluated in both a liquid and mixed diet. Glucose polymers may also

influence zinc absorption and should also be evaluated.

The trend toward increased energy intake and the increased muscle mass in the uremic patient after zinc supplementation should be further studied. This investigation would require an improved method for the delivery of the supplement to assure compliance. With an improved method for administering zinc and the determination of a safe, but higher, level of supplemental zinc, the current hypotheses should be retested.

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APPENDIX A



Children's

HOSPITAL of MICHIGAN

DETROIT MEDICAL CENTER • 3901 Beaubien Boulevard / Detroit, Michigan 48201

Dear

As you have probably noticed, children with Chronic Renal Failure do not grow to the same height as do other children. Dr. Fleischmann and I are interested in studying this problem. We are requesting your consent to include your child in this study.

Enclosed is a consent form explaining the study. Please read the consent form, sign it if you agree to have your child take part in the study, and return the signed form in the postage paid envelope. If you have questions, Dr. Fleischmann and I will be available to answer your questions by telephone at 494-5605 (Dr. Fleischmann) and 494-5331 (Dorothy Hagan). Please feel free to call us about any and all questions you may have.

Only through research such as this, have the tremendous advances in the treatment of Chronic Renal Failure been made. We appreciate your participation.

Sincerely,

Mrs. Dorothy W. Hagan, R.D., M.S.
Director of Dietetics
Principal Investigator

DH/ad

CONSENT FORM

RE: Zinc Supplementation in Chronic Renal Failure

Children with kidney disease do not grow as tall as children without the disease. Why this happens is not clearly known. Some studies on children who failed to grow showed they did not have enough zinc in their systems. This research study is designed to see if taking zinc will help children with kidney disease to grow.

In this research study, I understand that the following will take place:

1. X-rays will be taken of my child's wrist at the beginning and end of the study.
2. Height, weight, arm and fat measurements will be taken at the beginning of the study and again at three and six months.
3. About once a month, when blood is being taken for other purposes, an extra 2-3 teaspoonfuls will be taken for tests.
4. A snip of hair will be cut from the back of the neck.
5. Regular laboratory tests will be performed as required for treatment. This data will be used in the study.
6. A regular physical examination will be completed by the doctor.
7. At the start of the study, I will be asked what my child eats and what he has been eating in the last 24 hours. 24-hour food recalls will be obtained monthly throughout the study. I will be asked to keep a three day food record at one, three and six months.
8. My child will be asked to drink some of a sugar drink each day. This will be given to us free. There is no known risk in drinking this.
9. My child will take Zinc Acetate pills to provide more zinc than is in normal foods eaten. There is no known risk in taking zinc pills of this size.

I understand that if the zinc pills and sugar drink work, my child's growth may speed up and catch-up growth may begin.

I may ask any questions I may have about the study. Dr. Larry Fleischmann and Mrs. Dorothy Hagan will be available to answer

any additional questions I may have throughout this study. Dr. Larry Fleischmann's telephone number is _____ and Mrs. Dorothy Hagan's telephone number is _____.

This is a research project and it may not be of any direct benefit to me/my child. I may withdraw or withdraw my child from the study at anytime. If I do withdraw from the study, the hospital and doctors will give me/my child the best care they can.

I understand that in the event of physical injury resulting from taking part in this study, no compensation and no medical treatment or reimbursement is offered.

Information about what is learned from this study may be published, but the name of my or my child will not be used, but will be held in confidence.

By signing this paper, I am saying that I have read and understood it and that I agree or agree to have my child take part in this study.

Witness

Parent

Date

Parent

The child assented to participation in this study.

Investigator



Children's

HOSPITAL OF MICHIGAN

DETROIT MEDICAL CENTER • 3901 Beaubien Boulevard/Detroit, Michigan 48201

Dear Parent:

As part of our zinc study, we need to have you keep a three day food record on your child. We would like you to record everything your child eats or drinks during the course of the day for three full days. Please write down the time of the meal or snack, the food eaten, the amount, and then a complete description of the food.

EXAMPLE

<u>TIME OF DAY</u>	<u>FOOD</u>	<u>AMOUNT</u>	<u>COMPLETE DESCRIPTION</u>
7:00 a.m. Breakfast	Orange Juice	½ c	frozen orange juice
	Egg	1	scrambled in butter
	White Bread	1 slice	toasted
	Margarine	1 tsp	unsalted margarine
10:30 a.m. Snack	Orange	1	medium size
	Pop	1 can	pepsi (12 oz)
1:00 p.m. Lunch	Milk	1 c	white whole milk
	Grilled Cheese	1	
	Sandwich:		
	Cheese	1 slice	american
	Bread	2 slices	white bread
	Tomato	2 slices	medium size
	Butter	2 tsp	

FOOD RECORD

NAME: _____

[illegible]

APPENDIX B

Subject No: 5
 Description: Black, Male
 Primary Diagnosis: Hypoplastic Dysplastic Kidneys
 Age of Onset: Birth
 Duration of Dialysis Therapy: 7.9 years
 Dialysis Treatment: CAPD; 500cc; 4 times/da; PD-2 - 2.5%
 Medications: Multivitamin tablet; Folic Acid; Calcium Carbonate;
 Osmolite; Nutra-Phos; Potassium Chloride

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	7.6 yrs	8.6 yrs
Bone Age:	3.5 yrs	4.5 yrs
Tanner Score:	I	I-II
Anthropometrics:		
MAC:	5th	< 5th
TSF:	< 5TH	< 5th

Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
BUN:	43	61	Kcal:	1276	1320
Creatinine (mg/dl):	7.0	8.9	Protein (gm):	42	39
Na (mEq/L):	138	135	Ca (mg):	594	549
K (mEq/L):	4.0	4.1	P (mg):	982	694
Cl (mEq/L):	101	95	Na (mg):#	2022	1165
Ca (mg/dl):	9.9	10.3	K (mg):	875	864
P (mg/dl):	5.3	3.5	Mg (mg):#	69	167
Mg (mg/dl):	2.0	2.8	Cu (ug):	321	174
Co ₂ (mmoles/L):	23.1	27.2	Zn (mg):#	4.94	12.38
Alk. Phos. (IU/L):	283	452	Fe (mg):#	4.13	7.88
Hb. (gm/dl):	8.4	7.4			
Hct. (%)	25.8	22.6			
Total Pro. (gm/dl):	5.6	5.7			
Albumin (gm/dl):	3.3	3.2			
Zn (ug/dl):	127	111			
Cu (ug/dl):	218	153			

Comments: Due to a decrease in food intake, this subject was placed on Osmolite, an enteral feeding fed through a gastrostomy tube. Therefore, significant dietary intake correlation coefficients obtained for sodium ($p < 0.05$), magnesium, zinc, and copper ($p < 0.01$) between the supplemented and non-supplemented period were probably due to the controlled dietary regime, not to zinc acetate supplementation. Note the increase in the number of bones of the wrist in the following radiographs of the hand-wrist.

