Archives of Disease in Childhood, 1979, **54**, 909–917

Review article

Current status of zinc in health and disease states

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Even though brass, a zinc-copper alloy, had been known for centuries, metallic zinc was not isolated in Europe until 1509. The metal was then named zinken because of its superficial similarity to tin (German–zinn) (Wootton, 1910).

Zinc (atomic number 30; atomic weight 65·37) has a completed d subshell with 2 s electrons and the divalent cation is the only naturally occurring oxidation state. This relative stability, its ability to co-ordinate 4 or occasionally 6 ligands, and its capacity to act as a Lewis acid are probably fundamental to zinc's biological role. The biological importance of zinc was first discovered when Raulin (1869) demonstrated that it was necessary for the growth of *Aspergillus niger*. Subsequently, the ubiquitous distribution of zinc in nature was appreciated and the essentiality of zinc for higher plants (Mazé, 1914) and animals (Todd *et al.*, 1934) was established.

In man the medicinal use of calamine (zinc carbonate) is first recorded in *Papyrus Ebers* of 1550 BC (Ebers, 1937) but it was not until 1939 that it was suggested that zinc deficiency might contribute to the clinical manifestations of human vitamin deficiency syndromes such as beriberi (Eggleton, 1939). The first human zinc deficiency syndrome was identified in the early 1960s in malnourished adolescent boys in Iran and Egypt (Halsted *et al.*, 1972). A more profound deficiency state became apparent when Moyanhan and Barnes (1973) showed that treatment with zinc induced a complete and rapid clinical remission in a patient with acrodermatitis enteropathica.

Dietary sources and requirements

Good dietary sources of zinc (Underwood, 1977) are meat (20–60 μg (0·3–0·9 μmol)/g wet weight, and fish (15 μg (0·2 μmol)/g wet weight). Although cereals and vegetables have similar zinc contents (15–60 μg/g wet weight) to meats, the bioavailability of zinc from plant sources is reduced by their high phytate (inositol hexaphosphate) content which complexes the metal and prevents its absorption (Becker and Hoekstra, 1971). Diets containing phytate and zinc with a molar ratio in excess of 25:1 induce growth retardation in young rats (Davies and Oppin, 1979). Momcilovic *et al.* (1976) showed that the availability of zinc from a soya-based infant feed may be reduced by 20%. Complexation also occurs with fibre, hemicellulose, and clay; cellulose bulking agents reduce the absorption of the radioisotope ^{65}Zn (Becker and Hoekstra, 1971). Both calcium and phosphate reduce the utilisation of dietary zinc. Chelating agents such as EDTA, and animal protein may improve zinc availability from plant materials (Becker and Hoekstra, 1971), and its content in and availability from foodstuffs may be altered during food preparation (Halsted *et al.*, 1974).

The zinc content of cows' and human milk is variable (Picciano and Guthrie, 1976) and comparisons are unreliable. Human milk contains a low molecular weight zinc-binding ligand which probably facilitates absorption (see later); such a ligand is not present in cows' milk and zinc from this source to the human infant may be reduced (Eckhert *et al.*, 1977). A recent study on 6-month-old infants showed higher plasma zinc levels in those which were breast fed than in infants fed cows' milk-based formulae (Hambidge *et al.*, 1979). A longitudinal study has demonstrated that human breast milk zinc concentrations decrease with the duration of lactation (Vuori and Kuitunen, 1979). These are facts that need to be considered when evaluating the zinc nutritional value of infant feeds and of mature breast milk, especially when it is given to preterm infants in whom absorptive mechanisms may be immature (see later).

