ZINC DEFICIENCY IN MAN AND ANIMALS: ENDEMIC OR IMAGINARY?

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Summary

There is disagreement over the incidence and practical significance of naturally occurring zinc deficiency in man and animals. Part of the problem lies in differences in interpretation as to what constitutes a zinc deficiency, and part in not being able to accurately measure zinc status. This paper briefly describes what is known about zinc requirements from empirical studies, and offers some possible reasons why discrepancies might exist between predicted and observed outcomes in response to zinc supplements under natural conditions.

I. INTRODUCTION

While there is general agreement that both domestic animals and man have intakes of zinc below the recommended level (Underwood, 1977;Record et al. 1985; Thomas et al. 1986), there is little agreement as to the incidence and practical significance of zinc deficiency under natural conditions. For example, a review of the literature on human zinc deficiency reveals a wide divergence of opinions:

".. zinc deficiency is a world wide public health problem and effective methods of Zn enrichment of foods are needed". (Sandstead 1985).

"There is, as yet, no confirmation of widespread zinc deficiency in any community." (Golden and Golden 1985).

"... it is likely that zinc limited growth is quite common. If this is true then we can indeed generalise Hambidge's results and conclude that mild zinc deficiency affects an enormous number of children. Perhaps we should go back to adding ash to our food". (Golden and Golden 1988).

"It will not be possible to settle arguments surrounding zinc requirements until there are reliable measures of zinc status that can be routinely used. Clearly a great deal more research is needed in order to improve our understanding of the role of zinc in human nutrition". (Fairweather-Tait 1988).

"Nutritional zinc deficiency in pregnancy is common. Fasting serum zinc is a useful parameter that identifies patients at risk. Treatment with zinc citrate preparations reduces perinatal mortality" (Jameson et al. 1991).

"Marginal zinc status may be related to low birthweight, but there is no clearcut relation to pregnancy complications. ... Predicting whether poor maternal Zn status might result in pregnancy complications in humans is difficult because of the differing effects of zinc deficiency on pregnancy in different species" (Apgar 1992).

"Depending on the country, 5-30% of children suffer from moderate zinc deficiency,

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responsible for small-age-height" (Favier 1992).

The situation regarding the incidence of zinc deficiency in domestic animals is less controversial, although a consensus has not been reached. In Australia, soils in many regions are naturally deficient in zinc for plant growth, and pasture concentrations of zinc are frequently found to be well below that estimated by the ARC (1980) for normal health and production of sheep and cattle (Egan 1972; Masters and Somers 1980; Masters and Fels 1980, 1985; White et al. 1991). If zinc deficiency were defined as "a level of zinc intake below the recommended requirement", then a large proportion of the 160 million sheep in Australia would be classified as deficient for some period of the year. Despite this apparent low intake, there are only two reports of a production response to zinc supplements in sheep in Australia (Egan 1972; Masters and Fels 1980), whereas others have reported little or no effect (Masters and Fels 1985; White et al. 1991).

The aim of this paper is to examine some of the reasons behind the conflicting evidence and attempt to arrive at some conclusions about the practical significance of zinc deficiency in man and animals. There is insufficient space to adequately cover all aspects of zinc-responsive conditions, and since the role of zinc in reproduction has been recently reviewed (Apgar 1992), emphasis in this paper will be on zinc and growth.

II. ZINC DEFICIENCY

(a) Severe deficiency

Severe zinc deficiency is characterised in most mammalian species by anorexia, growth failure, alopecia and keratotic skin lesions (Underwood 1977). Age and stage of growth have a major bearing on the severity and type of lesions, with young rapidly growing animals being most susceptible. In sexually mature animals, severe zinc deficiency results in reproductive disorders in males and females (Apgar, 1992). Severe zinc deficiency has been rarely reported under natural conditions, but has been well described in several mammalian species under experimental conditions using semi-purified diets of zinc content < 3 mg/kg dry matter (DM) (Underwood 1977). There are, however, some notable naturally occurring cases of zinc deficiency. For humans these include hospital patients fed intravenous diets from which zinc has been omitted (Takagi et al. 1986), infants recovering from kwashiorkor and fed soy-protein-based diets (Golden and Golden 1981), infants with acrodermatitis enteropathica, a homozygous recessive genetic defect which results in reduced zinc absorption from the intestine (Moynihan and Barnes 1973), and infants of mothers carrying the gene for the "lethal milk" syndrome (Roberts et al. 1987; Atkinson et al. 1988). This last defect results in impaired transfer of zinc to breast milk.