* mean values

significant correlation coefficients pre/post zinc

Figure 3: Hand Wrist Radiograph of Subject 5 Before
Zinc Supplementation: Chronological Age
8.7 Years; Bone Age 3.5 Years

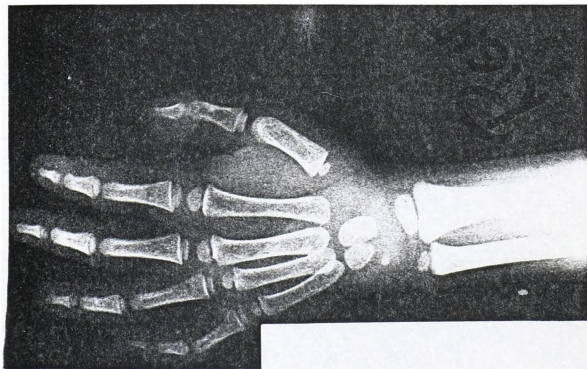
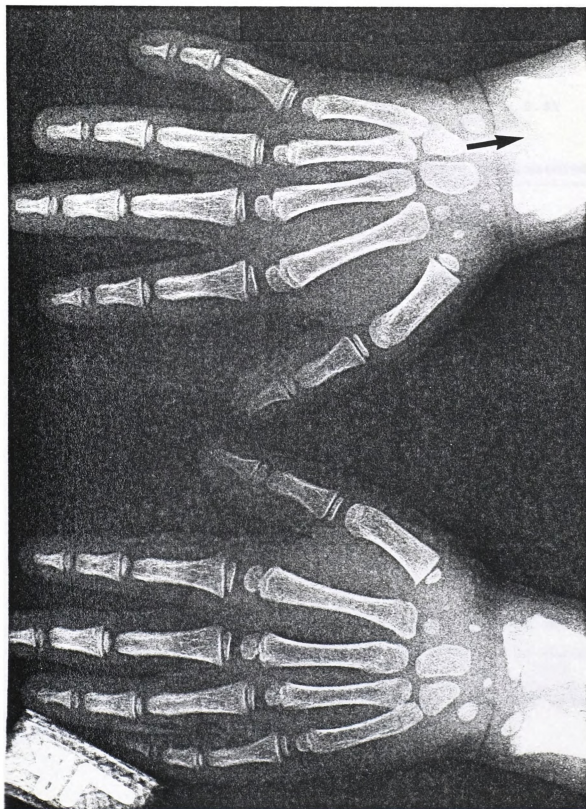


Figure 4: Hand Wrist Radiograph of Subject 5 After
Zinc Supplementation: Chronological Age
9.7 Years; Bone Age 4.5 Years



Subject No: 10
 Description: White, Male.
 Primary Diagnosis: Hemoch Schoelin Purpura
 Age of Onset: 11 years
 Duration of Dialysis Therapy: .8 years
 Dialysis Treatment: CAPD; 1000cc; 4 times/da; PD-2 - 2.5%
 Medications: Rocaltrol; Dialume, Tenormin; Apresoline;
 Multivitamin; Folic Acid

	Non Zinc Supplemented		Zinc Supplemented		
	-----		-----		
Decimal Age:	10.7 yrs		11 yrs		
Bone Age:	8.5 yrs		9.0 yrs		
Tanner Score:	I		I		
Anthropometrics:					

MAC:	50th		50th		
TSF:	50th		50th		
Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
-----	-----	-----	-----	-----	-----
BUN:	29	47	Kcal:	1293	1541
Creatinine (mg/dl):	9.5	11.1	Protein (gm):	56	69
Na (mEq/L):	134	133	Ca (mg):	645	436
K (mEq/L):	4.5	4.5	P (mg):	879	992
Cl (mEq/L):	95	93	Na (mg):	1470	1675
Ca (mg/dl):	10.2	10.8	K (mg):	2189	2176
P (mg/dl):	6.0	7.3	Mg (mg):	108	147
Mg (mg/dl):	1.8	2.9	Cu (UG):	548	665
Co ₂ (mmoles/L):	26.2	24.5	Zn (mg):	5.03	9.41
Alk. Phos. (IU/L):	86	114	Fe (mg):	7.49	12.76
Hb. (gm/dl):	9.5	8.9			
Hct. (%):	28.4	26.4			
Total Pro. (gm/dl):	6.1	6.7			
Albumin; (gm/dl):	3.6	4.0			
Zn (ug/dl):	91	107			
Cu (ug/dl):	189	200			

Comments: This subject was new to the dialysis program and joined the study while data collection was already in progress. Therefore data presented for this subject is based on 5 months instead of the research design of 1 year. Note the arrow showing the articular surfaces of the epiphyses of the metacarpals on the following radiographs of the hand-wrist.

* mean values

**Figure 5: Hand Wrist Radiograph of Subject 10 Before
Zinc Supplementation: Chronological Age
10.7 Years; Bone Age 8.5 Years**

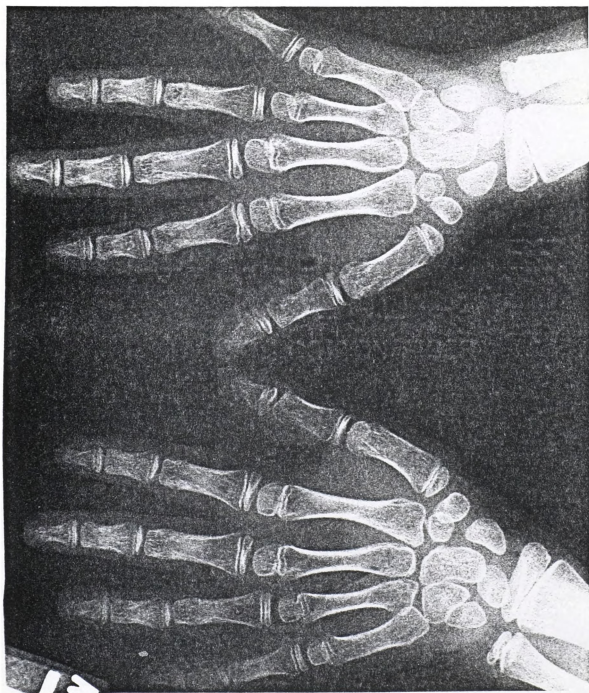
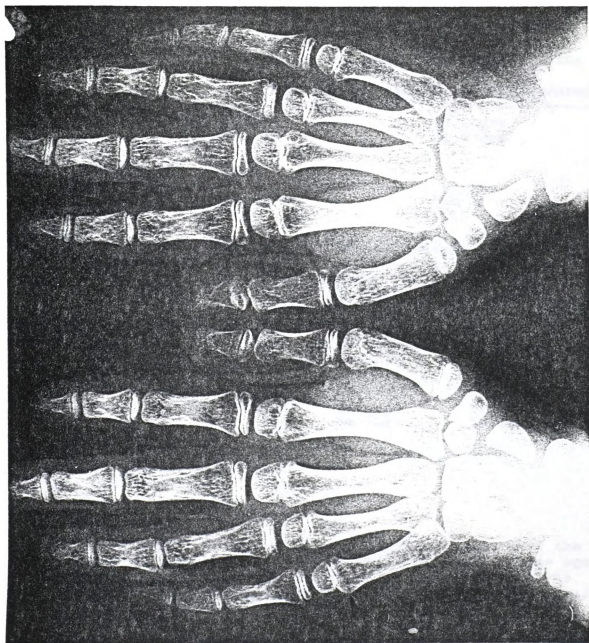


Figure 6: Hand Wrist Radiograph of Subject 10 After
Zinc Supplementation: Chronological Age
11.4 Years; Bone Age 9.0 Years



Subject No: 17
 Description: White male
 Primary Diagnosis: Focal Segmented Glomerulonephritis
 Age of Onset: 5 years
 Duration of Dialysis Therapy: 5.9 years
 Dialysis Treatment: CAPD; 750cc; 4 times/da; PD-2 - 2.5%
 Medications: Multivitamin Tablet; Folic Acid; Rocaltrol;
 Calcium Carbonate; Dialume; Kayexalate; Keflex

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	9.3 yrs	10.2 yrs
Bone Age:	5.0 yrs	6.0 yrs
Tanner Score:	I	I
Anthropometrics:		
MAC:	< 5th	5th
TSF:	15th	15th

Chemistries*	-Zn	+Zn	Dietary Intake*	-Zn	+Zn
BUN:	67	75	Kcal:	1623	1776
Creatinine (mg/dl):	9.1	9.9	Protein (gm):	61	70
Na (mEq/L):	136	137	Ca (mg):	1003	1015
K (mEq/L):	4.5	5.3	P (mg):	1074	1159
Cl (mEq/L):	97	98	Na (mg):	2860	2961
Ca (mg/dl):	8.2	8.7	K (mg):	2003	2019
P (mg/dl):	7.0	5.5	Mg (mg):	175	182
Mg (mg/dl):	1.8	1.9	Cu (ug):	820	993
CO ₂ (mmoles/L):	28.6	26.5	Zn (mg):	7.13	7.32
Alk. Phos. (IU/L):	689	686	Fe (mg):	10.46	12.65
Hb. (gm/dl):	6.8	7.2			
Hct. (%):	21.1	21.7			
Total Pro. (gm/dl):	4.2	4.5			
Albumin (gm/dl):	2.3	2.5			
Zn (ug/dl):	93	71			
Cu (ug/dl):	133	137			

Comments: The radiographs of the hand-wrist do not show the development of the lower ulna which would indicate a bone age of 7 years. There is an elongation of the humate, capitate, and triquetral bones in the later radiograph. The triquetral has become somewhat less convex.

