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A Syndrome of Acute Zinc Deficiency During Total Parenteral Alimentation in Man

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Changes in the plasma and urine levels of the trace metal zinc have been followed in a series of 37 adult patients totally supported by intravenous alimentation. Copper has also been determined in more recent cases. In such a seriously ill group, although urinary zinc loss may be very high at the height of catabolism, severe plasma depletion does not occur unless there is a subsequent phase of sustained anabolism and weight gain. In four patients plasma zinc fell to very low levels during this phase and three of this group developed a syndrome characterized by diarrhea, mental depression, para-nasal, oral and peri-oral dermatitis, and alopecia. The response to oral or intravenous zinc therapy is striking, except for hair regrowth which is delayed but eventually complete. The syndrome we have recognized in adult man has not been previously described. It resembles however the parakeratosis of zinc deficient swine and it is also very similar to Acrodermatitis enteropathica, a genetically determined disorder of infants very recently linked to zinc deficiency. Zinc is clearly essential to human metabolism and it should be included in all parenteral alimentation regimes particularly during the period of rapid, sustained, weight gain.

ZINC is an essential trace element and its importance and dietary indispensibility are well described in animals.[8]

In growing chickens severe deprivation leads to almost complete failure of feather development, leg weakness and skin lesions particularly on the feet and around the beak. Histologically, esophageal changes are striking with increased numbers of cells in the basal layers but without increase in mitotic activity.[18] These changes in the gullet resemble the parakeratosis described in the skin of zinc deficient swine where the fully developed syndrome may be fatal.[28]

Zinc is also and essential element in man and a component of numerous enzyme systems including carbonic anhydrase, carboxypeptidase and alcoholic dehydrogenase.[19] High levels are present in the pancreas and the testis. Zinc deficiency, once thought unlikely in man, is now known to occur in some Middle Eastern countries, probably because the high phytic acid content of cereals causes zinc malabsorption. Chronic zinc deficiency in this group is characterized by a hypogonodal type of dwarfism and both growth and sexual development improve rapidly with zinc supplementation.[9]

Although the need for trace metal supplementation during total parenteral alimentation is recognized,[1,11,13,31] the significance and importance of these elements is rarely emphasized and acute zinc deficiency has not been reported.

This paper documents the changes in zinc levels in the plasma and urine of selected patients managed by total intravenous alimentation. A syndrome of acute zinc deficiency is described, resembling the parakeratotic syndrome of swine and almost exactly similar to Acrodermatitis enteropathica, a genetically determined disorder in infants, very recently linked to zinc deficiency,[17] which is characterized by alopecia, diarrhea and an eruption which is pustular round the orifices and bullous, or verrucous, on the extremities.[24]

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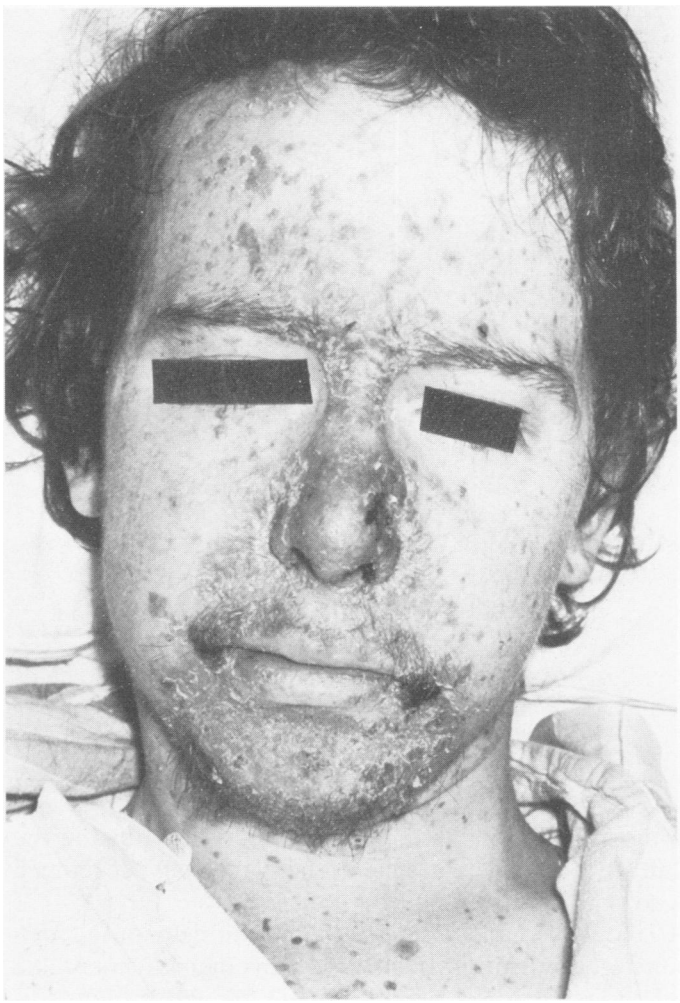

FIG. 1. S.G.—Severe facial dermatitis, 27th April, 1973.

Methods and Materials

Intravenous Nutrition

Central venous catheters were inserted using either the infraclavicular subclavian, or internal jugular routes so that the tip of the catheter lay in the superior vena cava at the entrance to the right atrium. Non protein calories were provided by 25 or 50% dextrose, sorbitol and, in some cases, by 10 or 20% Intralipid.

Soluble insulin was added to dextrose in amounts sufficient to maintain the blood glucose below 200 and the urine sugar below 2%.

Protein sources were provided by the crystalline amino acid preparations Aminofusin 600 and Aminofusin Forte.* Additional sodium, potassium, calcium and phosphate were given on a daily basis and magnesium and the vitamin preparation M.V.I.† on alternate days. Sick patients in the catabolic phase usually require a daily albumin infusion of at least 25g. Iron, folic acid and vitamin K were given parenterally at least three times a week; vitamin B12 was given at three weekly intervals.

Solutions were infused through a Y connection in a ratio of 150–200 non protein calories per gram of nitrogen.

All patients were weighed daily and had a full hematological and biochemical profile. Renal and extra-renal losses were measured and the electrolyte content determined.

Plasma and urinary zinc were measured three times a week. In addition plasma copper was determined on a similar basis but urinary copper was measured, in earlier patients, at more random intervals.

Collection of Specimens

Plasma. Great care was exercised to avoid zinc contamination. Rubber stoppers were found to be heavily contaminated and collection was made into plastic tubes closed with plastic stoppers and containing two drops of Heparin (1,000u/ml). Heparin in rubber stoppered ampules is an unsuitable source and to be zinc free this anticoagulent must be made from sodium Heparin powder and dissolved in deionized water. Blood was taken into plastic syringes, avoiding excessive contact with the black rubber plunger and spun down, optimally within one hour but always within four hours to avoid zinc contamination from the zinc content of red cells and platelets.

