

Copper and Human Health – A Review

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Copper Development Association

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Introduction

Although known to be a normal constituent of human tissues for over 140 years, copper was only recognised as an essential nutrient as recently as 1928. [1] The first good evidence of a nutritional copper deficiency was provided by studies on malnourished Peruvian children (6 months to 3 years) in the 1960s [2].

Much has since been learnt about the metabolism and importance of copper in animal and human nutrition; all indications are that further discoveries are just around the corner, particularly concerning the involvement of copper in several common diseases, including arthritis and cardiovascular disease. The significance of such involvements in either dietary or medical terms will require much more research. Although there is as yet no evidence of widespread copper deficiency in humans, the possibility that prolonged periods of low copper intake may be a predisposing factor in certain disease problems means that further elucidation of the mechanism by which copper functions could well prove to be highly valuable in solving such copper related diseases.

Information about human copper metabolism comes from several sources including studies on animals; biochemical investigations on processes known to occur both in man and animals that provide a basis for understanding the effects that might occur in man; studies of Menkes' disease and direct studies on humans suffering from copper depletion and deficiency.

It was the discovery in 1928 that healthy rats required both copper and iron to synthesise the blood protein haemoglobin [1] that triggered off investigations into the biological function of copper.

The earliest copper balance study, reported by Tompsett in 1936 [3], showed that humans excrete about 2.0 - 2.5 mg copper daily in faeces, urine, skin, saliva and menses. These values are somewhat higher than current estimates (about 1.6 mg copper per day) [4] of the minimal copper intake required to maintain balance, but curiously they are in line with the currently accepted recommended dietary allowances of the WHO [5] and the National Research Council (USA) [6] (2.0 - 3.0 mg Cu per day). Until recently little account has been taken of the losses of copper in sweat which may amount to 0.3 mg copper per day [7]. It is thought that the requirement during pregnancy is in the range 3-4 mg/day [8].

These values are to be set against a background of the total copper content of the adult body which is typically 70 - 80 mg [9].

The realisation that several diseases in man are associated with elevated serum copper levels clearly indicates the involvement and likely importance of copper in human health [10]; diseases in this category include Addison's disease, aplastic anaemia, Banti's syndrome, certain carcinomas, central nervous system disorders, collagen diseases, diabetes, Hodgkin's disease, iron deficiency anaemia, hyperthyroidism, leukaemia, malaria, pernicious anaemia, sickle cell anaemia, schizophrenia and thalassaemia. It must be said, however, that neither the mechanisms involved in the elevation of serum copper nor the implications of this for the pathogenesis of such disorders are fully understood.

Copper in Tissues

Copper is found in all organs and tissues of the human body, in concentrations varying from a few ppm to several hundred ppm; it is normally bound to proteins or to organic compounds and is not found as free copper ions. It is not surprising, in view of its capacity for storage, that high concentrations of copper are found in the liver; other organs that have high concentrations of copper are the brain, heart, stomach and various parts of the intestine.

	Copper $\mu\text{g/g}$ wet weight	
	Typical values [11]	
	Adult	Infant
Liver	5.1 (3 - 9.5)*	19.0 (2 - 57)*
Heart	3.0	2.6
Kidney	2.0	3.1
Brain	6.3	3.7
* Range		

The high concentration of copper in the foetal liver is remarkable. Not only is there a massive build up of liver copper in the normal child during the last three months of pregnancy, but the effect lasts about 4 years, by which time liver copper will have normally reverted to adult levels.

This build up of liver copper ensures adequate supplies for the infant in the first few months. Despite the absence of convincing evidence it is possible that the concentration of copper in the maternal diet may be involved in determining the rate of growth of the foetus and its post-natal development; in other words the high liver copper may simply be a reflection of the high demand of the foetus for copper. It must be said, however, that growth rates in the newborn appear to be more closely related to zinc than to copper.