* mean values



Figure 7: Hand Wrist Radiograph of Subject 17 Before
Zinc Supplementation: Chronological Age
10.4 Years; Bone Age 5.0 Years

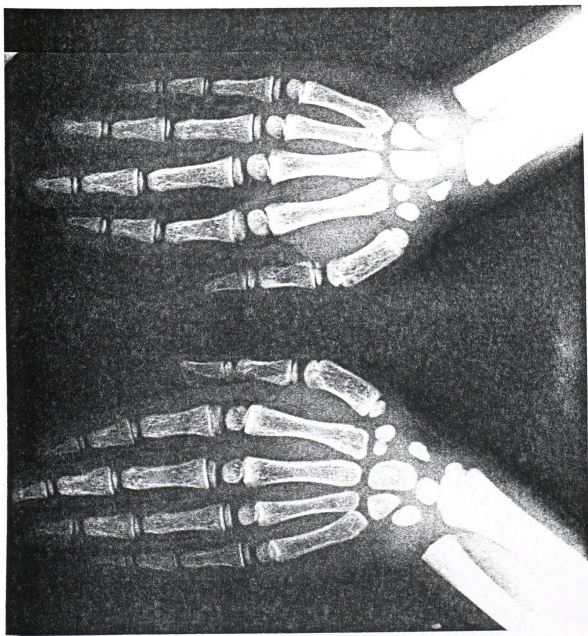
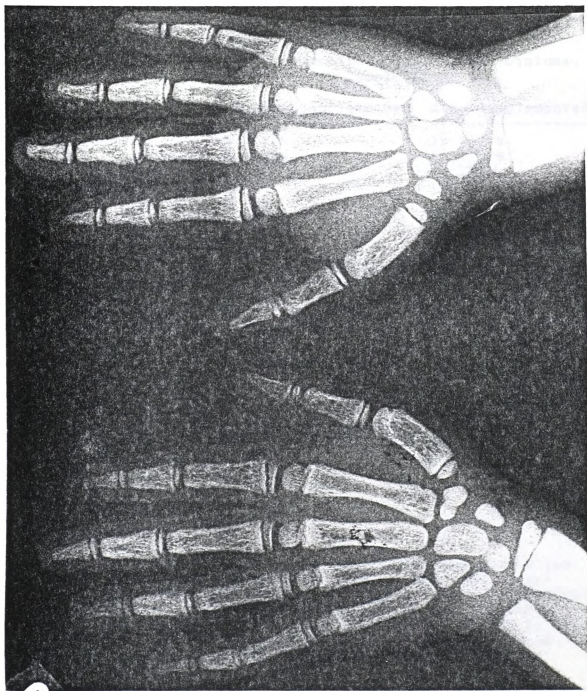


Figure 8: Hand Wrist Radiograph of Subject 17 After
Zinc Supplementation: Chronological Age
11.3 Years; Bone Age 6.0 Years



Subject No: 15
 Description: Black, Male
 Primary Diagnosis: Chronic Sclerosing Glomerulonephritis
 Age of Onset: 8 years
 Duration of Dialysis Therapy: 6.3 years
 Dialysis Treatment: Hemodialysis 3 times /wk.
 Medications: Rocaltrol; Phenobarbitol; Folic Acid; Dialume;
 Calcium Carbonate; Valporic Acid;

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	11.7 yrs.	12.9 yrs.
Bone Age:	9.5 yrs.	11.0 yrs.
Tanner Score:	II-III	-
Anthropometrics:		
MAC:	15-50th	15th
TSF:	15-50th	5th

Chemistries*	-Zn	+Zn	Dietary Intake*	-Zn	+Zn
BUN:	99	90	Kcal:	1572	1465
Creatinine (mg/dl):	12.0	13.6	Protein: (gm)	90	59
Na (mEq/L):	135	136	Ca (mg):	519	430
K (mEq/L):	4.6	5.3	P (mg):	988	730
Cl (mEq/L):	100	99	Na (mg):#	1766	241
Ca (mg/dl):	9.8	9.8	K (mg):	1995	2012
P(mg/dl):	7.1	8.5	Mg (mg):	209	142
Mg (mg/dl):	-	2.0	Cu (ug):	555	596
CO ₂ (mmoles/L):	22.5	18.3	Zn (mg):	12.11	7.34
Alk. Phos. (IU/L):	294	605	Fe (mg):	10.46	9.61
Hb. (gm/dl):	7.2	7.1			
Hct. (%):	20.8	22.5			
Total Pro. (gm/dl):	-	7.1			
Albumin (gm/dl):	-	4.6			
Zn (ug/dl):	113	108			
Cu (ug/dl):	192	173			

Comments: Dietary intake records post zinc supplementation included only 2 observations. Therefore, the significant correlation coefficient ($p < 0.01$) for sodium, pre versus post supplementation, is questionable. This subject was mentally slow. Thus there is uncertainty as to the compliance in the taking of the zinc acetate. Note the arrow on the second radiograph showing the enlargement of the pisiform which forms at 10 years of age.

* mean values

significant correlation coefficient pre/post zinc

Figure 9: Hand Wrist Radiograph of Subject 15 Before
Zinc Supplementation: Chronological Age
13.2 Years; Bone Age 9.5 Years

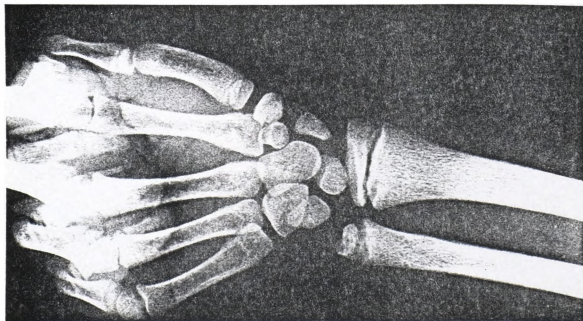
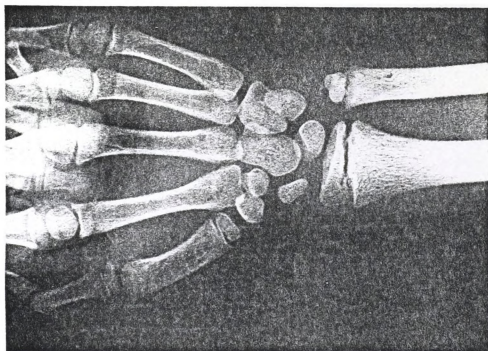
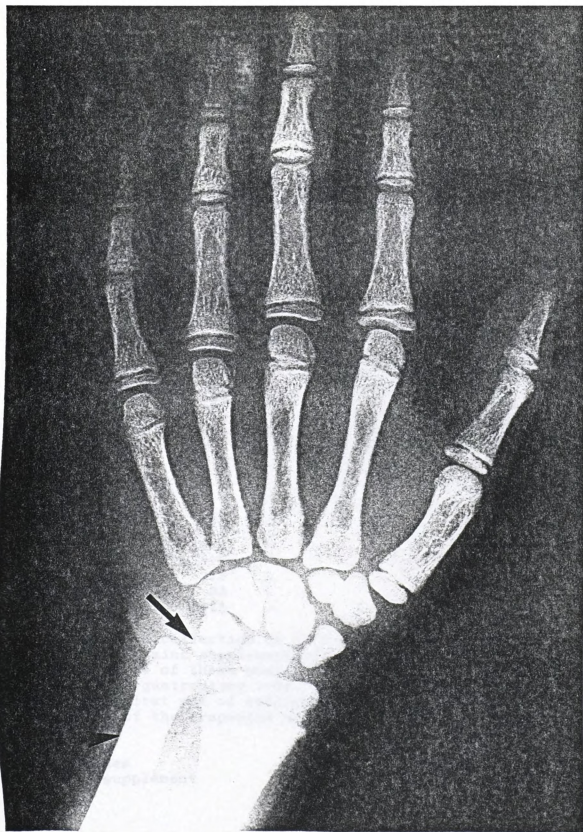