An adult consumes 10–15 mg (Underwood, 1977) of dietary zinc a day and the following age- and sex-related daily dietary allowances have been recommended by the National Research Council

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Food and Nutrition Board (1974): 0–6 months, 3 mg (46 μmol); 6–12 months, 5 mg (76 μmol); 1–10 years, 10 mg (152 μmol); adolescent children, adult men, and nonpregnant women, 15 mg (230 μmol); pregnant women, 20 mg (305 μmol), and lactating mothers 25 mg (382 μmol). A WHO Expert Committee (World Health Organisation, 1973) prepared recommendations based on the bioavailability of dietary zinc but all such recommendations can only serve as tentative guidelines. In healthy children in the UK, Alexander *et al.* (1974) demonstrated an average daily intake of 0·3 mg (4·6 μmol)/kg; about 20% of which was absorbed.

Absorption

Zinc absorption occurs throughout the small intestine but most rapidly in the duodenum and proximal jejunum (Methfessel and Spencer, 1973), and is probably a carrier-mediated process (Davies, 1974). *In vitro* uptake studies in human small intestinal mucosa suggest that it is also an active energy-dependent process (Atherton *et al.*, 1979) and isopycnic ultracentrifugation studies (unpublished) on isolated enterocytes from this material indicate that the absorbed zinc is almost totally distributed in the cytosol fraction. ^{65}Zn can be detected in plasma 15 minutes after ingestion and reaches a peak 4 hours later (Spencer *et al.*, 1966); patients with an ileojejunal bypass appear to have reduced zinc absorption (Andersson *et al.*, 1976).

Low molecular weight (8000–10 000) zinc-binding ligands (ZBL) have been reported in the small intestine and pancreas of rats, in the pancreatic secretions of dogs (Evans, 1976a), and in rat and human milk (Hurley *et al.*, 1978). Although the precise functions of these ZBL have not been defined, they almost certainly facilitate zinc absorption from the intestinal lumen. The mucosal ZBL is absent in the newborn rat which is dependent on the maternal milk ZBL for optimum zinc absorption. This dependence is lost after 18 days, by which time the mucosal ZBL has developed and the exogenous ZBL no longer enhances zinc absorption (Duncan and Hurley, 1978). A similar process may operate in the human since some term and low birthweight preterm infants have an impaired capacity to absorb zinc (Cavell and Widdowson, 1964; Dauncey *et al.*, 1977) and the human breast milk ZBL content is highest in colostrum and diminishes thereafter (Hurley *et al.*, 1978).

A low molecular weight cytoplasmic zinc-metalloprotein designated zinc-metallothionein (Zn-MTN) because of its high cysteine content, has been identified in the liver and small intestinal mucosa (Cherian and Goyer, 1978), and its synthesis can be induced by parenteral or oral administration of zinc (Richards and Cousins, 1975). Its precise function is undefined but it may participate in the homeostatic regulation of zinc metabolism and absorption, and provide a source of zinc at times of deprivation. The relationship between ZBL and intestinal Zn-MTN has not been clarified. Zn-MTN may regulate zinc absorption by sequestering zinc within the enterocyte. This possibility is supported by the observation that there is an inverse relationship between intestinal zinc uptake and intestinal MTN content (Richards and Cousins, 1976). It has been suggested that zinc is taken up from the enterocyte basolateral membrane by transferrin and conveyed to the liver via the portal vein (Evans, 1976a, b). The mechanism of cellular uptake of zinc and its incorporation into metalloproteins has not been elucidated but the latter probably occurs after the synthesis of the apoprotein.

Excretion

The main excretory route for zinc is in the faeces (Underwood, 1977). Biliary losses are small but pancreatic secretion may contribute 25% of endogenous zinc loss (Stake *et al.*, 1974). The relative contributions to the remaining faecal loss by desquamation of surface epithelial cells or intestinal secretion has not been defined.

Renal conservation of zinc results in a daily urinary loss <600 μg ($<9{\cdot}2$ μmol) (Underwood, 1977). The zinc concentration in neonatal urine may be 5 times that of adults (Cavell and Widdowson, 1964).