In the case of Wilson's disease, which is considered later, it would appear that the liver is unable to develop from the high copper accumulating condition of the foetus to the normal adult condition of maintaining a stable liver copper status; the accumulation of liver copper in the case of Wilson's disease can be fatal.

Copper in the Blood and Fluids

Total blood copper levels in healthy humans normally range from 1.1 - 1.5 $\mu\text{g/ml}$, although these values can fluctuate with age, exercise and health condition [12]. Plasma copper levels, however, do not appear to increase after meals or decrease during short-term fasting, but in pregnancy the level of copper in the blood almost doubles just before parturition; values return to normal one to two months after delivery [10].

Major amounts of blood copper, normally about 90 - 95% of the copper in the plasma, is bound to ceruloplosmin, a plasma protein [13]. There is a smaller, but no less important fraction of copper found in association with plasma albumin and amino acids.

Copper found in erythrocytes is either associated with superoxide dismutase or with a complex mixture of amino acids [14].

All fluids of the body contain copper complexes, and very high concentrations are found in bile, and to a lesser extent in pancreatic juice. Bile provides the major excretory route for copper.

Considerable amounts of copper may be found in sweat, and some studies have indicated that this could account for as much as 45% of the total dietary intake of copper [15]. On the other hand, urine contains very low levels of copper, and it has been estimated that no more than 3% of copper intake is lost in urine [16].

Metabolism of Copper

Western diets commonly provide 1.5 - 2.5 mg copper per day. Minor sources of copper include tap water, copper bangles, intrauterine devices and copper cooking utensils; of these sources tap water may on occasions be significant but claims about the other sources can largely be discounted. Copper is mainly absorbed in the acid medium of the stomach and upper intestine very probably in complexes with amino acids such as histidine and with peptides; copper can also be absorbed from the lower parts of the intestine [17].

Not all the copper in the diet is absorbed and estimates vary from 25% to more than 60% of the copper intake being absorbed [18].

The presence of competing metals or of copper complexing agents in the diet can have a marked effect on the absorption of copper.

Zinc and cadmium (which is many times more potent than zinc) are very strong antagonists of copper absorption [19]. Prolonged or excessive supplementation of the diet with zinc can lead to copper deficiency, very probably due to the zinc stimulated induction in the intestinal mucosa, of metallothioneins which not only have the ability to complex excess zinc but also any copper that is present. The desquamation of such cells into the intestinal lumen leads to the excretion of the copper.

It is now fashionable to postulate that metallothioneins are responsible for copper homeostasis following their stimulation by "excess" copper, but the fact that copper is a weak stimulator of metallothioneins compared with cadmium or zinc, suggests that this is unlikely.

Large doses of iron may also reduce copper absorption, as does ascorbic acid, which itself enhances iron absorption [20]. This has been demonstrated in children suffering from severe protein malnutrition (Kwashiokor) in Peru [21].

Phytate and fibre can hinder copper absorption [22] but the effect is relatively minor and does not give rise to serious concern, a situation to be contrasted with that relating zinc absorption and phytate. Excess molybdenum is known to cause copper deficiency in ruminants, but the relevance to humans is not known [17].

On entering the blood from the gut, copper binds strongly to serum albumin, and it is only on arrival in the liver that it is incorporated in ceruloplasmin [23].

About 5% of the liver copper is normally associated with metallothioneins and the greater part is used for the production of ceruloplasmin.

A variable quantity is involved in biliary excretion in unknown forms. It is thought that there is very little reabsorption of biliary copper [24].

There is controversy about the significance of ceruloplasmin as a major carrier of functional intracellular copper. For example, injected ceruloplasmin has the ability to restore cytochrome C oxidase activity in rats to normality faster than free copper or other complexes of copper [25].

Biological Functions of Copper

Copper Enzymes

The nature of the fundamental importance of copper is clearly revealed when the enzymes that require copper are considered. The presence of the same enzymes in man and in the animals used in studies on the function of copper enzymes ensures the relevance to man of information gained from such studies.

