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# The physiological roles of copper

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Despite increasing evidence of the physiological importance of copper, the scarcity of diagnostically specific pathological manifestation of copper deficiency in human subjects makes it difficult to assess its precise nutritional significance.

Although the same diagnostic difficulty is encountered with domesticated animals it is widely appreciated that health and physiological performance may respond to increased provision of copper although specific clinical signs of deficiency are absent.

Recent dietary surveys and balance studies accompanied by biochemical investigation of copper-dependent functions suggest that human intakes of copper in some developed countries are declining to the point that the adequacy of copper status must be questioned, increasingly.

Copper is an essential component of at least eight enzymes in mammalian tissues. Its presence in at least six other enzymes has been suggested but whether as a contaminant or as an essential component remains a matter of controversy. Nevertheless, the roles for which its significance is not in doubt are of fundamental importance. Copper enzymes are involved in vital processes such as the control of cellular energetics for synthetic activities, for muscular activity and heat production, for the structural organisation of basement membranes and connective tissues essential for the integrity of both skeletal and soft tissues. The Cu-enzymes, caeruloplasmin and superoxide dismutase are involved in the fine control of potentially damaging peroxidative systems and in defences against infection.

Despite this quite extensive understanding of the enzymic roles of copper it is often difficult to identify cause and effect relationships between changes in cuproenzyme activity initiated by dietary deficiency of copper and the pathological changes that follow. While, for example, it is reasonable to suspect that a reduced activity of the cuproenzyme, lysyloxidase, accounts for defective cross-linking of connective tissue elastin and of some types of collagen, such understanding of the pathogenesis of resulting lesions in the cardiovascular system and skeleton is atypical. Thus, we cannot yet account for the particular sensitivity to a low tissue copper of specific forms of collagen and glycosaminoglycans that is revealed at early stages of copper depletion by damage to basement membranes of the heart, pancreas and kidneys. Nor do we know the origins of anaemia, neutropenia and defects in catecholamine metabolism during copper deficiency.

A wide range of clinical responses to copper deficiency is found in different species. Gross clinical manifestations are rarely specific. Exceptions are the ataxic manifestations of neurological damage in copper-deficient lambs ('swayback' or enzootic ataxia) and the characteristic structural damage to hair ('pili torti') in infants with genetically defective copper metabolism (Menkes' disease) which, like the 'steely' wool of copper deficiency in sheep, reflects an unidentified role of copper in mediating maturation of keratin. These exceptions apart, other consequences such as growth failure, increased susceptibility to infection, cardiac arrythmias and haematological changes typified by neutropenia and anaemia, lack diagnostic specificity and thus must be backed by more specific biochemical or histopathological evidence when the significance of copper deficiency is being assessed or the attempt made to quantify copper requirements.

The economic significance of copper deficiency in farm animals is established beyond question. Its significance as a cause of nutritional disease in man is clearly established for situations in which rehabilitation from malnutrition or chronic illness has been attempted with nutritional formulae providing too little copper. The consequences of such errors have included osteoporosis, neutropenia and, it is suggested, some indications of enhanced susceptibility to respiratory infections and emphysema.

The wider significance of copper deficiency in human health is now attracting greater attention in the face of

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evidence that some copper intakes are declining to levels that would induce pathological changes in experimental animals. There are reasonable grounds to enquire whether the copper intake of some populations in developed countries is now declining to levels that may begin to prejudice the integrity of processes most sensitive to a restricted supply of copper. These include protection of tissues against peroxidative damage induced by external challenges, maintenance of the integrity of basement membranes and connective tissue in the pancreas and cardiovascular system and, lastly, the maintenance of macrophage and neutrophil function in the defence against infection.

From a review (Mills, 1991) of published data on human studies of the influence of low copper intakes on cardiovascular function, blood pressure during exercise and biochemical evidence of changes in the activity of copper-dependent enzymes it appears likely that we must regard copper intakes falling within the range of 1·0–0·6 mg/day as increasingly likely to induce metabolic defects attributable to a low copper status. Because of the wide variability of data for individual subjects it is frequently difficult to interpret input/output balance data for copper. Nevertheless, published data from more than 200 individuals are not inconsistent with the view that intakes of <1·0 mg copper/day are probably insufficient to maintain an adequate copper status in many adults. Evidence from a recent UK dietary survey (Gregory *et al.*, 1990) indicating that the 2·5$^{th}$ percentile of the adult UK population has copper intakes lower than 0·8 mg/day suggests, when considered in the light of the above conclusions, that it would be unwise to disregard the possibility that a suboptimal status may induce pathological consequences in some individuals.

The fact that most early covert pathological effects of copper deficiency in all species lack diagnostic specificity should not be allowed to delay the quest for improved biochemical indices of deficiency in human subjects. In the face of evidence of a steady decline in copper intake of most Western societies it is increasingly unrealistic to assume that copper deficiency is only a problem during the treatment of malnutrition in the Third World.

## REFERENCES

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