Sweat zinc loss is negligible in preadolescent children studied in temperate areas (Harrison *et al.*, 1975), but in tropical climates it may be significant. Secretion by this route is reduced with acclimatisation and in zinc deficiency states (Prasad *et al.*, 1963).

Body zinc distribution and mobilisation

A 70-kg man contains 1·4–2·3 g (21–35 mmol) of zinc (Widdowson *et al.*, 1951) and a term neonate has about 60 mg (0·9 mmol) (Widdowson and Spray, 1951). In the adult, this amount is about 40% of the total body content of iron and 10–20 times that of copper; there is relatively less zinc in the neonate and the corresponding ratios are 20% and 5 times respectively. Next to potassium, calcium, and magnesium, zinc is the most abundant intracellular metal and is located principally in the supernatant, microsomal, and nuclear fractions (Thiers and Vallee, 1957). Highest tissue concentrations (>500 μg ($>7{\cdot}7$ μmol)/g dry weight) are found in the uveal tract, and postpubertal prostate gland and seminal fluid. Hair, nails, skin, and bones have a zinc

content of 90–250 μg (1·4–3·8 μmol)/g, and the pancreas, liver, kidney, and muscle contain 140–230 μg (2·1–3·5 μmol)/g (Halsted *et al.*, 1974). Muscles in newborn animals have a similar zinc content but active muscle groups soon develop higher concentrations than less active groups (Cassens *et al.*, 1967).

Studies using ^{65}Zn show poor exchange of zinc deposited in bone, skin, and muscle and poor zinc mobilisation from these sources in rats at times of increased requirements, such as pregnancy (Hurley and Swennerton, 1971), suggest that these tissues which collectively contain 70–80% of the total body content of zinc do not provide an effective storage depot. In the young growing animal, however, release of bone zinc during the remodelling process may provide a reserve source (Brown *et al.*, 1978). The fetal zinc content increases in proportion to body weight and there is little evidence of intrauterine storage of the element; however the possibility that hepatic zinc in the neonate may provide an additional store remains to be elucidated.

Erythrocyte zinc (10–14 μg/g) (Halsted *et al.*, 1974) is predominantly located in the enzyme carbonic anhydrase and comprises 75–88% of the whole blood zinc content, the remainder being principally in the leucocytes (3%) and plasma (12–20%) (Vallee and Gibson, 1948); individual leucocytes contain about 25 times as much zinc as erythrocytes. Most of the plasma zinc is bound to albumin (50%) and an α_2-macroglobulin (30–40%), a small amount is associated with a β-globulin (transferrin) and with free amino-acids (2–8%) (Prasad and Oberleas, 1970).

Analytical values of plasma zinc vary slightly with the technique used for their assay but most laboratories providing such a service have determined their own normal range. The paediatric range established at The Hospital for Sick Children, London (Aggett *et al.*, in preparation) is 11–24 μmol/l (72–157 μg/100 ml).

Plasma zinc levels fall within hours of stress—such as surgery, trauma, or inflammation—and remain low with chronic stress. This is caused by a protein, leucocyte endogenous mediator (LEM), which is released from activated phagocytes and which enhances hepatic uptake of zinc and iron as well as synthesis of acute phase proteins including caeruloplasmin (Beisel *et al.*, 1976). Zinc is redistributed among its plasma ligands, and increased binding to low molecular weight ligands such as amino-acids may underlie the zincuria which can accompany stress. It is unclear at present whether LEM is a number of similar proteins or a single multifunctional entity. Plasma zinc levels are also frequently depressed in patients with neoplasia.