Copper contamination is not a problem, but all collecting vessels were regularly checked.

Urine. Urine collections were made into plastic containers with an additive of 10 ml of concentrated (12N) hydrochloric acid.

Measurement of plasma zinc and copper. The methods of Davies et al. for zinc[4] and Sunderman and Roszel for copper,[25] have been combined so that both metals are determined on the supernatant after protein precipitation with a mixture of trichloracetic acid (TCA) and hydrochloric acid. Sunderman used separate additions of 1.4 N hydrochloric acid to dissociate copper from ceruloplasmin and followed this with 20% TCA. In this laboratory no difference has been found between results using Sunderman's procedure and results when hydrochloric acid and TCA are combined and added as a single reagent. The combined reagent was prepared by adding 12 ml of concentrated HCL to 10 g of TCA and made up to 100 ml with deionized water. Two milliliters of TCA/HCL reagent are added to 1 ml of plasma.

Blanks of deionized water, copper standards of 100 and 200 μg/100 ml and a zinc standard of 100 μg/100 ml were prepared similarly.

The tubes were covered with parafilm, shaken vigorously and allowed to stand for 30 minutes. They are

* Fawns & McAllan Pty. Ltd., Victoria, Australia.

† USV Pharmaceutical Corp. N.Y., U.S.A.

then mixed again and centrifuged at 2,500 rpm (1300 g) for 8 minutes.

Readings were made on a Techtron AA5 atomic absorption spectrophotometer using a nebulizer uptake of 3.0 ml/min. For zinc the 213.9 nm line is used with an air flow of 7.0 l/min; acetylene flame (flow 2.4 l/min); burner height of 9 mm; lamp current 5 mA and slit set at 200 microns. The scale expansion should be approximately ×2, setting the 100 μg/ml standard to read .200 on the absorbance scale.

For copper the 324.7 nm line was used with coal gas; (flow 3.3 l/min); burner height 8 mm; lamp current 3 mA and slit set at 100 microns. The scale expansion is approximately ×4, setting the 100 and 200 μg/100 ml standards to read 0.100 and 0.200 on the absorbance scale. No departure from linearity was found for either metal.

Urine. The same instrument settings were used except that for zinc the 1,000 μg/l standard was set to read .500 and the 1,000 μg/l copper standard to read .200. The urines were sprayed undiluted for zinc or diluted 1:10 for higher values. The copper levels although not highly precise, (±10 μg/24 hr) were considered adequate and it was not felt to be necessary to use the more accurate extraction method described by Sunderman.[25]

Case Reports

Zinc and copper studies have been carried out on 37 patients since June, 1973. Four of this group will be described in detail.

Case 1. S.G., a 23-year-old man with chronic perianal infection was first seen in June 1971. Barium studies and rectal biopsy confirmed Crohn's colitis with possible small bowel involvement. Imuran was started in October, 1971 and continued until June 1972 with no improvement.

Prednisone given from November 1972 until March 1973 was also of no benefit and his weight had slowly declined from 64 to 49 kg. Intravenous alimentation was commenced on March 23, 1973 and maintained without sepsis or catheter change for 9 weeks during which he achieved a weight gain of 12 Kg.

At the peak of maximum intake he received 5,400 calories as dextrose and intralipid and 32 g of nitrogen as crystalline amino acid. Total bowel rest was maintained.

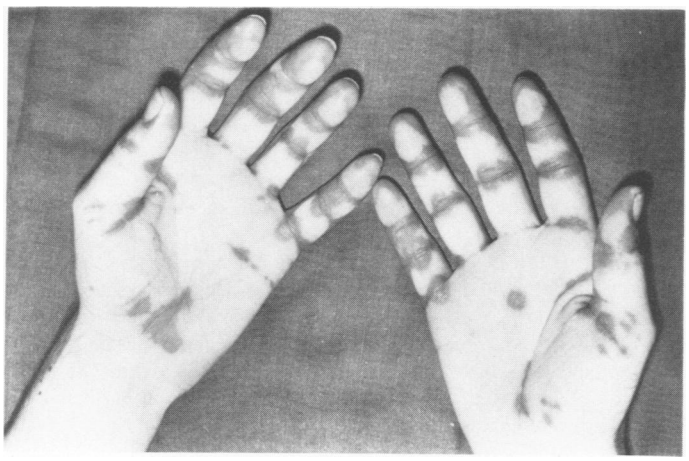

FIG. 2. S.G.—Distribution of lesions on the fingers.

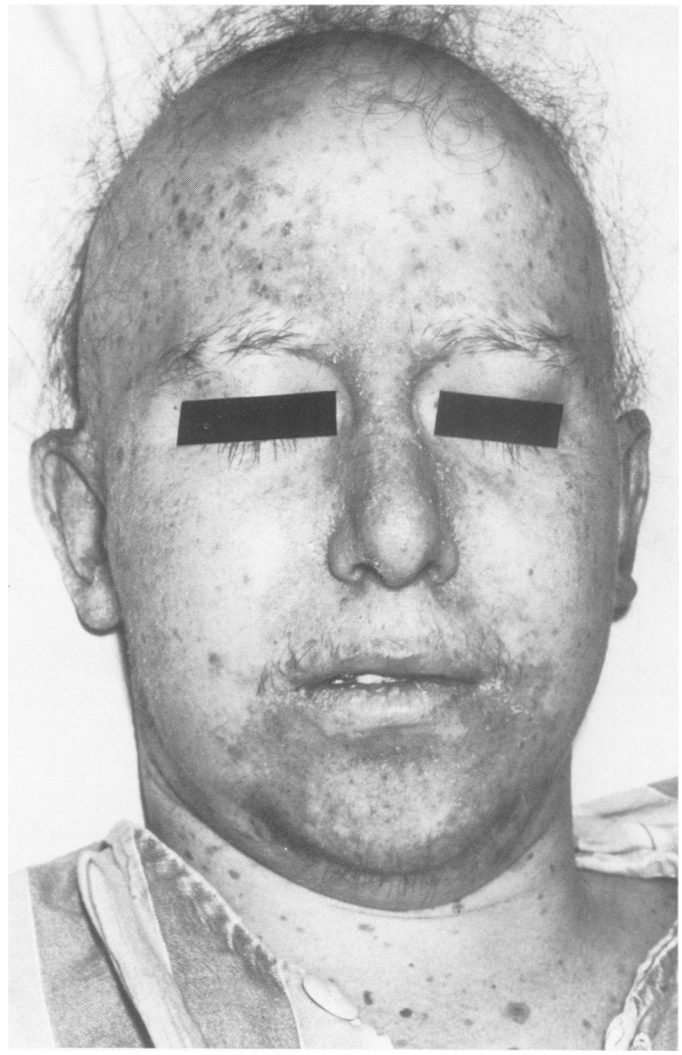

FIG. 3. S.G.—Marked alopecia, 29th May, 1973. The facial rash is healing.