Copper enzymes are widely distributed within the body; they perform several diverse functions [10] including transport of oxygen and electrons, catalysis in oxidation reduction reactions and the protection of the cell against damaging oxygen radicals.

At least ten enzymes are known to be dependent upon copper for their function, and whilst this may be a small number, relative to zinc dependent enzymes, it is self evident that the impaired function of any enzyme is likely to have deleterious effects.

Cytochrome C oxidase is required by cells to produce the energy needed to drive biochemical reactions.

Dopamine B hydroxylase is required in the conversion of dopamine to noradrenaline, a neural hormone that plays a vital part in the transmission of nerve impulses.

Lysyl oxidase is required for the proper cross-linking of elastin and collagen during the building, maintenance and repair of connective tissue [26].

Superoxide dismutase, which is being given an increasing amount of attention, is required to prevent the accumulation of the superoxide radicals which cause cellular damage; the enzyme responsible is a copper/zinc metalloenzyme found in the cytosol of all cells [27].

Copper is also required for a number of amine oxidases that are responsible for the breakdown of amines that are no longer required.

The involvement of copper in these varied enzyme systems means that disturbances to the copper metabolism have the potential for several quite wide reaching effects; some are general through the provision of energy, whilst others are more specific via disturbances to connective tissue and the nervous system.

Haemoglobin Synthesis

The finding, in rats, that copper and only copper prevented an iron resistant anaemia has been followed by other work that has revealed a remarkable interdependence between copper and iron. In pigs, for example, copper deficiency can lead to defective absorption of iron from the gastrointestinal tract, a restricted flow of iron from reticuloendothelial cells to the plasma, excessive retention of iron in the liver, and an impaired production of haem [10]. Ceruloplasmin plays a key role in mobilising iron from the reticuloendothelial cells.

Copper in Pregnancy

There can be little doubt that copper plays a major part in the rate of foetal growth and early post-natal development. It is likely that full-term infants are able to withstand the stresses of a mildly copper deficient diet for several months after birth, whereas, in contrast, premature infants with reduced storage of liver copper are much more likely to develop copper deficiency [28].

Chronic diarrhoea can be a predisposing cause of copper deficiency, as was the case in the study of malnourished young children in Peru in which copper supplements modulated, but did not correct, the severity of the deficiency [29].

Although there has been an isolated case of a copper responsive diarrhoea in a child [28], it seems more likely from studies on rats and cattle (but not sheep) that copper deficiency in children arises because of the diarrhoea and the severe losses of copper from the body [30]. More awaits to be learnt about this aspect both in humans and in other species.

A pertinent, and as yet unresolved question, exists as to whether infants, especially in the first few months normally get adequate amounts of copper. The use of diets and formulae based on

unfortified cows milk which is significantly lower in copper than human milk, enhances the concern [28].

The WHO recommend that infants receive 80 μg Cu per kg per day and older children 40 μg [5]. These levels are to be contrasted with the accumulation of copper by the human foetus between 28 and 36 weeks gestation of about 50 μg per kg per day and the supply of 80 μg Cu per kg per day by 200 ml per day human breast milk [31]. In contrast 200 ml of cows milk would supply only about 25 μg Cu.

The provision of such amounts of copper to the foetus and in milk means that daily intakes of copper during pregnancy and breast feeding should be 3 - 4 mg per day [8].

Women on oral contraceptives have considerably increased serum copper concentrations (double normal) [32] and accumulate more copper, which curiously is likely to be beneficial in the event of pregnancy. Release of copper from intrauterine contraceptive devices containing copper has been shown to be significant, amounting to about 10 mg copper per year [33].

The rapid accumulation of copper in the least three months of pregnancy means that consideration should be given to treating all premature infants with small doses of copper for several months to prevent copper deficiency.