Assessment of zinc status

There is no reliable means currently available for determining the body zinc status in routine clinical practice. Plasma zinc levels are subject to acute variations and a single low value should be interpreted cautiously in conjunction with other factors, such as the patient's clinical condition. Serum levels are 16% higher than plasma levels partly as a result of the release of zinc from platelets and unavoidable haemolysis (Foley *et al.*, 1968). Hair zinc levels correlate poorly with plasma levels but provide historical information which is of value in epidemiological studies. Low hair zinc levels in one study were associated with zinc-responsive symptoms (Hambidge *et al.*, 1972) and probably represented previous zinc nutritional status. The interesting report of Heinersdorff and Taylor (page 958) showing a lower hair zinc content in boys aged 10–11 compared with similarly aged girls may reflect other, possibly physiological, influences which merit further investigation. Erythrocyte or leucocyte zinc determinations may prove to be more reliable then plasma levels, but the fact that the erythrocyte zinc content rises progressively during the first 12 years of life (Berfenstam, 1952) limits its application in children. Determination of urinary zinc is also unreliable, but it has been suggested that the urinary sulphate content could be of some value (Hsu and Anthony, 1971). In some studies salivary zinc has been measured (Henkin *et al.*, 1975a). Tissue analysis, ^{65}Zn turnover, and balance studies are essentially research tools. It should be stressed that all specimens for zinc determination must be collected with great care and stored in zinc-free containers to avoid haemolysis and contamination. Reduced activity of zinc-dependent enzymes, such as alkaline phosphatase, often accompanies a reduction in plasma zinc in deficiency states, and may provide a valuable clue particularly when facilities for determining zinc are not readily available. At present, the best criterion of zinc deficiency is an unequivocal clinical response to zinc administration.

Biological functions

Enzyme activities. Zinc is essential for the activity of at least 90 enzymes which participate in all the major metabolic pathways. Over 40 metalloenzymes exist in which zinc is bound tightly to the apoenzyme in specific stoichiometric ratios and in which it serves one or more structural, regulatory, or catalytic functions (Riordan and Vallee, 1976). Mammalian metalloenzymes include carbonic anhydrase, carboxypeptidases, aminopeptidases, alkaline phosphatase, alcohol, retinol, malate, lactate, glutamate, and glyceraldehyde-3-phosphate dehydrogenases. Some

metalloenzymes require additional metals for activity, cytosolic superoxide dismutase, for example, has a requirement for copper as well as for zinc.

Other metalloenzymes have only been identified in lower species and the particular metal dependence of an enzyme varies between species. Both DNA and RNA polymerases are zinc metalloenzymes in *Escherichia coli*; it has not been established that these are metalloenzymes in mammals but studies on animals indicate that thymidine kinase activity and nucleic acid synthesis are zinc-dependent in mammals. In some oncogenic viruses the reverse transcriptase (that is, RNA-dependent DNA polymerase) is a zinc metalloenzyme (Vallee, 1977). There is evidence that zinc is important for optimal activity of aspartate transcarbamylase, δamino-laevulinic acid dehydratase activities (Riordan and Vallee, 1976), ornithine transcarbamylase (Rabbani and Prasad, 1978), and in fatty acid metabolism (Hambidge *et al.*, 1978).

Zinc-deficient animals have impaired collagen synthesis and poor wound healing. This may reflect a generalised defect in protein and nucleic acid synthesis; however some evidence suggests that zinc deficiency alters the quantity and type of collagen cross links (Fernandez-Madrid *et al.*, 1976).

Cell function. Zinc is essential for all phases of the cell cycle, but, as yet, there is little evidence to relate this directly to its effects on nucleic acid and protein synthesis. Deficiency is associated with RNA disaggregation and increased ribonuclease activity (Prasad and Oberleas, 1973), and the ability of zinc to inhibit adenylate cyclase and phosphodiesterase may indicate a role in cell function and genetic expression by regulating the relative intracellular concentrations of cyclic-AMP and cyclic-GMP (McMahon, 1974). Cell replication rates in the oesophagus and pancreas of zinc-deficient rats are increased (Fell *et al.*, 1973), suggesting that a loss of genetic regulation precedes an effect on nucleic acid and protein synthesis. In human lymphocytes zinc acts as a mitogen, but here again the mechanism is unclear but appears to be mediated by monocytes (Rühl and Kirchner, 1978). Zinc stabilises plasma and subcellular membranes (Chvapil, 1976) as well as nucleic acids and microtubules (Nickolson and Veldstra, 1972); it stabilises lysosomes and high concentrations *in vitro* inhibit leucocyte mobility and phagocytosis while enhanced macrophage migration has been described in zinc-deficient guinea-pigs (Chvapil, 1976); membrane lipid peroxidation is increased in zinc deficiency states, and it has been proposed that zinc protects membranes from free radical oxidation (*Lancet*, 1978).