During the third week of alimentation he developed crusted lesions in the naso-labial folds and on the chin. Culture from these areas showed a mixed growth of gram positive and gram negative organisms. Cephalosporins were used for one week without effect; scrapings for monilia were negative and treatment with 0.025% Fluocinolone Acetonide and 3% Clioquinol (Synalar-C)* was not helpful.

By April 28, in the fifth week of treatment, the rash had spread to involve the face, the perineum and scrotum, the extensor aspects of the elbows, the back and the fingers and toes. The lesions were seen to form as bullae, varying in size and sterile to culture and shallow pustules which broke down to large eroded areas which were granulating but not vegetating (Figs. 1 and 2). The condition was thought to resemble that variety of dermatitis vegetans known as pyodermite végétante of Hallopeau which may be seen in association with ulcerative colitis[2] and malnutrition.[16] Nevertheless, the extremely large bullae on the feet were unusual and vegetations were lacking.

Weight was maintained during this time despite persistent pyrexia to 38 C and a tachycardia between 120 and 140. He had become de-

* I.C.I.

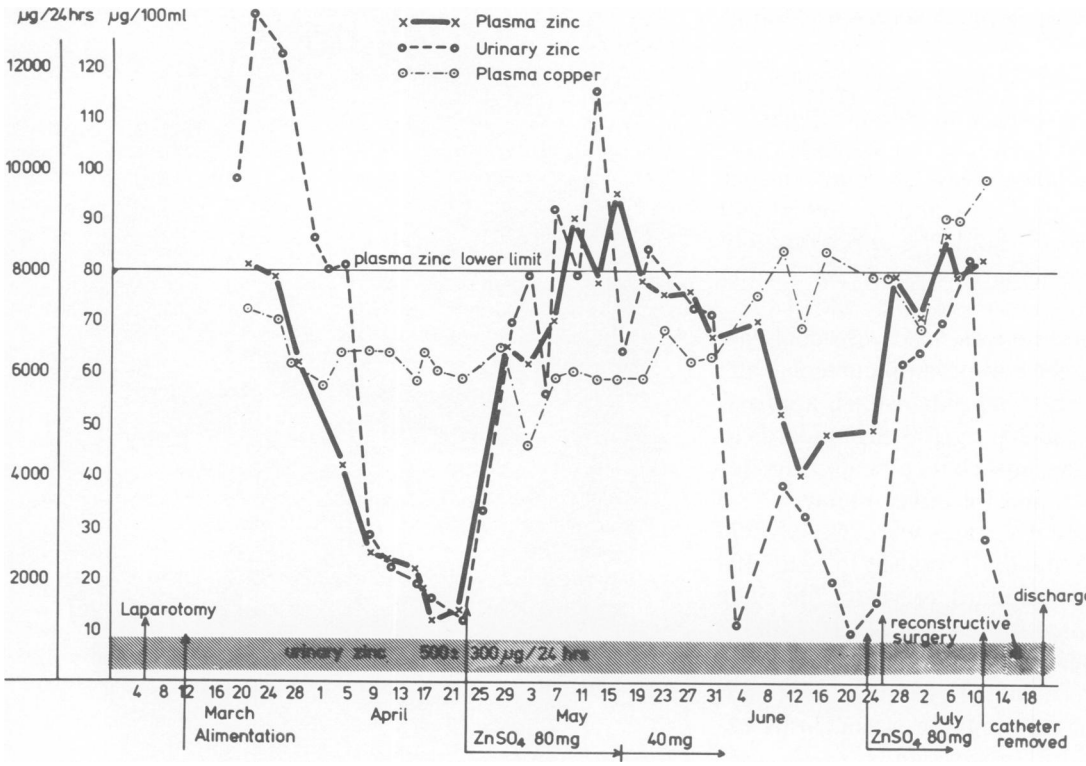

FIG. 4. V.G.—Urine and plasma zinc, and plasma copper during 17 weeks of total parenteral alimentation. The low point of plasma zinc was reached during the sixth week at the peak of a 15 Kg. weight gain.

pressed and withdrawn and was having 6 to 8 loose bowel movements a day without evidence of steatorrhea and there was no apparent change, either in the state of the Crohn's colitis, or the perianal sepsis.

In the sixth week of alimentation he showed obvious loss of scalp hair and progressed to almost total alopecia over the subsequent 3 weeks (Fig. 3). During this period some of the erosions dried leaving lightly pigmented areas but new lesions also developed.

On May 17, at the end of the seventh week, plasma levels of zinc and copper were measured. Zinc was found to be very low at 12 µg/100 ml (N = 80–130) but copper was less depressed, 62 µg/100 ml (N = 80–140). The urinary zinc excretion was also measured at this time and found to be 1160 µg/24 hr (N = 500 ± 300 µg).

Zinc supplementation was started on May 20, given orally as zinc sulfate, 220 mg daily and continued until June 7. Intravenous alimentation was discontinued on May 25, at the end of the ninth week, and by this time there was marked improvement in skin condition, stool frequency and some improvement in the mental status.

Biopsy of a healing lesion on the anterior chest wall showed hyperkeratosis with layers of keratin infiltrated by neutrophils. Apart from acanthosis the epidermis showed no other abnormality. There was slight edema and a mild increase in vascularity of the upper dermis.

Total proctocolectomy was carried out on June 27, from which time his convalescence was uneventful.

Appreciable restoration of hair growth was apparent by early August and the plasma zinc and copper levels on the 7th of that month were 75 and 167 µg/100 ml.

His subsequent course was complicated by osteoporosis and spinal pain probably secondary to inadequate calcium supplementation during alimentation. Since the correction of his calcium deficit he has remained in excellent health.

Case 2. V.G., a 36-year-old housewife, was admitted to Auckland Hospital for nutritional support on March 12, 1974. She had undergone a gynecological procedure on February 10, 1974 followed by laparotomy for intestinal obstruction due to widespread plastic adhesions. This second procedure was complicated by the development of a fecal fistula and total wound breakdown. She had lost 8 kg in weight and was very ill with gross sepsis, fever and tachycardia. On admission she was anemic, hypoalbuminemic, hypocholesterolemic and in a severe catabolic phase.