Figure 10: Hand Wrist Radiograph of Subject 15 After
Zinc Supplementation: Chronological Age
14.0 Years; Bone Age 11.0 Years



Subject No: 1
 Description: Asian, Male
 Primary Diagnosis: Focal Sclerosis Nephrotic Syndrome
 Age of Onset: 6 years
 Duration of Dialysis Therapy: .7 years
 Dialysis Treatment: CAPD; 500cc; 4 times/da; PD-2 - 2.5%
 Medications: Multivitamin; Folic Acid; DHT; Amphojel;
 Apresoline;

	Non Zinc Supplemented		Zinc Supplemented		
Decimal Age:	5.7 yrs		-		
Bone Age:	4.0 yrs		4.5 yrs		
Tanner Score:	I		I		
Anthropometrics:					

MAC:	5th		50+		
TSF:	15-50th		50-75th		
Chemistries*	-Zn	+Zn	Dietary Intake*	-Zn	+Zn
BUN:	51	-	Kcal:	824	-
Creatinine (mg/dl):	4.7	-	Protein (gm):	27	-
Na (mEq/L):	132	-	Ca (mg):	444	-
K (mEq/L):	3.6	-	P (mg):	506	-
Cl (mEq/L):	96	-	Na (mg):	896	-
Ca (mg/dl):	11.2	-	K (mg):	957	-
P (mg/dl):	3.9	-	Mg (mg):	124	-
Mg (mg/dl):	3.4	-	Cu (ug):	333	-
CO ₂ (mmoles/L):	24.3	-	Zn (mg):	5.82	-
Alk. Phos. (IU/L):	255	-	Fe (mg):	4.49	-
Hb. (gm/dl):	9.9	-			
Hct. ((%):	29.7	-			
Total Pro. (gm/dl):	5.3	-			
Albumin (gm/dl):	2.5	-			
Zn (ug/dl):	83	-			
Cu (ug/dl):	175	-			

Comments: Data collection on this subject occurred for 6 months with no zinc supplementation. He was new to dialysis therapy. For 4 of these months, he was fed an enteral feeding via a gastrostomy tube. Note the missing trapezium bone on the first set of radiographs (arrow) and the development of the trapezium on the second set of radiographs.

* mean values

+ no zinc supplement

Figure 11: Hand Wrist Radiograph of Subject 1 at
Beginning of Study Period: Chronological
Age 4.2 Years; Bone Age 4.0 Years

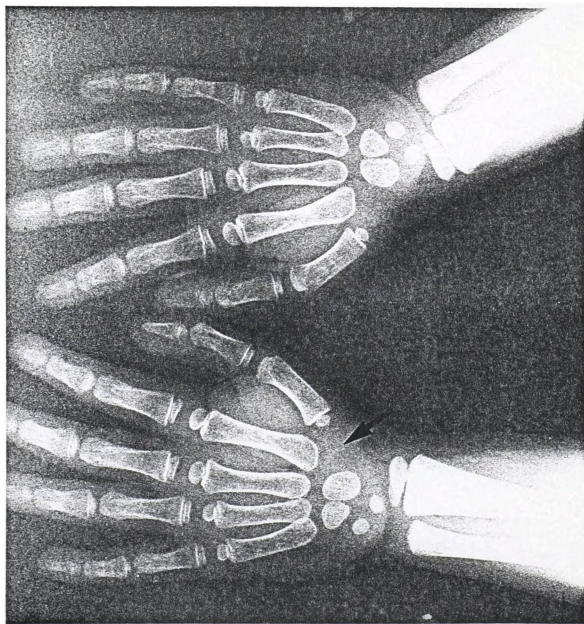
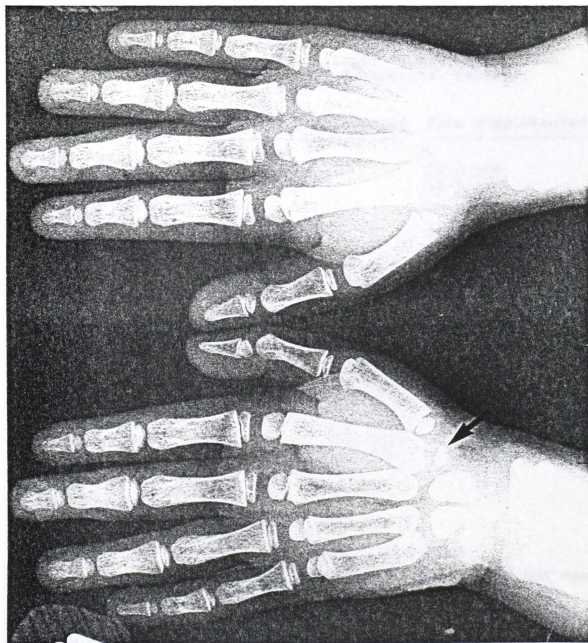


Figure 12: Hand Wrist Radiograph of Subject 1 at End
of Study Period: Chronological Age 5.5
Years; Bone Age 4.5 Years



Subject No: 9
 Description: White, Male
 Primary Diagnosis: Obstructive Uropathy Secondary to
 Posterior Urethral Valves at Birth
 Age of Onset: .8 years
 Duration of Dialysis Therapy: 4.3 years
 Dialysis Treatment: CAPD; 1500cc; 4 times/da; PD-2 - 2.5%
 Medications: Multivitamin; Folic Acid; Rocaltrol; Calcium
 Carbonate; Anphojel; Kayexalate; Senokot;
 Vitamin C.

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	13.6 yrs	-
Bone Age:	8.5 yrs	10.0 yrs
Tanner Score:	II	II
Anthropometrics:		
MAC:	15th	15-50th ⁺
TSF:	15th	15th

Chemistries*	+Zn	-Zn	Dietary Intakes*	+Zn	-Zn
BUN:	72	-	Kcal:	1936	-
Creatine (mg/dl):	8.4	-	Protein (gm):	78	-
Na (mEq/L):	137	-	Ca (mg):	1522	-
K (mEq/L):	5.5	-	P (mg):	1623	-
Cl (mEq/L):	96	-	Na (mg):	2531	-
Ca (mg/dl):	9.5	-	K (mg):	3179	-
P (mg/dl):	6.0	-	Mg (mg):	277	-
Mg (mg/dl):	1.9	-	Cu (ug):	1081	-
CO ₂ (mmoles/L):	28.9	-	Zn (mg):	8.97	-
Alk. Phos. (IU/L):	342	-	Fe (mg):	7.59	-
Hb. (gm/dl):	7.4	-			
Hct. (%):	20.9	-			
Total Pro. (gm/dl):	5.4	-			
Albumin (gm/dl):	3.1	-			
Zn (ug/dl):	89	-			
Cu (ug/dl):	163	-			

Comments: This patient refused zinc supplementation, but was followed for the entire study period. Note the small dot shown by the arrow. This dot is the formation of the pisiform occurring at 10 years of age. Note also the renal rickets depicted in the denseness of the bones.