Endocrine function. Insulin is stored in the β-cells of the pancreas as a hexamer with 2 atoms of zinc (Adams *et al.*, 1969), and zinc appears to influence insulin binding and degradation at the hepatocyte plasma membrane (Arquilla *et al.*, 1978). In some studies impaired glucose tolerance and insulin response have been associated with zinc deficiency, but this has not been a consistent feature (Kirchgessner *et al.*, 1976).

Prostatic androgen metabolism is modified by the intracellular concentration of zinc, and both high and low tissue concentrations inhibit the transformation of testosterone to dihydrotestosterone (DHT) (Habib, 1978). Hartoma *et al.* (1977) demonstrated improved sperm counts and testosterone levels in hypozincaemic oligospermic males as a result of zinc administration; this treatment has also reversed uraemic impotence and increased DHT levels in patients with renal dialysis (Antoniou *et al.*, 1977).

Taste. It has been suggested that zinc may play a physiological role in taste (Henkin *et al.*, 1975a, b) and in this context is it of interest that 2 similar zinc metallo-proteins, gustin and nerve growth factor, have been isolated from human and murine saliva respectively and appear to combine with their respective taste buds and to be essential for their normal morphology and optimum function (Henkin, 1978).

Zinc deficiency states

Zinc deficiency can result from an inadequate dietary intake, malabsorption, increased body losses, intravenous feeding, or a combination of

Table 1 *Causes of zinc deficiency*

Inadequate dietary intake
Protein-calorie deficiency
Vegetarianism
Patients on protein-restricted diets
Synthetic diets
Malabsorption
Acrodermatitis enteropathica
Coeliac disease and other enteropathies
Pancreatic insufficiency
Chronic inflammatory bowel disease
Immaturity of absorptive systems
Increased body losses
Starvation
Burns
Diabetes mellitus
Ketoacidosis
Diuretic treatment
Proteinuria
Hepatic disease
Intravascular haemolysis (for example, sickle cell anaemia)
Porphyria
Chelating agent therapy
Chronic blood loss
Parasitic infection
Dialysis
Exfoliative dermatitis
Excessive sweating
Intravenous feeding

several of these predisposing factors. Some examples are listed in Table 1; in some instances there is no conclusive evidence of zinc deficiency (see above) but all constitute 'at risk states' and have been associated with markedly reduced plasma or serum zinc levels, some of which deserve comment.

Inadequate dietary intake. Protein-calorie malnutrition in the developing parts of the world is probably the most common cause of zinc deficiency, but Western populations may be at risk from a marginal zinc intake. This may be the case in vegans, vegetarians (Bodzy *et al.*, 1977), low socioeconomic groups subsisting on low meat diets (Hambidge *et al.*, 1972, 1976), and patients with chronic renal disease on low protein diets (Rose and Willden, 1972). Synthetic diets used in the treatment of children with inborn errors of metabolism and dietary intolerances require zinc supplements (Alexander *et al.*, 1974; Thorn *et al.*, 1978), and this may be the case for soya-based infant formulae although it has not yet been assessed. It is conceivable that the ingestion of texturised vegetable protein meat extenders and other novel protein sources, or calorie-controlled diets may be at risk. The need for fuller evaluation of feeding practices is stressed by the work of Walravens and Hambidge (1976) who demonstrated an improved growth rate in baby boys receiving standard formulae containing zinc supplements.