Intravenous alimentation was commenced through a left infraclavicular subclavian catheter. Catabolism was slowed and reversed with a gradual weight gain of 15 kg in 5½ weeks, control of sepsis and resolution of the abdominal wound to 4, matured, small bowel fistulous openings.

Zinc and copper levels in plasma and urine were measured on a regular basis throughout the 17 weeks of alimentation (Fig. 4). Urinary zinc excretion was initially high with a peak loss of 13,100 µg/24 hr. As the clinical state improved, and with reversal of the weight loss, urinary zinc excretion fell, so that by the end of the sixth week it was only 1320 µg/24 hr and near the normal range.

Zinc loss was also measured in the fistulous fluid and averaged about 1,000 µg in a daily volume of approximately 750 ml. Copper in the fistulous fluid was barely detectable but urinary copper loss was significantly increased and averaged 214 µg/24 hr. (N = 40–70 µg) over the 13 weeks of measurement without discernible change in the pattern of excretion. Despite this loss plasma copper never fell below 46 µg/100 ml and was usually near 60 µg/100 ml and rose to near normal values at the end of the twelfth week without copper supplementation.

Plasma zinc levels over the first 6 weeks fell sharply from the lower limits of normal to 12 µg/100 ml. Scaling and thickening of the palms and soles of the feet were prominent at this time and palmar erythema with scattered spider naevi over the left deltoid and upper chest wall were noted in the fifth week of treatment. Hepatic biopsy showed distortion, but preservation, of the lobular architecture, liver cell fatty change and cholestasis but the fibrous connective tissue was not increased. There was a notable increase in iron pigment.

Intravenous zinc supplementation was commenced on April 23, (the 7th week of alimentation) with 80 mg of zinc sulphate daily. Plasma zinc levels were rapidly restored to normal but were only just maintained when the daily supplement was reduced to 40 mg.

Zinc infusion was discontinued between June 1 and June 23, with an associated fall in both the plasma level and urinary excretion of this cation, but normal values were restored when treatment was reinstituted prior to operation.

Reconstructive surgery was carried out on June 26 with division of adhesions, minimal small bowel resection and three entero-anastomoses. The peritoneum and muscle defect was closed with nylon mesh and a flap of skin and subcutaneous tissue. Wound healing was excellent and all sutures were removed by the eighth postoperative day. She was discharged from hospital after 17½ weeks of total intravenous support and has remained in excellent health.

Case 3. E.G., a 58-year-old man, underwent an abdominal total gastrectomy for carcinoma on July 17, 1974. On the third postoperative day he developed a fever and tachycardia and by July 22 his condition had deteriorated with episodes of hypotension and a fistula draining foul, bile stained fluid. He was transferred to Auckland Hospital in critical condition with evidence of peritonitis, leakage of radiopaque contrast medium into the left subphrenic space and radiographic signs of hydropneumopericardium. At laparotomy both the oesophago-jejunal and the jejuno-jejunal anastomoses had clearly broken down and there was some doubt about the viability of the duodenal stump. The Roux-en-Y anastomosis was reconstructed and large sump drains inserted to the sites of actual and potential leakage. The pericardium, which contained a large quantity of infected fluid, was drained with a No. 28 Malecot catheter through a small left extra-pleural incision and intravenous alimentation was begun through a left infraclavicular subclavian catheter. The initial course was very stormy with severe sepsis, cholestatic jaundice and cardiac arrythmias with congestive heart failure. In addition a duodenal stump fistula was confirmed. Despite these hazards he gradually began to improve with control of infection, and reversal of catabolism was achieved by the end of the fourth week.

Urinary zinc losses were initially very high, reaching a peak of 22,600 μg/24 hr during the third week. With control of sepsis the excretion of zinc began to fall, but it did not approach the normal range until the middle of the sixth week.

Plasma zinc levels remained in the low normal range during the early critical phase but then fell slowly in association with the heavy urinary zinc loss at this time.

By the fifth week the esophagojejunal anastomosis had healed and a liquid and semi-solid diet was resumed. Plasma zinc rose, but not into the normal range and then declined further as anastomotic stricturing led to increasing problems with oral feeding.

Repeated dilatation of the stricture was carried out, but with increasing difficulty, and intravenous feeding was resumed on October 15 after a 6 week interval during which the patient lost another 5 kg of weight.

The intravenous caloric intake was quickly built up above 5,000 calories and a steady weight gain was achieved adding 10 kg in 3 weeks.