Cases of severe zinc deficiency of similar aetiology to that seen in humans have also been reported in animals. Zinc-responsive parakeratosis has been reported in pigs fed natural diets containing high concentrations of soy-protein and calcium (Tucker and Salmon 1955). Murine pups suckled by dams carrying the lethal milk syndrome (Piletz and Ganschow 1978) show symptoms of severe zinc deficiency, as do calves with the genetic defect called adema disease. Adema disease is thought to be equivalent to acrodermatitis enteropathica. It has been reported in cattle of Friesian descent in Denmark, Germany, Italy and the Netherlands (Luecke 1984).

All these cases of severe zinc deficiency in man and animals can be prevented or reversed by supplying extra dietary zinc, and all appear to be rare.

(b). Mild, or sub-clinical zinc deficiency.

Mild zinc deficiency in sheep and cattle, characterised by subnormal growth, fertility and plasma zinc values but without other clinical signs, appears to be more widespread than earlier believed (Underwood 1981). Egan (1972) in South Australia reported a 20% increase in lambing in Dorset Horn ewes supplemented with zinc when basal pastures contained between 16 and 29 mg Zn/kg. Plasma zinc levels were not reported. Likewise, in Western Australia Masters and Fels (1980) reported a 14% increase in the number of lambs born to zinc-supplemented Merino ewes grazing pastures with a zinc content as low as 13 mg/kg. Mean plasma zinc concentration in the supplemented ewes was increased from the control value of 0.56 up to 0.74 mg/L. However, attempts at reproducing and extending these findings were not entirely successful (Masters and Fels 1985), suggesting that seasonal or other factors were influencing zinc supply or demand. For cattle, Mayland et al. (1980) reported a 6% increase in growth of calves in Idaho when their dams were supplemented with zinc. The forage contained less than 20 mg Zn/kg, but plasma zinc concentration was in the normal range for both control and supplemented cows and calves (>0.8 mg/L). In a study involving 21 farms in Scotland, heifer beef calves given supplementary zinc grew at a marginally increased rate of 0.05 kg/d compared with unsupplemented controls fed diets containing between 13 and 32 mg Zn/kg (Price and Humphries 1980). There were no effects on growth of steers or bulls, and the effect on heifers was only significant for the middle weighing period. Mean plasma zinc concentrations were in the normal range for animals on all properties (0.73 to 1.1 mg/L), and they were unaffected by zinc supplementation. There was no significant correlation between plasma zinc concentration and growth. Earlier studies had reported a growth response to zinc supplements in calves, but the responses were not significant in all replications and the reasons for the variations were uncertain (Perry et al. 1968; Beeson et al. 1977)

In contrast to these studies there are reports of no effect of additional zinc on growth or reproduction in cattle (Miller et al. 1963; Smith et al. 1964; Pringle et al. 1973) or sheep (Neathery et al. 1973; Bedi and Sawhney 1980; Pond 1983; Masters and Fels 1985; ; White et al. 1991) when dietary zinc concentrations were in a similar range.