Malabsorption. Defective absorption of zinc may be secondary to the immaturity of its absorption systems, as may be the case in newborn babies especially if preterm (Dauncey *et al.*, 1977). Any individual with gastrointestinal disease is potentially at risk of developing zinc deficiency, particularly if the condition is long standing. Deficiency may result from intraluminal binding of zinc to high affinity ligands, impaired secretion of pancreatic ZBL, defective uptake into mucosa, reduced mucosal ZBL, or increased secretion into the intestinal lumen. The pathophysiological mechanisms which operate in the genesis of zinc deficiency in various disorders of the gastrointestinal tract present an important and challenging area for future research.

In 1973 Moynahan and Barnes made the important discovery that all the clinical manifestations of acrodermatitis enteropathica (AE) resolved strikingly with oral zinc treatment (Moynahan, 1974). This historic discovery undoubtedly added a major motivation and impetus to research concerned with zinc in health and disease states in man. Impaired ^{65}Zn absorption has been shown in AE (Lombeck *et al.*, 1975), and balance studies have shown that patients are in a net negative state with respect to zinc, and that this is accounted for by increased faecal losses (Aggett *et al.*, 1978). Although these observations suggest malabsorption of zinc, they do not define the pathogenesis of malabsorption. We have demonstrated a pronounced defect in the *in vitro* uptake of zinc in jejunal biopsies obtained from patients with AE, both when they are in remission and relapse (Atherton *et al.*, 1979). Thus the primary abnormality in AE may be defective zinc uptake into the enterocytes and the condition represents an addition to the known selective inborn errors of absorption (Harries, 1977). Recently preliminary evidence of defective zinc binding by duodenal juice of patients with AE has been reported (Casey *et al.*, 1978).

Increased body losses. Increased body losses may occur in a wide variety of conditions, as shown in Table 1.

Intravenous feeding. Intravenous feeding, particularly if prolonged, carries a risk of zinc deficiency. This is in part secondary to the variable but low content of zinc in the administered solutions (van Caillie *et al.*, 1978) and to the excessive urinary losses of zinc complexed with carbohydrates or amino-acids, or both (Freeman *et al.*, 1975). It is particularly likely to occur during an anabolic phase where there is an abrupt increase in body requirements and it is important to monitor zinc status during and after reintroduction of oral feeding (Fleming *et al.*, 1976).

Clinical manifestations of zinc deficiency

The variable and protean clinical manifestations of zinc deficiency are listed in Table 2. Anorexia, growth retardation, and impaired taste and olfactory sensation, are early features as is mood alteration. Most neurological features have been described in adults with induced zinc deficiency (Henkin *et al.*, 1975b); jitteriness and altered behaviour have been

Table 2 *Clinical manifestations of zinc deficiency*

Anorexia
Impaired taste and smell
Pica
Growth retardation
Hypogonadism
Impotence in renal dialysis patients
Depression, mood lability, impaired concentration
Intention tremor
Nystagmus
Dysarthria
Jitteriness
Photophobia, night blindness, blepharitis
Skin lesions (digits, perineum, parietal, nasolabial folds)
Paronychiae with monilial superinfection
Nails (growth arrest, loss, Beau's lines)
Hair growth arrest or alopecia
Delayed wound healing
Diarrhoea

reported in infants (Sivasubramanian and Henkin, 1978). Cutaneous signs range from a rough skin to a severe eczematous dermatitis affecting the digits, perineum, mouth, and nasolabial folds.

The biochemical consequences of zinc deficiency in human adults include reduced plasma alkaline phosphatase and lactate dehydrogenase activities, raised plasma ammonia, and increased plasma ribonuclease activity (Prasad *et al.*, 1978b).

Impaired night vision might be more associated with impaired retinol dehydrogenase activity (Huber and Gershoff, 1975) than with any specific effect zinc deficiency may have on retinol-binding protein synthesis (Carney *et al.*, 1976).