Urinary zinc excretion again fell to near the normal range but this

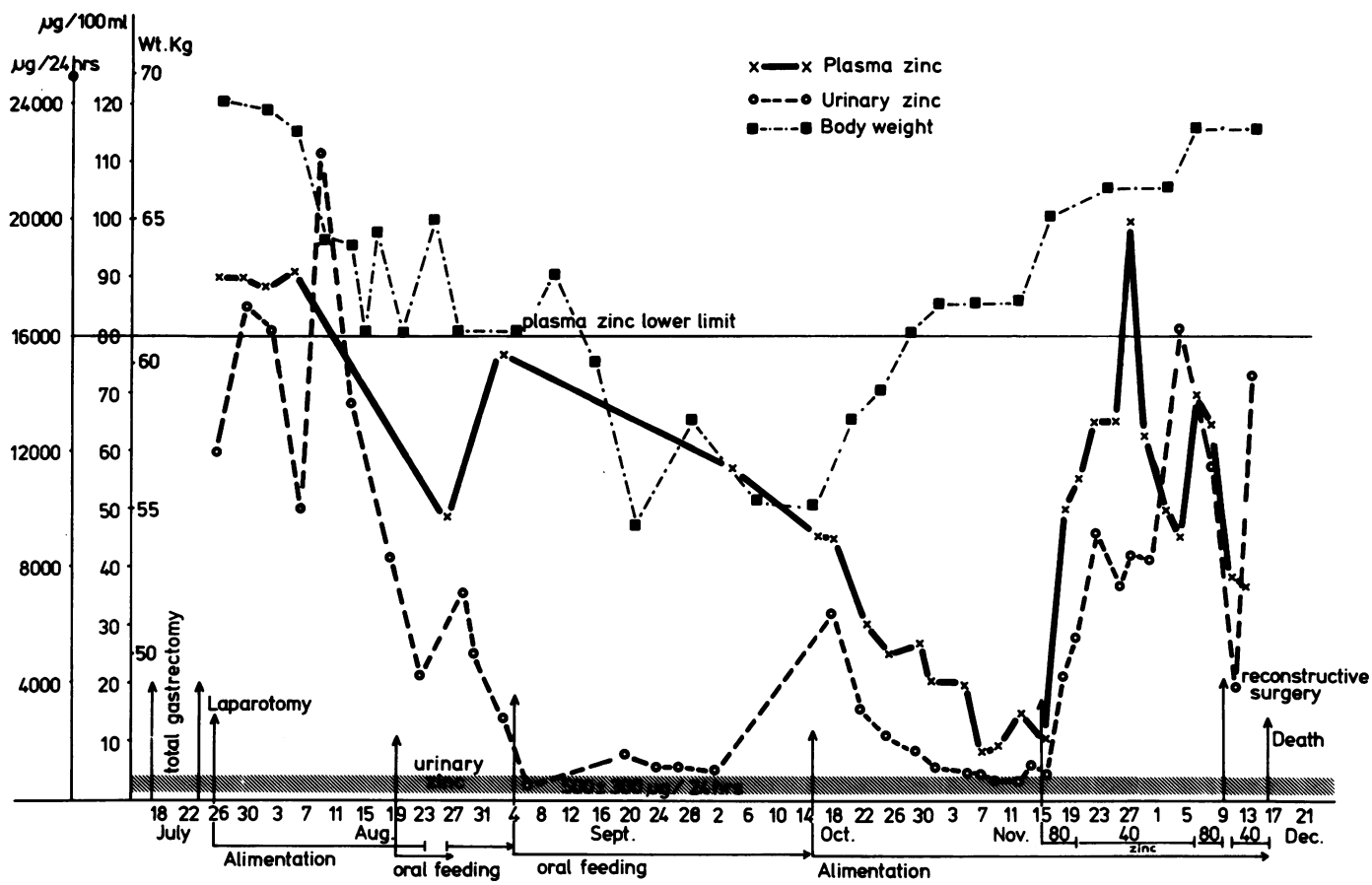

FIG. 5. E.G.—Urine and plasma zinc, and body weight changes. Although the peak urinary zinc loss has occurred at the height of the illness, plasma zinc has only fallen significantly during the phase of sustained weight gain.

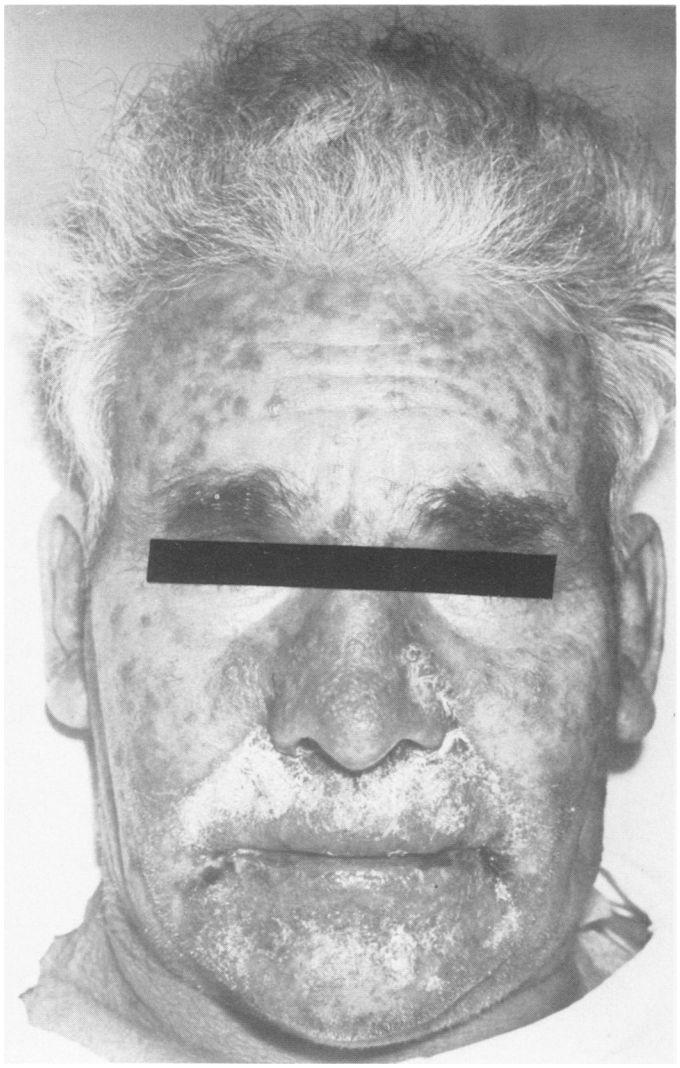

FIG. 6. E.G.—Severe peri-oral and para-nasal dermatitis.

did not influence the decline in plasma zinc which, by the first week in November, 10 weeks from the onset of the illness, had fallen to the very low level of 8 μg/100 ml (Fig. 5).

The patient's condition deteriorated and he complained of quite severe abdominal pain associated with marked tenderness and guarding in the right iliac fossa. Limited exploration through a right transverse incision failed to locate sepsis and gentamycin and cephalosporin were administered for 7 more days. In early November he also became mentally confused and developed a moist scrotal rash which was initially thought to be of fungal etiology although only an occasional yeast was cultured and there was no response to aqueous Gentian Violet. By November 8 there was also widespread involvement of the oral mucosa with swelling of the lips and very early perioral crusting. The scrotal rash was now regarded as an infectious eczematoid dermatitis but it failed to respond to gentamycin cream and by 15th November the skin changes were very severe (Fig. 6) and some loss of scalp hair was apparent.

Plasma zinc level remained very low at 9 μg/100 ml and intravenous zinc supplementation was commenced on this day at a dose level of 80 mg of zinc sulfate intravenously daily, reduced to 40 mg after 5 days. The response to zinc therapy was impressive and within 48 hours the rash and mental condition showed improvement although loss of scalp hair continued. Ten days after zinc treatment both the scrotal and facial skin changes had cleared completely (Fig. 7) leaving only faint pigmentation, but alopecia was very marked. The mental state was normal and his general condition excellent.

Reconstructive surgery was carried out on December 10 through a left thoraco-abdominal incision. The adhesions were dense in the left upper quadrant but with sharp dissection the anatomy was clearly displayed and the strictured anastomosis resected and reconstructed without tension.

His initial course was excellent until the fifth postoperative day when he rapidly deteriorated with bilateral chest signs, tachycardia and hypoxia. There was no response to vigorous resuscitation and he died within 24 hours.

Postmortem examination showed widespread bronchopneumonia. The anastomosis was intact but there was a 5 cm metastasis on the superior aspect of the right lobe of the liver, previously concealed by adhesions.