* mean values

+ no zinc supplement

Figure 13: Hand Wrist Radiograph of Subject 9 at
Beginning of Study Period: Chronological
Age 13.8 Years; Bone Age 8.5 Years

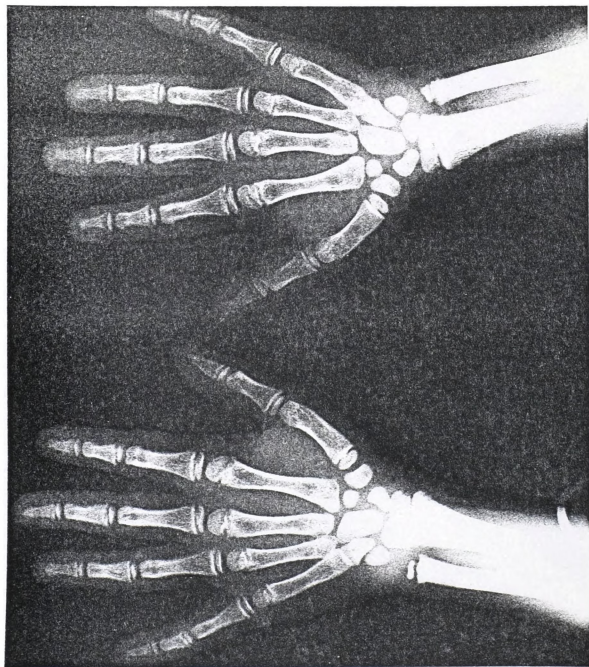
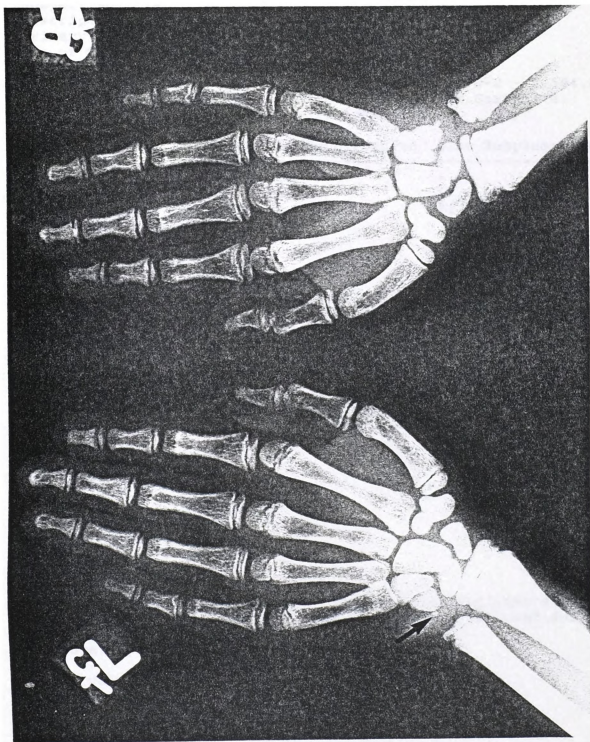


Figure 14: Hand Wrist Radiograph of Subject 9 at End
of Study Period: Chronological Age 14.7
Years; Bone Age 10.0 Years





Subject No: 14
 Description: White, Male
 Primary Diagnosis: Acute Glomerulonephritis
 Age of Onset: 10 years
 Duration of Dialysis Therapy: 7.7 years
 Dialysis Treatment: CAPD; 1500cc; 4 times/da; PD-2 - 2.5&4.5%
 Medications: Multivitamin; Folic Acid; Calcium Carbonate;
 Dialume; Rocaltrol; Apresoline

	Non Zinc Supplemented	Zinc Supplemented	
Decimal Age:	15.5 yrs	-	
Bone Age:	11.5 yrs	12.0 yrs	
Tanner Score:	II	II	
Anthropometrics:			

MAC:	< 5th	< 5th ⁺	
TSF:	15-50th	< 5th	
Chemistries*	-Zn +Zn	Dietary Intakes* -Zn +Zn	
-----		-----	
BUN:	56 -	Kcal: 1320 -	
Creatinine (mg/dl):	11.5 -	Protein (gm) 40 -	
Na (mEq/L):	139 -	Ca (mg): 507 -	
K (mEq/L):	4.2 -	P (mg): 576 -	
Cl (mEq/L):	100 -	Na (mg): 1871 -	
Ca (mg/dl):	9.6 -	K (mg): 1202 -	
P (mg/dl):	5.8 -	Mg (mg): 94 -	
Mg (mg/dl):	2.3 -	Cu (ug): 381 -	
CO ₂ (mmoles/L):	26.6 -	Zn (mg): 4.05 -	
Alk. Phos. (IU/L):	151 -	Fe (mg): 6.81 -	
Hb. (gm/dl):	6.9 -		
Hct. (%):	20.9 -		
Total Pro. (gm/dl):	5.3 -		
Albumin (gm/dl):	3.5 -		
Zn (ug/dl):	98 -		
Cu (ug/dl):	127 -		

Comments: This patient refused zinc acetate supplementation at the initiation of the second phase, but was followed for the entire study period. Note the severe renal osteodystrophy in this patient.

* mean values

+ no zinc supplement



Figure 15: Hand Wrist Radiograph of Subject 14 at
Beginning of Study Period: Chronological
Age 15.8 Years; Bone Age 11.5 Years

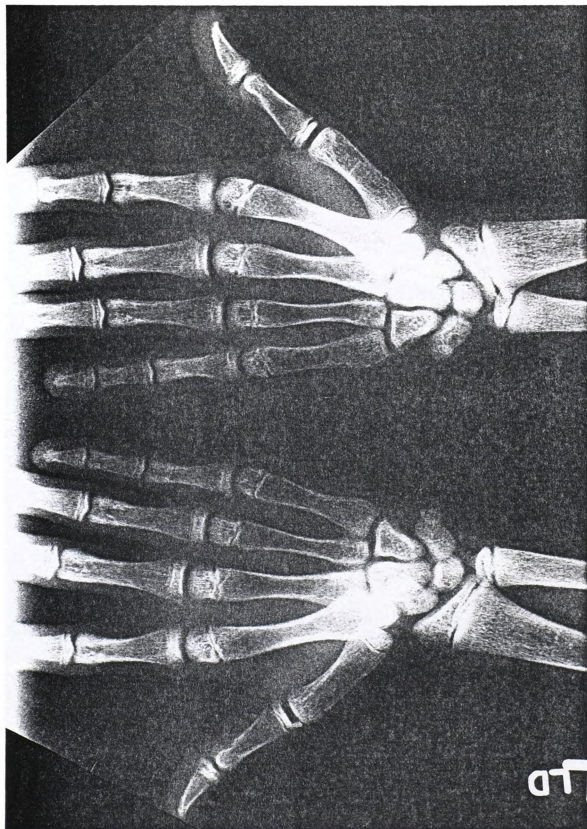
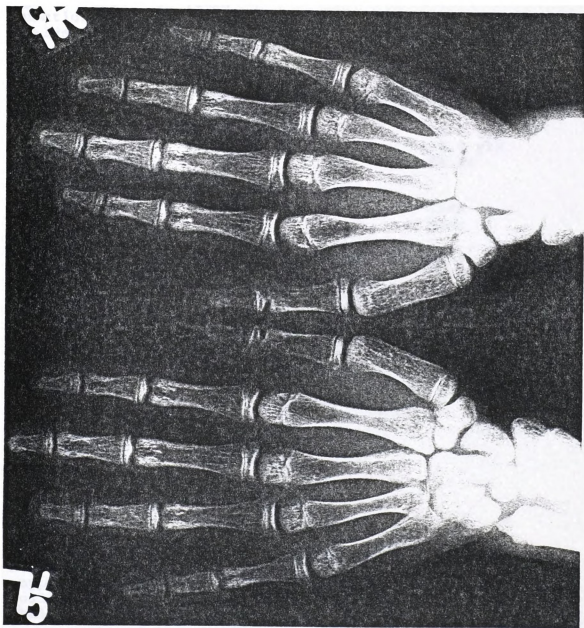


Figure 16: Hand Wrist Radiograph of Subject 14 at End
of Study Period: Chronological Age 16.5
Years; Bone Age 12.0 Years



Subject No. 18
 Description: White, Female
 Primary Diagnosis: Chronic Polynephritis
 Age of Onset: 15 years
 Duration of Dialysis Therapy: .8 years
 Dialysis Treatment: CAPD; 1000cc 4 times/da; PD-2 - 2.5&4.25%
 Medication: Multivitamin; Folic Acid; Rocaltrol; Dialume;
 Senekot.