For humans, if specific cases of conditioned zinc deficiency caused by alcoholism, medication and certain diseases are excluded, then there remain numerous reports of significant correlations between some disease or performance parameter and some measure of zinc status (see reviews by Hambidge 1991; Sandstead 1991; Apgar 1992). However, correlations are not evidence of causation, and there are often logical explanations for low zinc status that are unrelated to low zinc intakes (Underwood 1977, King 1990). Even the pioneering studies of Prasad et al. (1963a, 1963b) and Halstead et al. (1972) on Egyptian village dwarfs, which are quoted extensively as being the first reported cases of naturally occurring zinc deficiency in man, are flawed and do not constitute unequivocal evidence of zinc deficiency. The most serious problem with this work was the failure to administer zinc supplements independently of other treatments. In addition, the controls were not matched to the treated subjects and data on several subjects were deleted for no apparent reason. All subjects were fed hospital diets in addition to zinc supplements, and most were given iron supplements as well as treatment for parasite infections at the same time as zinc. The zinc supplements may have been responsible for some of the reported increase in growth, but unfortunately any possible effects of zinc could not be separated from those due to other

treatments. It was perhaps significant that there were no responses to zinc supplements in villagers when appropriate controls were included (Carter et al. 1969).

If we accept evidence only from supplementation studies with a blind or double blind design and with suitably matched controls, then two have reported a small effect of zinc supplements on vertical growth in children from the US and Canada (Walravens et al. 1983, 1989), and two reported no effect (Hambidge et al. 1979; Gibson et al. 1989). Gibson et al (1989) reported a response in a sub-group of children, but not in the main group of subjects initially selected. Where a vertical growth response was recorded, there was no effect of zinc on body weight. In all studies the number of subjects was small and they were selected on the basis of either low zinc status or short stature for age. For effects on pregnancy, two studies showed no effect on foetal weight or pregnancy complications (Hunt et al. 1984; Mahomed et al. 1989), one showed a slight effect only on one parameter (reducing hypertension), out of several measured (Cherry et al. 1989). Only in one study with 52 subjects, who were classified as high risk for delivering small-for-gestational-age babies, did zinc supplements reduce the number of induced labours and caesarean deliveries (Simmer et al. 1991).

Thus, for growth in young children fed western type diets, there is evidence of a small growth response to zinc supplements but it appears to be restricted to linear growth in a population group that is perhaps vulnerable to low zinc intakes or absorption. Likewise, for pregnant women there is evidence of a response to added zinc in terms of reducing the number of pregnancy complications, but there is considerable unexplained variability between experimental outcomes and the results are not conclusive.

III. ZINC REQUIREMENTS

The requirements for energy, protein and zinc for optimum growth in the immature pig, sheep, rat and child are summarised in Table 1. For the following discussion, a critical or minimum requirement is one that is determined experimentally using semi-purified diets. It is a level of concentration of zinc, below which growth is retarded and above which growth is optimum. A recommended allowance, on the other hand, is derived from a variety of sources and represents an amount or concentration of zinc which meets the needs of a population under practical dietary conditions. A recommended allowance includes a generous safety margin and as such is not designed for use as a diagnostic measure of deficiency in an individual. For the pig, the large (five-fold) difference between the critical value and the recommended value is due to the fact that practical diets are often based on soy-protein. Soy-protein contains high levels of phytic acid and this reduces zinc availability by forming a Zn-Ca-phytate complex in the gut (Oberleas 1983; Mills 1985).

The critical requirement for zinc for growth is related principally to protein requirement and rate of weight gain (Table 1). The Australian recommended dietary intake (RDI) for zinc for a 10 year old child is 6 mg/d, or approximately 10 mg/kg DM. The critical requirement has not been measured, but if we assume that it is half the RDI, then a 30 kg child has a critical zinc requirement for growth of 3.2 mg/day or 5 mg/kg DM. This represents a low amount compared with other species when expressed in terms of energy intake, but a relatively high amount when expressed in terms of protein and growth rate. The value of 320 mg/day per kg live weight gain

(LWG) for a child is eight to ten times higher than that for the pig, sheep and rat (Table 1).

Table 1. The protein, energy and zinc requirements for growth in the pig, sheep, laboratory rat and pre-adolescent child.