Infants who become copper deficient due to the exclusive consumption of cows milk, or of a copper-free diet, are reported to develop hypochromic anaemia, microcytic anaemia, hypoferraemia, and hypoproteinaemia [34]. Growing children have a high requirement for copper which can not usually be met by cows milk. It is thought that the disturbances to blood formation are mainly due to defects in iron transport in the gastrointestinal tract induced by copper deficiency; dramatic reversal of the symptoms is reported following oral administration of copper [8].

Fertility and Reproduction

Copper deficiency in cows can delay oestrus, and in rats and guinea pigs it results in a greater incidence of foetal death and resorption [12].

Pigmentation

One of the early signs of copper deficiency in animals is loss of colour in hair or achromotrichia. The chemical basis for this phenomenon is an alteration to the metabolism of tyrosine, a precursor of melanin.

Nerve Function

Several disorders of the central nervous system including ataxia, tremor, clonic seizure, hypomyelination or demyelination and reduced levels of sphingolipides are symptomatic of copper deficiency [10].

Experimental animals raised on copper deficient diets show necrotic lesions in the brain [35].

The function of copper in the brain is probably associated with dopamine and noradrenaline, which are found in subnormal concentrations in the brain stem region of lambs suffering from swayback and in brains of copper deficient rats [36]. Low adrenaline and dopamine concentrations are associated with Parkinson's disease in humans, a disease characterised by mild tremors and motor disorders [37].

Protection Against Oxygen Radicals

The dismutation of super oxide anions by the copper zinc enzyme superoxide dismutase renders the potentially damaging superoxide anions less harmful by converting them to less reactive H_2O_2 . The superoxide anion radical can also result in the formation of the dangerous hydroxyl radical. The targets for these radicals are various cellular components and membranes.

Connective Tissue

It was as recently as 1961 [38] that it was discovered that copper plays a part in connective tissue maturation, a function of copper which is closely linked with the activity of lysyl oxidase a copper dependent enzyme found almost exclusively in connective tissue. The proper cross-linking of the protein chains to form a structurally sound extracellular network of collagen and elastin is dependent on reactions catalysed by lysyl oxidase [39]; prolonged copper deficiency in chicks and pigs results in the affected arteries having sparse and fragmented elastic fibres [40].

The most vulnerable organs to connective tissue disturbances include the cardiovascular system, lungs and bones.

Cardiovascular Integrity

Probably the most dramatic indication of copper deficiency is the sudden rupture of a major artery, or even of the heart, effects observed in pigs, chickens, cats, rabbits and cattle [30] [41]. Rupture of a major artery or arterial thrombosis is frequently the terminal event in patients with Menkes' disease [42].

In virtually all species so far examined cardiac enlargement is one of the earliest features of copper deficiency.

Closely associated to its function in the maturation of connective tissue is the role of copper in maintaining the major arteries.

Lungs

Normal lung function depends upon lung parenchyma cells being supported by extracellular collagen and elastin. Pulmonary emphysema, which usually results from the destruction of the supporting structure, can also be due to failure of its formation as observed in copper deficient mice and rats [43].

Bones

Skeletal abnormalities have been reported in several species [10] and in patients with Menkes' disease [38].

Osteogenesis is impaired and the cortex and trabeculae of long bone is thin [44]. Bones from copper deficient animals are more fragile than normal. While total collagen content in deficient bones may be unaffected, there are strong signs from collagen solubility studies that impaired collagen maturation accounts for the bone defects associated with copper deficiency [45].

A common symptom of copper deficiency in sheep is an increased incidence of spontaneous bone fractures [12]. The defect appears to be associated with the organic components and not the crystalline material of the bone, and the underlying cause is believed to be the improper crosslinking of collagen [45].

Immuno Competence

There are indications from recent work with mice of a highly significant reduction in the number of antibody-producing cells in animals fed low dietary copper [47]; this finding provides a basis for the earlier reports of a reduced ability of mice to withstand infection from *Salmonella typhimurium* when fed insufficient copper in the diet [48].