	Non Zinc Supplemented		Zinc Supplemented	
Decimal Age:	14.8 yrs		15.3 yrs	
Bone Age:	13.5 yrs		15.0 yrs	
Tanner Score:	B5,P5		B4,P4	
Anthropometrics:				
MAC:	95th		85th	
TSF:	50th		95th	
Chemistries*	-Zn	+Zn	Dietary Intake*	-Zn +Zn
BUN:	59	56	Kcal:	1530 1931
Creatinine (mg/dl):	9.3	9.8	Protein (gm):	68 61
Na (mEq/L):	140	141	Ca (mg):	898 788
K (mEq/L):	4.1	3.6	P (mg):	1136 1070
Cl (mEq/L):	104	105	Na (mg):#	1763 3501
Ca (mg/dl):	10.8	10.0	K (mg):	2446 1481
P (mg/dl):	3.7	4.2	Mg (mg):	217 153
Mg (mg/dl):	2.1	2.0	Cu (ug):	1002 519
CO2 (mmoles/L):	24.0	22.5	Zn (mg):	10.20 7.60
Alk. Phos. (IU/L):	95	180	Fe (mg):	11.70 11.67
Hb. (gm/dl):	10.6	10.5		
Hct. (%):	31.1	31.4		
Total Pro:(gm/dl):	6.3	6.0		
Albumin (gm/dl):	3.6	3.6		
Zn (ug/dl):	126	105		
Cu (ug/dl):	192	188		

Comments: This patient participated in the study for 5 months pre-supplementation, and 5 months post-supplementation. Note the arrows on the following radiographs and the degree of fusion of the phalanges and wrist between the 13.5 and 15 years.

* mean values

significant correlation coefficient ($p < 0.02$) pre/post zinc

Figure 17: Hand Wrist Radiograph of Subject 18 Before
Zinc Supplementation: Chronological Age
14.9 Years; Bone Age 13.5 Years

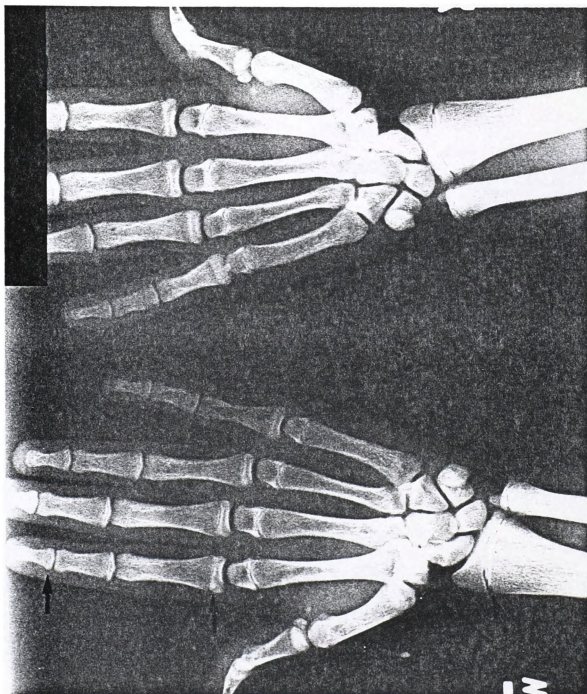
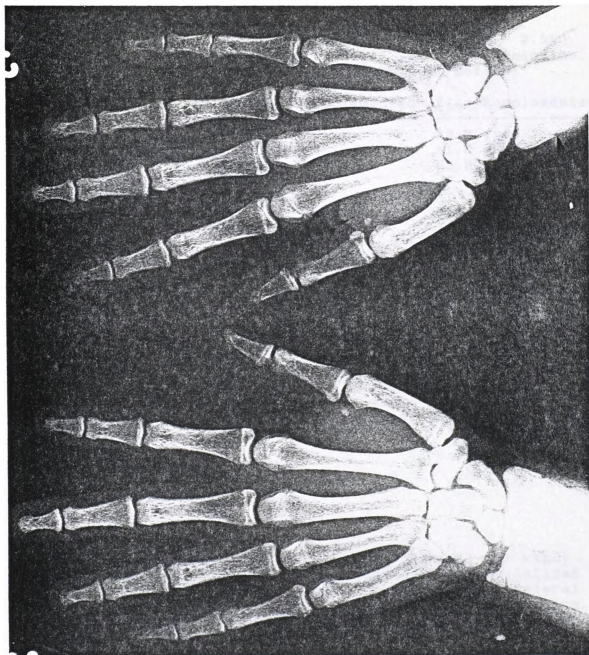


Figure 18: Hand Wrist Radiograph of Subject 18 After
Zinc Supplementation: Chronological Age
15.6 Years; Bone Age 15.0 Years



Subject No. 19
 Description: Black, Female
 Primary Diagnosis: Focal Segmented Glomerulonephritis
 Age of Onset: 10 years
 Duration of Dialysis Therapy: 5.9 years
 Dialysis Treatment: CAPD; 1500cc 4 times/da; PD-2 - 2.5%
 Medications: Multivitamin; Folic Acid; Inderol; Apresoline;
 Sloe K; Dialume; Phenobarbital; Keflex;

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	14.3 yrs	15.3 yrs
Bone Age:	9.0 yrs	11.0 yrs
Tanner Score:	B2,P3	B2,P3
Anthropometrics:		
MAC:	5th	5th
TSF:	5-15th	5-15th

Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
BUN:	64	43	Kcal:	1876	2173
Creatinine (mg/dl):	14.4	10.5	Protein (gm):	70	89
Na (mEq/L):	135	133	Ca (mg):	462	764
K (mEq/L):	4.3	3.7	P (mg):	986	1241
Cl (mEq/L):	97	95	Na (mg):	2625	3660
Ca (mg/dl):	9.4	10.2	K (mg):	2238	2466
P (mg/dl):	7.1	5.8	Mg (mg):	147	383
Mg (mg/dl):	3.5	2.7	Cu (ug):	864	830
CO ₂ (mmoles/L):	24.3	23.5	Zn (mg):	7.74	11.59
Alk. Phos. (IU/L):	284	197	Fe (mg):	12.46	19.77
Hb. (gm/dl):	7.3	7.0			
Hct. (%):	22.6	21.0			
Total Pro. (gm/dl):	6.5	6.7			
Albumin (gm/dl):	4.2	3.9			
Zn (ug/dl):	112	151			
Cu (ug/dl):	225	226			

Comments: During the zinc supplemented phase of the study this patient developed severe anorexia and was hospitalized for two months. She was nourished through total parenteral nutrition and did not receive the supplemental zinc acetate. Note the arrow in the second radiograph showing the pinpoint ossification of the flexor sesamoid of the thumb.

* mean values

Figure 19: Hand Wrist Radiograph of Subject 19 Before
Zinc Supplementation: Chronological Age
15.5 Years; Bone Age 9.0 Years