Plasma copper levels were followed throughout the course of the illness and values were depressed about 12% below normal during the period of intravenous alimentation. During oral feeding however normal values were maintained despite the increasingly inadequate caloric intake and weight loss which occurred.

Case 4. A.K., a 29-year-old woman, had a 3-year history of nausea,

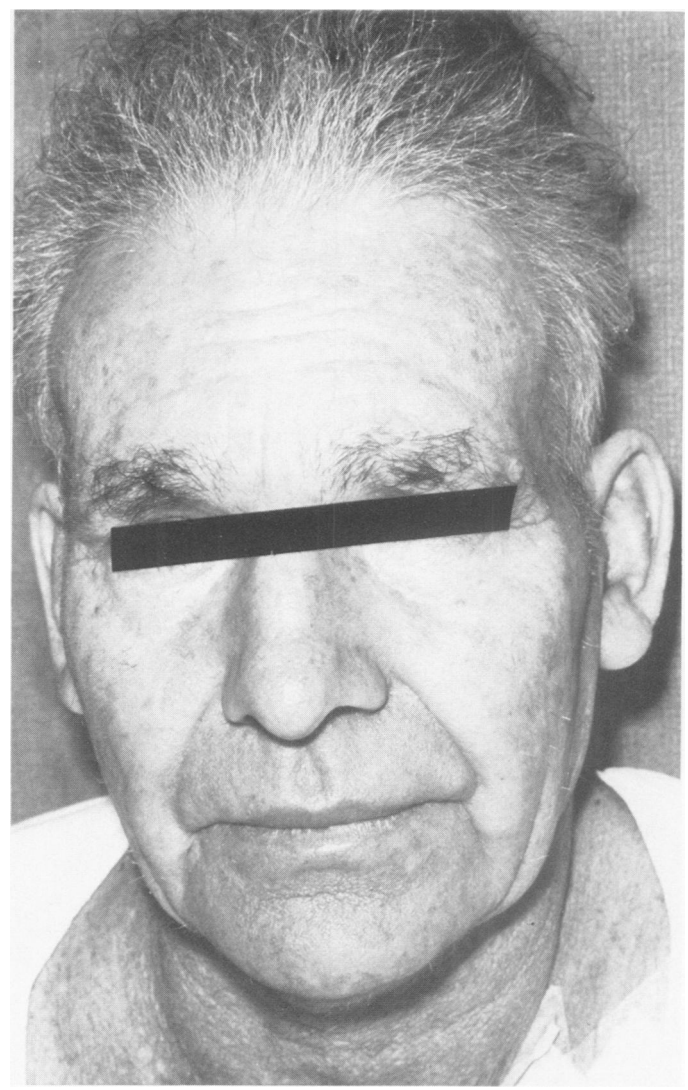

FIG. 7. E.G.—Marked improvement after 10 days intravenous zinc therapy.

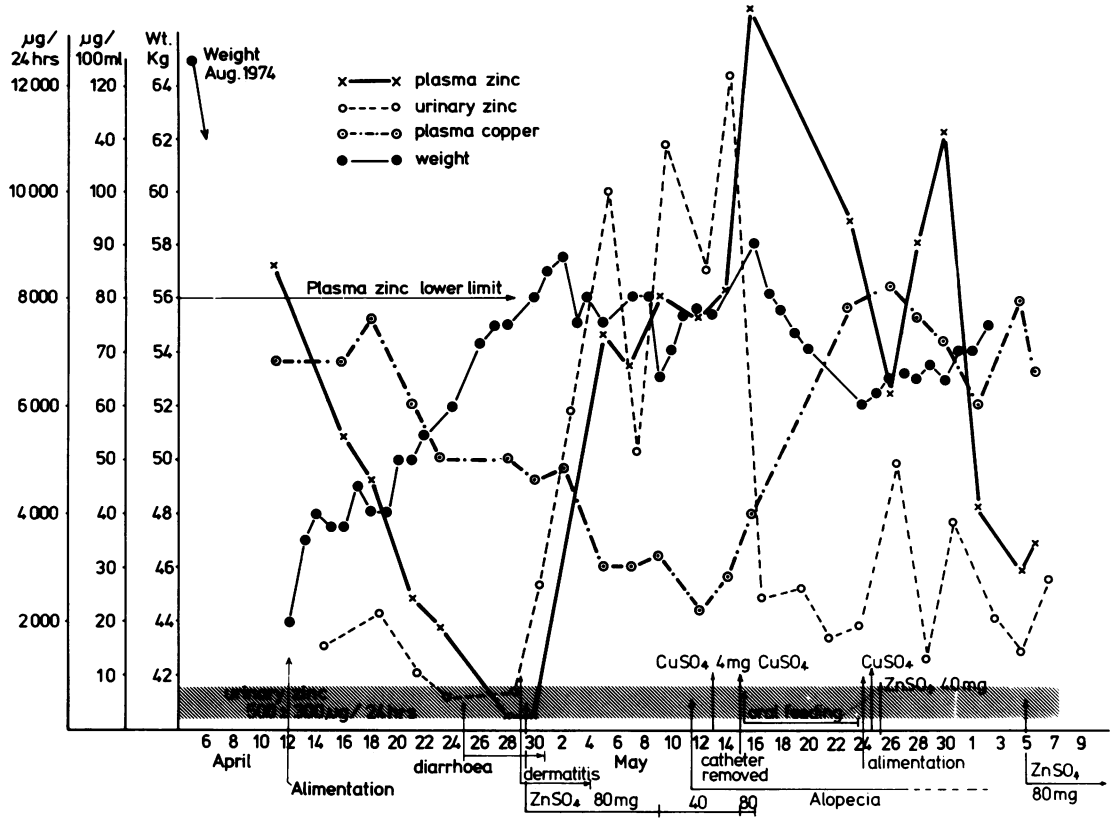

FIG. 8. A.K.—Plasma and urinary zinc, plasma copper and body weight changes during alimentation. Although urinary zinc loss is not excessive there is a striking fall in plasma zinc during the period of rapid weight gain. Low plasma copper has responded well to intravenous copper sulphate.

epigastric fullness and intermittent vomiting. X-ray studies suggested duodenal ileus and in May 1973 she underwent a posterior gastrojejunostomy. This procedure proved of no benefit. Nausea and vomiting increased and in October 1973 the gastrojejunal anastomosis was taken down and a duodenojejunostomy constructed. Following this operation she remained well for 3 months before a similar pattern of symptoms gradually returned and in May 1974 she was referred to this hospital for further investigation and management. Psychiatric assessment was not helpful and a period of treatment with Doxepin conferred no benefit. Metoclopramide HCl similarly proved of no value.