	Pig	Sheep	Rat	Human
Weight (kg)	30[1]	30[2]	0.1[3]	30[4]
Percent mature wt	12	40	18	40
LWG (g/d)	600	300	6	10
Feed intake (DM) (g/d)	1700	1300	15	640
Recommended diet composition:				
ME (MJ/kg DM)	13.3	10.5	17.3	13.4
Protein (N x 6.25;%)	16	15	12	5
Zinc requirement expressed as:				
Recommended allowance (mg/kg DM)	50[1]	20[2]	12[3]	10[4]
Experimental (critical) minimum (mg/kg DM)	11[5]	10[6]	5-12[7]	5[8]
mg/MJ ME	0.8	1.0	0.3-0.7	0.4
mg/kg protein	69	66	42-100	100
mg/kg live weight gain	31	43	13-30	320

1. NRC (1973). 2. NRC (1985). 3. NRC (1978). 4. NH&MRC (1991) for a ten year old child. 5. Derived from data on baby pigs (Hankins et al. 1985). 6. Mills et al. (1967); White (1989). 7. The zinc requirement for the rat is dependent upon the level of dietary protein (Hunt and Johnson 1992). 8. This is simply half of the Australian RDI (NH&MRC 1991). 9. Whitney et al. (1991).

Can this apparent difference in zinc requirements between the child and other species be justified? There is no evidence that availability of dietary zinc is less in humans than other mammals, or that endogenous loss is greater (Turnlund and King 1983; Hambidge et al. 1986), and neither is there any evidence that tissue concentrations of zinc are higher in humans than other species. For the sheep, the estimated minimum dietary zinc requirements for growth (43 mg/kg LWG, Table 1) represents about twice the mean concentration of zinc in growing tissue (24 mg/kg fresh weight; ARC 1980). This supports the observations by others that net utilisation of dietary zinc is efficient (> 50%) when zinc intakes are low (Weigand and Kirchgessner 1980; Baer and King 1984, 1990; SCA 1990). On this basis, if humans contain 30 mg Zn/kg fresh weight (Sandstead 1991), and if the zinc requirement for growth in humans is equivalent to that of animals, then the minimum net zinc requirement for growth of a 10 year old child growing at 10 g/d is approximately 0.6 mg/day, or 0.9 mg/kg dry diet. This is about half the factorially estimated requirement (WHO 1973). Add to this an estimated endogenous loss of 0.6 mg/d (Baer and King 1984), then the minimum dietary requirement is of the order of 2.4 mg/d, or 3.8 mg/kg diet if efficiency of absorption is 50%. There is no direct evidence that dietary phytic acid is reducing zinc availability in humans and recent studies suggest that the phytic acid content of human diets is unlikely to pose a practical problem for zinc absorption (see reviews by Mills 1985; Hambidge et al. 1986).

There are two implications from the results presented above. Firstly, since zinc

requirements are a function of growth rate, and since growth is a function of feed quality and quantity, it can be deduced that in the absence of any zinc antagonists, sheep or cattle grazing poor quality dry pastures containing low concentrations of zinc are unlikely to show growth responses to zinc supplements unless the dietary zinc concentration falls below 1 mg/MJ ME. This corresponds to a zinc concentration of approximately 6 mg Zn/kg DM in poor quality herbage. It is possible that pregnant and lactating animals will have a greater need for zinc, as demonstrated by Egan (1972) and Masters and Fels (1980) for sheep and Mayland et al (1980) for cattle.

The second implication from Table 1 is that the zinc requirement for growth in a 10 year old human can be met by less than 2.4 mg/d provided zinc availability is nt impaired in some way. To put this in perspective, a hamburger supplies 4.5 mg zinc (Whitney et al. 1991), and to meet normal energy requirements the average child consuming an average western diet would consume 8-12 mg Zn/day (Welsh and Marston 1983). This indicates that only under abnormal circumstances would the level of zinc in western diets be insufficient for growth. There has been speculation about possible zinc deficiencies in populations that consume diets based on cereal grains and legumes, but there is no unequivocal experimental evidence that these diets are deficient in zinc for growth. Vegetarians in western society have concentrations of zinc in plasma that are in the normal range (King et al. 1981; Keis et al. 1983).

