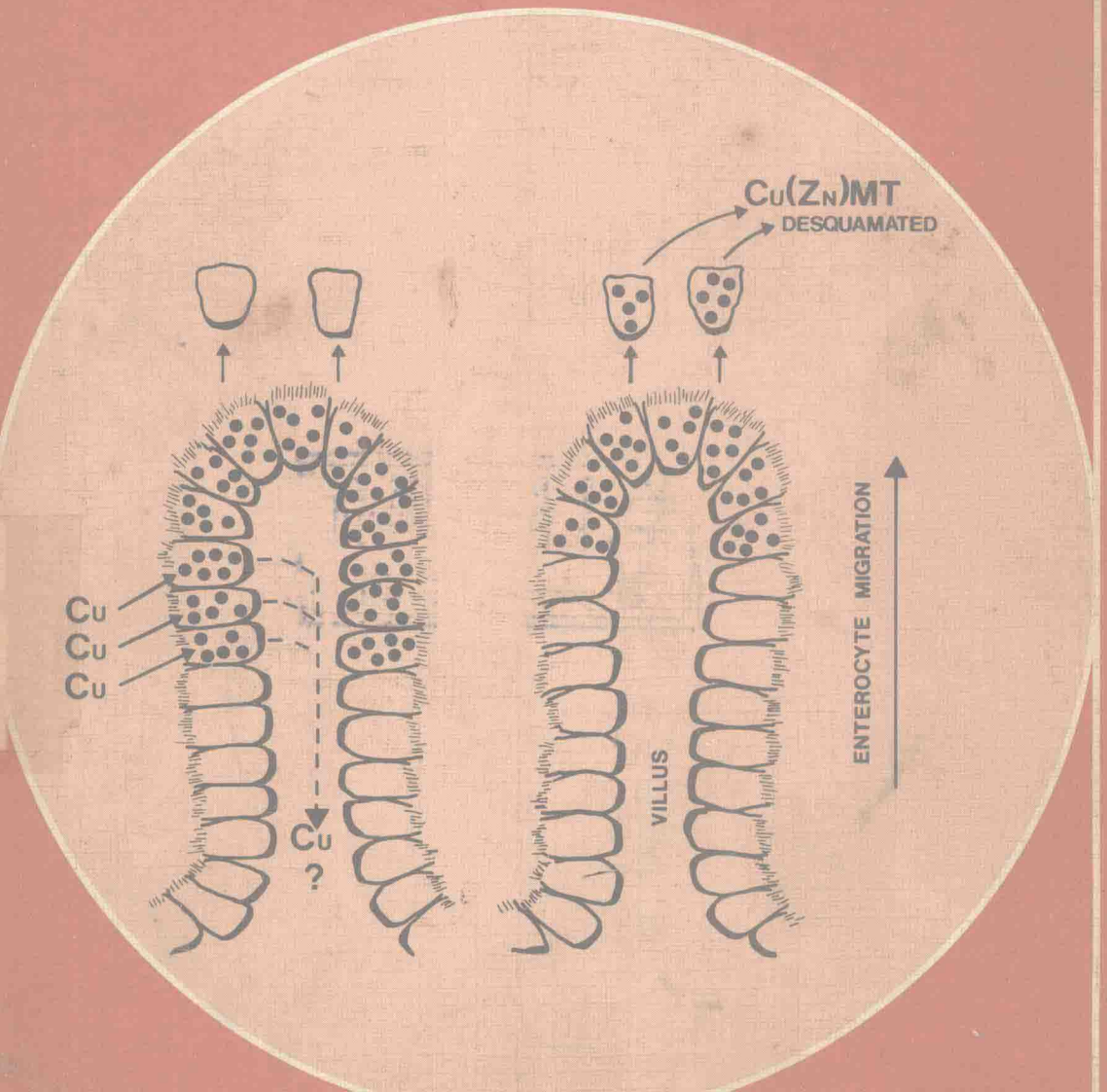
Ciba Foundation Symposium 79 (new series)

Biological Roles of Copper



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Biological roles of copper

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Chairman's introduction

COLIN F. MILLS

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As a participant in a previous symposium organized by the Ciba Foundation (1979), I appreciate that much of the success of the Foundation's meetings is due to the opportunity that they present for discussions to be informal, spontaneous and hard-hitting. One of the particular benefits of fairly small meetings is that the participants can get to know one another and can discuss outstanding and controversial problems.