Radiological studies revealed atonia and grossly disordered duodenal and upper jejunal peristalsis with retrograde re-cycling through the duodeno-jejunal anastomosis and intermittent strong retrograde duodenal peristalsis.

In July 1974 further surgery was carried out restoring normal anatomy. There was no improvement and by April 1975 her weight had fallen 20 kg to 49 kg and she was re-admitted for intravenous alimentation and further study.

On April 12th a right infraclavicular subclavian catheter was inserted and the caloric intake built up in excess of 3,000 non protein calories. Response to alimentation was striking with an 11 kg weight gain during the initial 3 weeks.

At the onset of treatment the plasma zinc was 86 µg/100 ml but during the period of rapid weight gain it fell very sharply and within 16 days the level was unrecordable and certainly less than 10 µg/100 ml. Urinary zinc excretion was only modestly elevated, never higher than 2,200 µg/24 h and during the third week fell to within the normal range (Fig. 8).

Zinc supplementation was commenced on April 29th giving 80 mg of zinc sulphate intravenously daily. Plasma zinc levels quickly responded so that after 10 days the dose was reduced to 40 mg. Urinary zinc loss increased with supplementation to between 6,000 and 12,000 µg/24 h but this fell significantly after dose reduction.

Diarrhea first occurred on April 25th almost two weeks from the institution of alimentation and at a time when the plasma zinc level was below 20 µg/100 ml and falling. Over the next 3 days stool frequency increased but with zinc supplementation there was a rapid improvement and complete bowel control within 48 hours.

On April 29th, 4 days after the onset of diarrhea, the patient, who had been rather miserable and depressed, complained of a sore mouth and was noted to have an inflamed oral mucosa and small moist eczematoid areas in the nasolabial folds (Fig. 9). These changes coincided with a plasma zinc level below 10 µg and were consistent with zinc deficiency. Appropriate therapy was immediately commenced.

The response to intravenous zinc was very striking for not only was there a marked improvement in mood, but within 5 days the skin and oral mucosal changes had completely returned to normal. Nevertheless, on May 11th the first scalp hair loss was noted and this continued, despite zinc treatment, although the alopecia was less severe than in Cases 1 and 3.

The level of plasma copper also fell rather rapidly in this patient and reached a low point of 22 µg/100 ml in the fifth week of alimentation. Urinary copper excretion however was not strikingly elevated, except during the third week, when two measurements were over 200 µg/24 h and there was no increase in excretion following copper sulphate administration given intravenously in 4 mg boluses.

This patient remains under treatment.

Discussion

The human body contains between 1 and 2 gm of zinc. Distribution is wide with a predominant intracellular location largely as an essential cofactor of certain enzymes and proteins.[29] Within the plasma up to 98% of zinc is protein bound and only 2–8% has been shown to be ultra filterable. A specific transport protein equivalent to the role transferrin plays for iron has not been completely

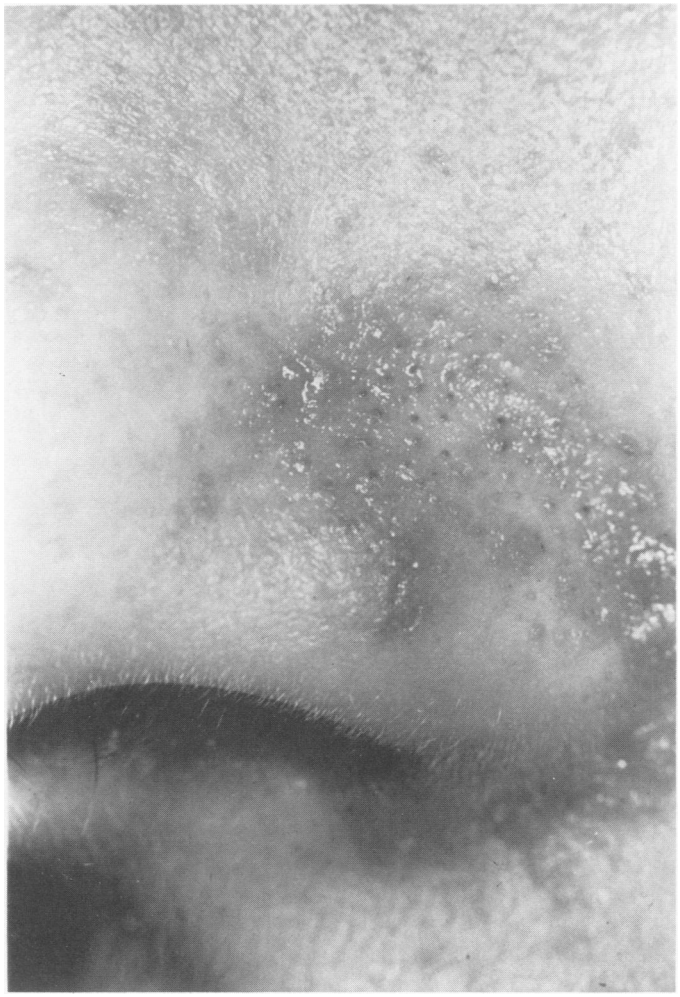

FIG. 9. A.K. — Very early eczematoid changes in the naso-labial fold.

characterized, although there is some evidence that this may be an alpha 2 macroglobulin.[21]

Under normal circumstances most of the average dietary intake of 8–15 mg of zinc is excreted in the faeces. In metabolic stress situations however, such as major surgery,[15] burns[10] and trauma to long bones,[3] urinary zinc excretion is considerably increased with losses of as much as three times normal. Much of this increased excretion is believed to originate from the catabolism of skeletal muscle, which is known to have a high zinc content.[6]

Many patients requiring nutritional support are in a severe catabolic phase and significant zincuria was therefore to be expected. Indeed, daily urinary losses of between 4,000 and 8,000 μg have been frequently observed but, in some patients, the zinc losses have been much higher and in one case reached 22,600, μg/24 h close to 50 times normal.

With control of the catabolic state the urinary excretion of zinc declines and as such it forms a useful index of metabolic control; generally associated with weight gain and a less frequent need for albumin supplementation.