Impaired cell-mediated immunity with poor lymphoblast response, absent skin sensitivity reactions (Golden *et al.*, 1978), thymic hypoplasia (Golden *et al.*, 1977), and defective monocyte and polymorphonuclear leucocyte mobility have been associated with zinc deficiency and may contribute to the infections which occur particularly in patients with AE (Weston *et al.*, 1977).

In the pregnant rat even transient zinc deficiency results in an increased incidence of fetal resorption, stillbirths, and abnormalities of the CNS, skeleton, lung, urogenital tract, and palate in the offspring; moreover, the newborn rats tend to be of low birthweights with altered learning and behavioural patterns (Hurley and Mutch, 1973). The last features have also been described in rhesus monkeys (Sandstead *et al.*, 1978). The one abortion and the 2 congenital abnormalities reported in the 7 recorded pregnancies of 3 women with AE suggest that similar effects may apply to the pregnant human (Hambidge *et al.*, 1975). It has been speculated that the high incidence of anencephaly in some Middle Eastern countries may be the result of environmental zinc deficiency (Sever and Emanuel, 1973). Serum zinc levels in women having abnormal deliveries or low birthweight or preterm infants were lower than in women not experiencing such abnormalities (Jameson, 1976). A causal relationship was not established however.

Treatment of deficiency states

Zinc can be administered as a sulphate (22·5 mg (350 μmol) of elemental Zn/100 mg), acetate (30 mg (460 μmol) Zn/100 mg), or oxide (80 mg (1·2 mmol) Zn/100 mg) salts. Zinc gluconate preparations are also used. In some individuals the salt, particularly the sulphate, can be irritant to the gastrointestinal tract and in these circumstances the zinc salt may be taken with a meal or capsulated preparations may be better tolerated; but zinc is less efficiently absorbed with meals and from capsules (Oelshlegel and Brewer, 1977). These zinc salts have a wide therapeutic index and their doses should be adjusted according to the clinical response. In deficiency states an initial daily dose of 15 μmol elemental Zn/kg is given orally, or 5 μmol/kg IV. For maintenance IV therapy 2 μmol/kg is given daily at first. Larger oral doses are necessary in patients with AE. Plasma zinc and copper should be monitored frequently in these circumstances.

Zinc salts have also been used in the treatment of gastric ulcers (Frommer, 1975), rheumatoid arthritis (Simkin, 1976), and acne (Michaëlsson *et al.*, 1977). These applications await further evaluation and the consequences of prolonged oral zinc administration (see below) indicate that such use of zinc should be undertaken cautiously.

Toxicity

Zinc salts are usually well tolerated, but toxic effects have been associated with oral ingestion of elemental zinc (Murphy, 1970), zinc sulphate capsules (Moore, 1978), the use of water from galvanised containers for drinking (Brown *et al.*, 1964) and home dialysis (Gallery *et al.*, 1972), sucking zinc alloy toys (Chunn, 1973), prolonged oral zinc supplements (Prasad *et al.*, 1978a), and intravenous overdosage (Brocks *et al.*, 1977). Symptoms include anorexia, nausea, vomiting, lethargy, dizziness, diarrhoea, and bleeding gastric erosions; raised serum amylase and lipase were noted by Murphy (1970), and copper deficiency with hypochromic anaemia with reduced plasma copper concentrations have been reported after prolonged treatment with oral zinc. Intravenous overdosage has been associated with acute renal failure and death. Contact dermatitis to zinc salts (Freeman, 1942) and zinc allergy in diabetics on zinc insulin preparations have also been described (Feinglos and Jegasothy, 1979).

We thank the Medical Research Council and the Cystic Fibrosis Research Trust for financial support to investigate various aspects of trace metal metabolism in childhood, participation in this work having greatly facilitated the preparation of this paper.

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