At this time of rapidly developing studies of the trace elements and their relationship to health and disease, there is a great need for discussion of conflicting issues. We can share pride in some recent achievements, although other aspects are perhaps not quite so satisfactory, either because of questionable standards of experimentation or because of questionable extrapolations of scanty data. This meeting will give us an opportunity to discuss our present knowledge of the biological roles of copper and to assess the inadequacies in our experimental approaches and in their interpretation.

Work on individual trace elements has progressed in a variety of ways. Twenty years ago research on the essentiality of zinc was stimulated primarily by clear evidence of the importance of zinc deficiency diseases in domesticated livestock. Interest in the role of zinc in human nutrition and health was to develop much later, after it had been recognized that the diets of some socially deprived populations, and some therapeutic diets, could effectively be zinc-deficient and that some human subjects had genetic abnormalities in zinc metabolism. Studies of selenium show the same pattern of development. There was great initial interest in the role of selenium in diseases of farm animals but only within the last few years, as firmer evidence has appeared that selenium may be involved in the aetiology of some human diseases, has interest greatly increased in its relevance as an essential nutrient for humans.

The pattern is very different for iron. The relevance of iron to the incidence

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and consequences of anaemia in humans was the initial stimulus to studies of its role and its metabolism and provides the continuing justification for most current research effort. However, some recent enquiries into the physiological effects of iron deprivation that precede the development of severe anaemia appear to have been initiated more by concern about the ethical acceptability of deliberately depriving meat-producing animals of iron for organoleptic reasons than by anxiety about the relevance of such effects to human health.

The historical development of studies of the role of copper has strongly reflected the importance of copper deficiency as a cause of disease in domesticated animals. The early appreciation of the importance of copper in normal haemopoiesis was succeeded by the conclusion that copper deficiency anaemia was likely to occur only rarely in humans, and few studies were then initiated on copper in human nutrition. In contrast, the first investigations of the roles of copper in nervous tissue metabolism, in maintaining the integrity of connective tissue, in melanogenesis and in body growth all grew directly from the awareness that copper deficiency was a cause of disease in farm livestock.

The present appreciation of the incidence and important economic consequences of copper deficiency in domesticated animals is accompanied, however, by a frequent inability to predict either the development of copper deficiency or the severity of its biochemical and pathological consequences. In humans, interest stimulated by work on copper deficiency of a nutritional origin has been heightened by the recognition, first, of Menkes' disease as a genetic defect in copper metabolism and, second – as with zinc – of the limitations of some therapeutic dietary regimes that have provoked clinical signs of deficiency.

Those faced with the task of detecting or assessing the significance of copper deficiency diseases in both humans and domesticated animals face similar problems: although adequate techniques are available to measure changes in the copper content of tissues that are accessible for sampling they rarely indicate whether such changes have metabolic or pathological significance. For example, we do not yet know the implications of the reductions in plasma copper and caeruloplasmin activity that are early consequences of copper deprivation and that can often precede by weeks or months the first overt indications of deficiency.

Similarly, we are well aware that in the severely copper-deficient animal marked decreases occur in both lysyl oxidase and cytochrome *c* oxidase activities, yet we know little about the relative sensitivities of target tissues to such changes, or whether the activity of these enzymes becomes rate-limiting

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at early or late stages of the syndrome. Answers to such biochemical uncertainties will influence not only future pathological studies of the pre-clinical stages of copper deficiency but also, in a wider context, future decisions about the physiological relevance of marginal deficiency or of severe but brief periods of suboptimal copper supply.

For these reasons it may be appropriate to suggest that during this meeting we should pay particular attention to the likely biochemical and pathological effects that arise at early stages of the copper deficiency syndrome in humans and animals. We might attempt to assess whether the measurements commonly used to determine copper status provide a realistic indication of the likelihood of lesions developing when there are no overt signs of deficiency.

Is our understanding of the processes that govern the absorption, transport, storage and subsequent utilization of copper adequate to explain how these processes can be interrupted by the presence of metabolic antagonists in the diet or environment, or to anticipate correctly the consequences of genetic defects in copper metabolism? Without understanding these processes we shall continue to find it difficult to predict conditions that are associated with a high risk or to suggest effective prophylaxis.