Because the zinc requirement of growing rats is very low[27] it has not been easy to produce acute zinc deficiency in this species and the significance of zinc in nutrition was therefore not fully appreciated until the zinc deficiency state of hogs, fed an experimental diet comparing hydraulic and solvent process peanut meals, was recognized by Tucker and Salmon in 1955.[28] Known as Parakeratosis, the syndrome included impaired growth, severe dermatitis, alopecia, diarrhea, anorexia and vomiting, loss of weight and even death in severe cases. Similar signs and symptoms are now recognized as zinc associated in many other animal species including chickens, goats, lambs, rabbits and guinea pigs.[8]

In man, a syndrome of chronic zinc deficiency, characterized by hypogonadal dwarfism, was first recognized by Prasad in 1961.[22] The evidence for acute zinc deficiency however is much less precise and reports of the beneficial effects of oral zinc supplementation on wound healing[20] and varicose ulcers[7] are not conclusive because plasma zinc levels in these groups were invariably normal. Studies in the rat do, however, support a role for zinc both in the rate of healing and development of tensile strength of incised wounds.[23]

It is clear that 3 of the 4 cases described in this paper show many of the classical features of swine Parakeratosis with diarrhea, moist eczematoid dermatitis, particularly severe in the periorificial regions, and marked alopecia. Case 1 was particularly severe and the classical Beau's lines (Fig. 10) seen in this patient are indicative of growth arrest at the height of the illness which was also accompanied by confusion and depression.

Diarrhea, which may be severe, has invariably preceded other components of the syndrome and it may occur at plasma zinc levels not seriously depleted below the normal range. Apart from the described cases it has also been seen in a number of other patients, but all have responded promptly to zinc supplementation with complete control within 2 to 3 days.

Apathy and depression are more difficult to define but also seem to be fairly early features, whereas dermatitis and alopecia, which occurred in 3 of the group did not develop until the plasma zinc level fell below 20 μg/100 ml.

Dermatitis is first manifest in the naso-labial folds and oral mucosa but without treatment there is a rapid progression to more widespread involvement, particularly of the face and scrotum. The lesions have the appearance of being fungal in origin, particularly in the provocative setting of broad spectrum antibiotic usage, but anti-fungal agents are of no benefit whereas the response to zinc therapy is very striking.

Alopecia occurred some 7 to 14 days later than the dermatitis and the onset and initial course appear largely uninfluenced by zinc supplementation, although experience with Case 4 suggests that the severity of the hair loss may be reduced if the early skin changes are recognized

and promptly treated. Zinc associated alopecia appears to be completely reversible but full regrowth of scalp hair may take some months.

In the first case in this group the analogy to animal syndromes of zinc deficiency was not initially recognized and treatment with oral zinc sulphate was quite empirical and based on a randomly determined plasma zinc level. Marked improvement occurred from this time but as this also coincided with the resumption of oral feeding and in retrospect, quite severe calcium depletion, the etiological association with zinc deficiency was suspected but unproven.

These factors did not obscure the relationship in later cases and the highly effective response to treatment with intravenous zinc sulphate is convincing evidence of the significance of zinc in man. This is further supported by the recent recognition of Acrodermatitis enteropathica as an inherited human zinc deficiency disorder in infants and young children[17] in which the clinical features are very similar to those we have observed in adults.

Patients who are totally dependent on intravenous nutritional support, using essentially zinc free solutions such as the crystalline amino acids, intralipid and dextrose are clearly exposed to the threat of acute zinc deficiency. This is not, however, a simple matter of inadequate intake in a setting of severe catabolism and zincuria because these latter factors played little part in the etiology of the fourth case in which, despite only a modest urinary zinc loss, there was a rapid and progressive fall in plasma zinc. The significant association, clearly evident in this patient, and, in retrospect in other cases, is the striking fall in plasma zinc at a time of rapid weight gain. It would seem that a tissue demand for zinc during anabolism, in the absence of exogenous intake, rapidly depletes the plasma stores and that it is this factor, rather than the intracellular level of the cation, which determines the overt manifestations of the syndrome.

Although plasma zinc also fell to low levels in the second case, none of the features of acute zinc deficiency were observed, although scaling and thickening of the palms of the hands and the soles of the feet was obvious at this time and these features appeared to improve in association with zinc supplementation.

The reason why this patient failed to show more overt evidence of zinc deficiency is unclear. It is possible that the syndrome described is not one of pure zinc depletion despite the rapid response to this metal. Selenium and manganese are also essential trace elements and although there is no described deficiency in man a certain minimal tissue level may be required to prevent the more overt manifestations of zinc deficiency. Indeed the interaction between zinc and other cations is poorly understood and the renal handling of zinc differs markedly from other divalent cations.[26] Adequate zinc does however seem to protect chicks and particularly swine, from high levels of

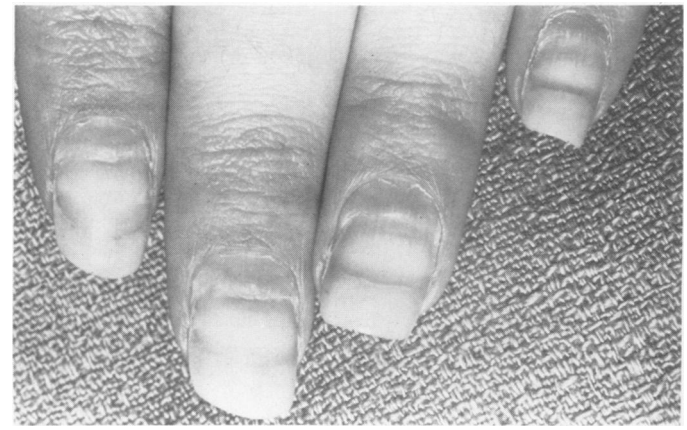

FIG. 10. S.G.—Beau's Lines: Nail growth arrest at the height of the illness.

calcium in the diet[18] and, by reverse analogy, the quite marked calcium depletion, which developed unrecognized in the first case, may have been responsible, to some extent, for the severity of the manifestations which occurred.

The treatment of zinc deficiency should not be reliant on the zinc content of the combination of solutions used for intravenous nutrition which is always less than 400 μg/day. Supplementation by plasma infusion is also inadequate to reverse the negative zinc balance of severe catabolism. Zinc sulphate is a satisfactory parenteral zinc preparation and used in doses of 40–80 mg daily is rapidly effective in reversing the clinical features of acute zinc deficiency.

Copper deficiency is said to be very rare in humans but it has been reported both in children[12] and adults[5] in association with intravenous alimentation. Anemia, leukopenia, and neutropenia, found in both groups, respond satisfactorily to copper administration.[30]

In the present group of patients, plasma copper values have generally fallen below normal, in association with increased urinary copper excretion and only two patients have received intravenous copper supplementation.

Experimental copper deficiency in pigs has shown the importance of this cation to both the absorption and utilization of iron[12] and this could explain the persistent drift into iron deficiency anaemia which we have observed in metabolically stable patients despite adequate serum iron and ferritin levels. For this reason copper should probably be included on a regular basis in all parenteral alimentation regimes.

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