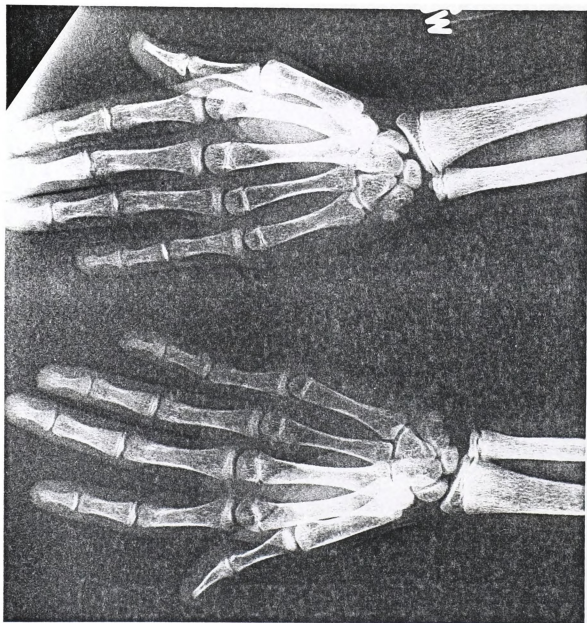
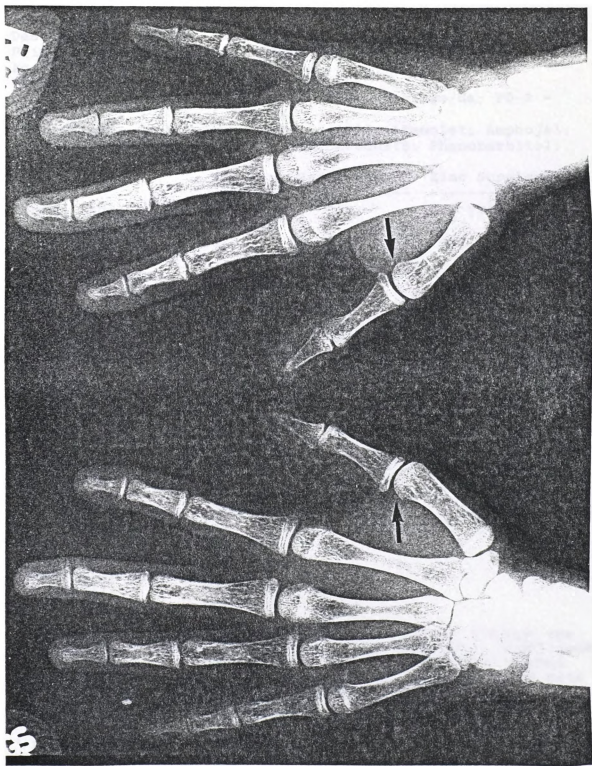


Figure 20: Hand Wrist Radiograph of Subject 19 After
Zinc Supplementation: Chronological Age
16.4 Years; Bone Age 11.0 Years



Subject No: 23
 Description: Black, Female
 Primary Diagnosis: Focal Segmented Glomerulonephritis
 Age of Onset: 3 years
 Duration of Therapy: 4.1 years
 Dialysis Treatment: CAPD & IPD; 500cc 5 times/da; PD-2 -
 1.5&2.5%
 Medications: Multivitamin; Folic Acid; Atenolet; Amphojel;
 Roclatrol; Calcium Carbonate; Phenobarbitol;

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	5.2 yrs	6.1 yrs
Bone Age:	4.2 yrs	-
Tanner Score:	B2	B2
Anthropometrics:		

MAC:	5-15th	5th
TSF:	< 5th	< 5th

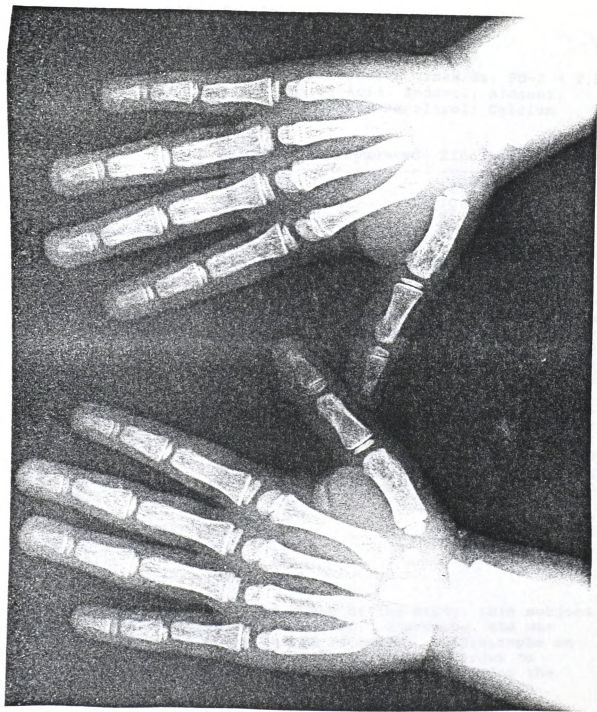
Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
BUN:	75	68	Kcal:	1196	1106
Creatinine (mg/dl):	8.6	8.9	Protein (gm):	56	47
Na (mEq/L):	137	138	Ca (mg):#	487	247
K (mEq/L):	4.5	4.6	P (mg):#	900	372
Cl (mEq/L):	100	99	Na (mg):	1452	1357
Ca (mg/dl):	9.4	9.5	K (mg):	1669	1089
P (mg/dl):	7.1	5.9	Mg (mg):	138	76
Mg (mg/dl):	3.0	2.2	Cu (ug):	1044	368
CO ₂ (mmoles/L):	22.0	25.0	Zn (mg):	6.32	5.45
Alk. Phos. (IU/L):	130	141	Fe (mg):	6.45	6.08
Hb. (gm/dl):	7.3	6.7			
Hct. (%):	22.3	20.7			
Total Pro. (gm/dl):	5.3	5.2			
Albumin (gm/dl):	3.1	2.7			
Zn (ug/dl):	78	86			
Cu (ug/dl):	142	202			

Comments: Child care problems developed midway through the zinc supplemented phase of this study. Therefore, compliance with the intake of the supplemental zinc acetate is unknown for the last 2-3 months of the study. Only 8 months of data after zinc supplementation were collected. Only the radiograph at the initiation of the study was obtained.

* mean values

significant correlation coefficients pre/post zinc for calcium ($p < 0.02$), phosphorus ($p > 0.01$)

**Figure 21: Hand Wrist Radiograph of Subject 23 Before
Zinc Supplementation: Chronological Age
6.4 Years; Bone Age 4.2 Years**



Subject No: 24
 Description: White, Female
 Primary Diagnosis: Hypoplastic Kidneys
 Age of Onset: 10 years
 Duration of Dialysis Therapy: 4.6 years
 Dialysis Treatment: CAPD & HD; 1000cc 5 times/da; PD-2 - 2.5%
 Medications: Multivitamin; Folic Acid; Inderol; Aldomet;
 Apresoline; Alternajel; Rocaltrol; Calcium
 Carbonate.

	Non Zinc Supplemented		Zinc Supplemented		
Decimal Age:	11.8 yrs		12.7 yrs		
Bone Age:	10.0 yrs		10.0 yrs		
Tanner Score:	B1,P2		B1-2,P2		
Anthropometrics:					
MAC:	5th		5th		
TSF:	5th		< 5th		
Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
BUN:	67	58	Kcal:	1260	1505
Creatinine (mg/dl):	10.7	11.2	Protein (gm):	45	49
Na (mEq/L):	138	137	Ca (mg):	633	594
K (mEq/L):	5.9	5.5	P (mg):	809	821
Cl (mEq/L):	99	98	Na (mg):	1617	1874
Ca (mg/dl):	9.3	9.3	K (mg):	1440	1726
P (mg/dl):	4.9	6.2	Mg (mg):	125	147
Mg (mg/dl):	2.2	2.2	Cu (ug):	369	648
CO ₂ (mmoles/L):	27.0	25.1	Zn (mg):	5.92	6.85
Alk. Phos. (IU/L):	635	896	Fe (mg):	8.23	8.18
Hb. (gm/dl):	7.0	6.4			
Hct. (%):	21.4	19.9			
Total Pro. (gm/dl):	5.4	5.6			
Albumin (gm/dl):	3.4	3.5			
Zn (ug/dl):	88	86			
Cu (ug/dl):	169	172			

Comments: During the second phase of the study, this subject developed medical problems with CAPD. Therefore, she was dialysed using CAPD daily and HD as needed. Radiographs on this patient show severe hyperparathyroidism (arrows to phylanges). Note also the arrow to the wrist showing the development of the pisiform which occurs at 10 years in girls.

* mean values

Subject No: 24
 Description: White, Female
 Primary Diagnosis: Hypoplastic Kidneys
 Age of Onset: 10 years
 Duration of Dialysis Therapy: 4.6 years
 Dialysis Treatment: CAPD & HD; 1000cc 5 times/da; PD-2 - 2.5%
 Medications: Multivitamin; Folic Acid; Inderol; Aldomet;
 Apresoline; Alternajel; Rocaltrol; Calcium
 Carbonate.