I expect that our discussions will reveal many important gaps in our knowledge of the biological roles of copper and of the significance of copper deficiency diseases. The success of the meeting and the value of the published proceedings will directly reflect our willingness to discuss such issues frankly in the congenial environment so willingly provided by the Ciba Foundation.

Reference

Ciba Foundation 1979 Development of mammalian absorptive processes. Excerpta Medica, Amsterdam (Ciba Found Symp 70)

Dietary sources of copper

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Abstract The dietary intakes of copper by children and adults who consume free diets are often significantly lower than the recommended daily allowances of the National Academy of Sciences (USA) or the World Health Organization. These lower-than-recommended intakes of copper appear to be adequate for healthy individuals since states of copper deficiency have not been observed in the absence of an accompanying metabolic disorder. Copper deficiencies have arisen in preterm infants of low birth weight as a result of breast-milk diets, and in children and adults as a result of fluids that are used for total parenteral nutrition. This paper describes the use of trace-metal balance studies to evaluate the adequacy of copper intake from these sources and from synthetic diets that are used in the treatment of inherited and acquired metabolic disorders.

The richest dietary sources of copper are animal livers, crustacea, shellfish, dried fruit, nuts and chocolate. The copper concentrations in these foods range from 300–800 μmol/kg (20–50 mg/kg) – some 500 times higher than the concentrations in milk and dairy produce, which are the poorest dietary sources of this element (Table 1). The copper content of drinking water can be very high if copper plumbing is used and can provide daily intakes of 12 μmol (0.8 mg).

Adult western-type diets are reported to provide 32–64 μmol (2–4 mg) per day (Underwood 1977) and it is claimed to be difficult to produce a varied diet that will supply less than 32 μmol (2 mg) per day (National Research Council 1977). The validity of this latter statement is questionable when one considers some of the published data on the measured dietary intakes of healthy adults and children (Table 2). Few of the adult diets provide the Recommended Dietary Allowance (RDA) of 32 μmol (2 mg) per day and many contain less than half of this value. Harland et al (1977) have suggested that intakes of less than the RDA may be inadequate but Klevay (1978) has queried the accuracy

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TABLE 1

Dietary sources of copper

Food	*Copper content*	
	μmol kg⁻¹	*mg kg⁻¹*
Animal livers, crustacea, shellfish	300 – 800	20 – 50
Poultry	30 – 80	2 – 5
Fish	15 – 30	1 – 2
Cereals	30 – 100	2 – 7
Vegetables		
lima beans, dried split peas;	120 – 140	8 – 9
beets, cauliflower, spinach, mushrooms;	15 – 40	1 – 2.5
cabbage, corn, carrots, soybeans.	8 – 16	0.5 – 1.0
Fruit		
dried figs, apricots, plums, olives, avocados;	50 – 80	3 – 5.0
citrus fruits, berries, apples.	<15	<1
Nuts		
brazil, hazelnut;	170 – 220	11 – 14
walnut, coconut.	50	3
Dairy produce	1.5 – 6.0	0.1 – 0.4
Drinking water	<1.5 – 13.1	<0.05 – 0.84

of some of the higher copper intakes that have been reported. Since copper deficiency has never been reported in adults receiving varied diets, it may be assumed that the intakes in Table 2 were adequate for health even though they were significantly lower than the RDA.

A similar conclusion may be reached from a consideration of the data presented in Table 2 for infants and young children. All the children studied were healthy and none had any overt signs of copper deficiency, yet their copper intakes were less than the suggested daily allowances. These intakes, in terms of body weight, ranged from 1.2 μmol (75 μg) per kg per day at one month of age to 0.7 μmol (43 μg) per kg per day at three months (for the breast-fed infants) and from 0.36 μmol (23 μg) to 0.51 μmol (32 μg) per kg per day (for the infants and young children). These intakes are lower than the suggested values of 1.3 μmol (80 μg) per kg per day for infants and 0.63 μmol (40 μg) per kg per day for older children (World Health Organization 1973,