How then can the reports of growth responses in zinc-supplemented children (Walravens et al. 1983; Gibson et al. 1989) be reconciled with what has just been presented? In the Walravens study, a total of 40 children aged between two and six were selected with the following characteristics: weight-for-age < 10th percentile, zinc intakes < 66% of the US RDA (NRC 1989), plasma zinc concentration < 0.7 mg/L and hair zinc < 105 mg/kg. Zinc supplements had no effect on plasma zinc concentration, and of the many variables measured, only vertical height was significantly increased in response to zinc, but only in the second half of the year, only in boys and only by 0.6 cm (<10%). Body weight was not significantly increased. Without any changes in plasma zinc concentration, it is difficult to know whether the reported effects were due simply to chance or whether some children really do have higher requirements for zinc than appears to be indicated by evidence from animal experiments and human metabolic studies. In the study of Gibson et al., children aged between 5 and 7 years old were selected for height-for-age percentiles < 15%, and with parents of height percentiles above 25%. The only significant response to zinc supplementation was an increase in linear growth in a sub-group of children with hair zinc less than 109 mg/kg. There was no effect on weight, and serum zinc concentrations were in the high normal range (1-1.2 mg/L). No clear justification was given for the selection of the cut-off value of 109 mg/kg and the authors admit to finding no other significant effects out of 20 examined. It is therefore not clear as to whether the increased growth in the selected sub-group was due to zinc deficiency or simply chance.

It is difficult at this stage to draw any firm conclusions about the incidence of zinc deficiency in the normal population of domestic animals and man. For man, the 1976-80 National Health and Nutrition Examination Survey of the zinc status of individuals in the US (Pilch and Senti 1985) showed that 1.3% of males and 2.9% of females between the ages of 3 and 74 had serum zinc levels below 0.7 mg/L. The incidence of low serum zinc in children was about 3% for both sexes. For the US these data suggest that approximately 6 million individuals have low serum zinc concentrations, and women and children are more susceptible. However, this cannot be construed as evidence that this number of people are at risk to zinc deficiency because serum zinc is notoriously unreliable as a predictor of zinc responsiveness, and besides, 0.7 mg Zn/L is

not normally low enough to be associated with reduced growth or signs of zinc deficiency in experimental animals. Nonetheless, the results provide some measure of the likely upper limit for the incidence of zinc deficiency in the human population in the US, and suggest that research needs to be targeted at individulas who are at risk to conditioned zinc deficiency, such as alcoholics, those on special medication or suffering from specific disease conditions that affect zinc absorption or retention.

For animals, there is evidence that marginal dietary zinc deficiency can limit production under natural grazing conditions, and that zinc supplements would prove to be cost-effective. However, responses have proven to be difficult to reproduce and there is a need for improved methods of measuring zinc status. With the exception of dietary phytate in monogastric species, there is a lack of information on factors influencing zinc availability in sheep and cattle. Research on this aspect of zinc metabolism will assist our understanding of zinc requirements in both man and animals.

In terms of diagnosing zinc deficiency, a reduced plasma or serum zinc concentration is currently the most sensitive and accessible indicator of zinc status under experimental conditions. However, it is also influenced to a variable degree by such factors as age, time to last meal, level of dietary protein intake, metabolic and infectious diseases, medication, contraceptive pills and pregnancy (Pilch and Senti 1985; King 1990), and is of limited value under practical conditions unless all these variables are controlled for. For this reason, plasma or serum should be sampled under standardised conditions, preferably soon after a "normal" meal and at a standardised time of day. Experimenters should also adopt standardised assessment criteria of zinc deficiency to avoid adding to the current confusion. Until a more useful measure of zinc status than plasma or serum zinc is developed, such criteria of zinc deficiency should include: (a), a reduced concentration of zinc in plasma of untreated subjects relative to both healthy individuals and appropriate zinc-supplemented subjects; (b), a reproducible physiological response to zinc supplementation; and (c), a demonstrable problem with the zinc supply. It is of concern that these three criteria were not met in most of the reports of zinc-responsive conditions.

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