	Non Zinc Supplemented		Zinc Supplemented		
Decimal Age:	11.8 yrs		12.7 yrs		
Bone Age:	10.0 yrs		10.0 yrs		
Tanner Score:	B1,P2		B1-2,P2		
Anthropometrics:					
MAC:	5th		5th		
TSF:	5th		< 5th		
Chemistries*	-Zn	+Zn	Dietary Intakes*	-Zn	+Zn
BUN:	67	58	Kcal:	1260	1505
Creatinine (mg/dl):	10.7	11.2	Protein (gm):	45	49
Na (mEq/L):	138	137	Ca (mg):	633	594
K (mEq/L):	5.9	5.5	P (mg):	809	821
Cl (mEq/L):	99	98	Na (mg):	1617	1874
Ca (mg/dl):	9.3	9.3	K (mg):	1440	1726
P (mg/dl):	4.9	6.2	Mg (mg):	125	147
Mg (mg/dl):	2.2	2.2	Cu (ug):	369	648
CO ₂ (mmoles/L):	27.0	25.1	Zn (mg):	5.92	6.85
Alk. Phos. (IU/L):	635	896	Fe (mg):	8.23	8.18
Hb. (gm/dl):	7.0	6.4			
Hct. (%):	21.4	19.9			
Total Pro. (gm/dl):	5.4	5.6			
Albumin (gm/dl):	3.4	3.5			
Zn (ug/dl):	88	86			
Cu (ug/dl):	169	172			

Comments: During the second phase of the study, this subject developed medical problems with CAPD. Therefore, she was dialysed using CAPD daily and HD as needed. Radiographs on this patient show severe hyperparathyroidism (arrows to phylanges). Note also the arrow to the wrist showing the development of the pisiform which occurs at 10 years in girls.

* mean values

Figure 22: Hand Wrist Radiograph of Subject 24 Before
Zinc Supplementation: Chronological Age
12.8 Years; Bone Age 10.0 Years

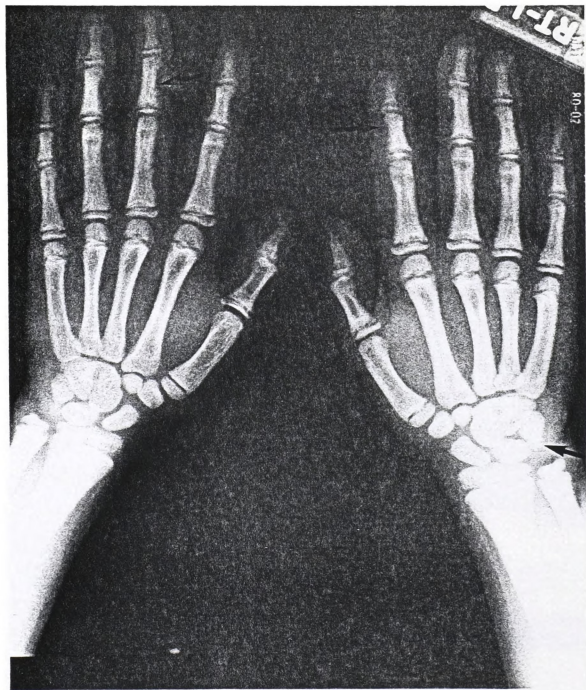
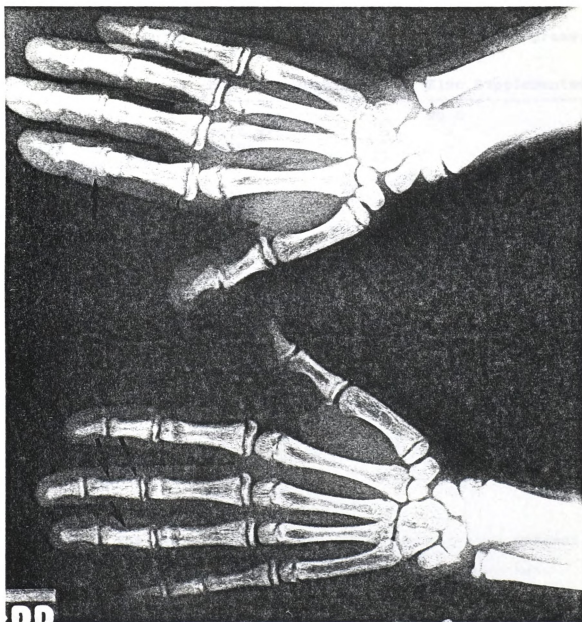


Figure 23: Hand Wrist Radiograph of Subject 24 After
Zinc Supplementation: Chronological Age
13.7 Years; Bone Age 10.0 Years



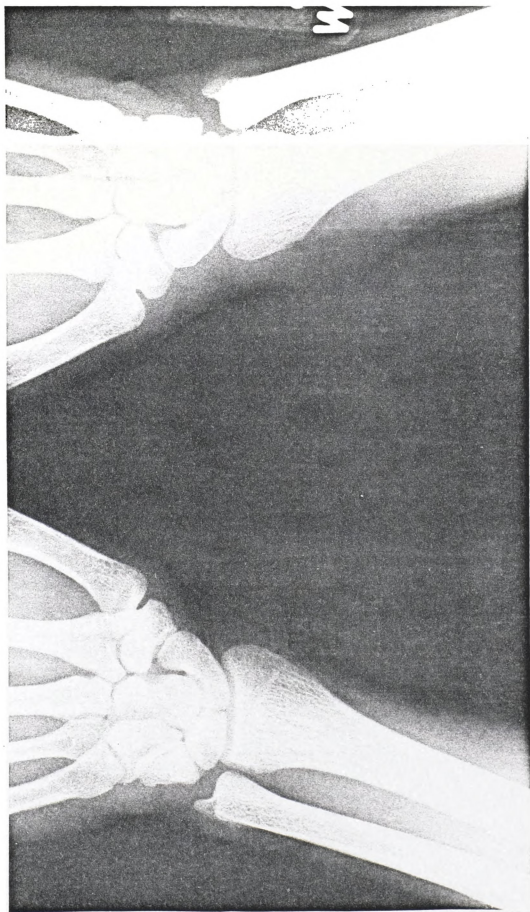
Subject No: 26
 Description: Black, Female
 Primary Diagnosis: Membranoproliferative Glomerulonephritis
 Age of Onset: 8 years
 Duration of Dialysis Therapy: 14.6 years
 Dialysis Treatment: HD.
 Medications: Multivitamin; Folic Acid; Roclatrol; Minipress;
 Calcium Carbonate; Digoxin.

	Non Zinc Supplemented	Zinc Supplemented
Decimal Age:	19.6 yrs	20.5
Bone Age:	17.0 yrs	-
Tanner Score:	B4,P5	-
Anthropometrics:		
MAC:	15th	50th
TSF:	< 5th	5th
Chemistries*	-Zn +Zn	Dietary Intakes* -Zn +Zn
BUN:	66 83	Kcal: 1364 1901
Creatinine (mg/dl):	14.5 15.0	Protein (gm): 58 72
Na (mEq/L):	137 137	Ca (mg): 521 558
K (mEq/L):	5.1 5.4	P (mg): 798 954
Cl (mEq/L):	105 102	Na (mg): 1609 1791
Ca (mg/dl):	8.6 7.9	K (mg): 1892 2157
P (mg/dl):	4.6 5.4	Mg (mg): 139 155
Mg (mg/dl):	3.7 -	Cu (ug): 683 787
CO ₂ (mmoles/L):	20.0 17.6	Zn (mg): 7.53 9.56
Alk. Phos. (IU/L):	210 417	Fe (mg): 9.58 11.87
Hb. (gm/dl):	7.7 7.6	
Hct. (%):	23.2 23.1	
Total Pro. (gm/dl):	6.1 6.7	
Albumin (gm/dl):	4.1 4.2	
Zn (ug/dl):	83 94	
Cu (ug/dl):	133 129	

Comments: The first radiograph of the wrist of this patient showed a bone age of 17 years (see following x-ray). Therefore, radiographs at the end of the study were not taken.

* mean values

Figure 24: Hand Wrist Radiograph of Subject 26 Before
Zinc Supplementation: Chronological Age
20.9 Years; Bone Age 17.0 Years



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