TABLE 2

Some measured dietary intakes of copper

Subjects	*n*	*Dietary intake of Cu*		*Reference*
		μmol/day	*μg/day*	
1–3 mth infants on breast milk (Finland)	27	3.9 – 4.9	250 – 310	Vuori 1979
Infants and children 3 mth–8 yr (UK)	11	2.5 – 14.2	156 – 900	Alexander et al 1974
Girls, 12–14 yr (USA)	14	46.3 ± 14.6	2940 ± 930	Greger et al 1978
Children and adults (USA)	20	3.1 – 54.8	200 – 3480[a]	Klevay 1978
Adults, 19–50 yr (New Zealand)	164	23.6 ± 12.6	1500 ± 800[b]	Guthrie et al 1978

[a]Only 2 out of 20 diets provided > 32 μmol (2 mg) Cu per day and 5 out of 20 diets provided < 16 μmol (1 mg) Cu per day

[b]Of 164 diets measured, 33 provided > 32 μmol (2 mg) Cu per day and 38 provided < 16 μmol (1 mg) Cu per day

National Research Council 1974). The lower intake of copper by breast-fed infants agrees with the earlier observations of Picciano & Guthrie (1976). The decrease in copper intake with time of lactation is to be expected from the significant 50% decrease in the copper concentration of human breast milk over the first three months of lactation (Vuori & Kuitunen 1979). Although it may be possible to produce copper deficiency in infants by prolonging breast-feeding this condition is more likely to occur in infants fed cow's-milk diets without supplementation, since cow's milk contains only one-fifth of the copper concentration in human milk.

The measurement of the dietary intakes of copper *per se* does not give sufficient information about the adequacy of the intake. Various dietary constituents such as phytate and fibre have been shown to impair the intestinal absorption of copper (Kelsay et al 1979), so some additional assessment of the copper status of the body is required. Valuable information about the adequacy of natural and synthetic diets can be obtained by the use of metabolic balance techniques in which the total dietary intake and total faecal and urinary excretion of copper (and other elements) are measured and the net absorption and retention are calculated. The net absorption is the difference between the dietary intake and faecal excretion, and the retention is the difference between dietary intake and the sum of the faecal and urinary excretion. Together with serum copper and caeruloplasmin measurements these results provide a good assessment of the body status of copper. Diets that have been evaluated using some of these measurements include: breast-milk

diets for preterm infants (Dauncey et al 1977); synthetic oral diets used in the treatment of inherited and acquired metabolic disorders and intolerance to food (Alexander et al 1974, Lawson et al 1977, Thorn et al 1978); and fluids used for parenteral nutrition (Shenkin & Wretlind 1978).

BREAST-MILK DIETS FOR PRETERM INFANTS

Fetal hepatic stores accumulate rapidly in the last three months of pregnancy, presumably to provide for the later needs of the full-term growing infant. Negative balances during the neonatal period have been well documented for full-term and preterm infants (Cavell & Widdowson 1964, Widdowson et al 1974) but it is the preterm infants with their much smaller body stores who are at greater risk of copper deficiency. Dauncey et al (1977) did serial metabolic balance studies of six preterm infants of low birth weight. The observed mean copper intake of 1.3 μmol (85 μg) per kg per day was higher than that reported by Vuori (1979) but the absolute intake of copper was lower, at 1.4–2.6 μmol (91–165 μg), because of the lower body weights of 1.05–1.43 kg. Copper balances were negative until about the 35th day of life and all the infants absorbed inadequate amounts of copper during the 72-day investigation. Three of the six infants experienced a net loss of copper during that period. The net accumulation of body copper was less than 10% of the intrauterine accumulation for an equivalent period. In contrast two light-for-dates but full-term infants were able to absorb significant amounts of copper from breast milk. The authors concluded that fetal immaturity of the alimentary tract was responsible for the impaired absorption of copper by the preterm infants and that such depletion of body copper stores could result in deficiencies in later infancy.

However, Wilson & Lahey (1960) did not detect any difference in indices of body copper status between one group of infants of low birth weight receiving only 0.22 μmol (14 μg) per kg per day for 7–10 weeks and another similar group receiving five to six times this amount. It is difficult to reconcile these observations with those discussed above and more particularly with the well documented cases of severe copper deficiency that have been reported in preterm infants who presented as early as three months of age (al-Rashid & Spangler 1971, Ashkenazi et al 1973).

SYNTHETIC DIETS

Synthetic diets are often used as part of the treatment of inherited and acquired metabolic disorders and of intolerance to foods. Some diets are

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