Lipid Metabolism and Cardiovascular Disease

Copper has been associated with lipid metabolism since 1973 [49] and it is interesting to reflect that lipid metabolism may be more sensitive to changed copper status than anaemia [50]; in copper deficient rats it is common to find that the percentage increase in plasma cholesterol exceeds the percentage decline in haematocrit [50]. An imbalance of zinc over copper has been associated with an increased incidence of hypercholesterolaemia in rats, and to a greater risk of ischaemic heart disease in humans [51].

Work on rats, and on monkeys, has shown that copper deficiency can markedly increase (sometimes double) the plasma cholesterol concentration [49]. Furthermore, the deficiency can decrease the percentage of the total plasma cholesterol that was bound to high density lipoprotein and increase the percentage bound to low density lipoprotein [52]. The implications of these results are that the risk of atherosclerosis, a disease in which fatty substances collect in artery walls, is higher when the high density lipo-protein cholesterol level is low and low density lipoprotein cholesterol is high.

The growing evidence that cardiac electrophysiology in rats may be abnormally affected by copper deficiency, adds weight to the hypothesis linking copper deficiency with ischaemic (coronary) heart disease [53].

In fact, humans with ischaemic heart disease exhibit several characteristics that are also found in animals suffering from copper deficiency: these include abnormal electrocardiograms, decreased myocardial copper, glucose intolerance, hypercholesterolaemia, hyperuricemia, necrosis of myocardial cells and sudden death [51].

Further evidence associating lipid copper metabolism has come from the identification of chemicals that can:-

(a) increase plasma cholesterol and inhibit copper absorption and retention, such as ascorbic acid, cadmium, fructose, glucose, histidine, sucrose and zinc [54]

or

(b) decrease plasma cholesterol and improve copper absorption and retention such as calcium, clofibrate and sodium phytate [54].

Diseases of Copper Metabolism

Apart from the diseases mentioned in the previous topic that result from or lead to alterations in copper metabolism, there are two rare and inherited diseases, Wilson's Disease and Menkes' Disease, which are genetic in origin and which are brought about by disturbances to the management of the bodily stores of copper.

Wilson's Disease

The basic characteristic of this inborn disease, which was first described in 1912 [55], is a massive accumulation of copper in the liver and brain due to the inability of Wilson's Disease patients to transport copper out of the affected tissues via the blood protein ceruloplasmin or via

biliary excretion [10]. Ultimately the accumulation of the copper leads to nervous disorders (mild tremors), and to pathological lesions especially in the liver. In extreme cases the light brown circles referred to as Kayser-Fleischer rings surrounding the iris, are seen, which are caused by the deposition of copper salts in the cornea [56]. Whilst much is known about the nature of Wilson's Disease which affects an estimated 1 in 160,000 people, the cause is as yet unknown.

Patients suffering from Wilson's Disease are treated with such drugs as the copper chelating agents penicillamine (introduced in 1960), that removes or modulates copper distribution [57].

Menkes' Disease

Symptoms of Menkes' Disease, an X-linked genetic disease of males, appears before the third month and usually terminates the life of the child before the fifth of sixth year. No cure is yet known, and attempts to control the course of the disease with copper therapy have proved disappointing despite correction of low liver and serum copper levels [42].

Described first in 1962 [58] the disease causes retarded growth with progressive neurological and vascular disturbances, pallid skin and brittle hair, often referred to as steely or kinky. Cerebral function is grossly affected and there is progressive brain degeneration [42]. A general impairment in copper metabolism was postulated as the major cause of the disease following the finding that Menkes' patients have abnormally low amounts of copper in liver and serum [59]. Unfortunately oral administration of copper to Menkes' patients is very poorly absorbed, with the copper tending to accumulate within the mucosal cells [60]. Intravenous copper therapy is normally only partially successful in treating the disorder [61].

Further parallels between copper deficiency and Menkes' disease have been revealed including similar if not identical connective tissue pathology and imperfections of the arterial walls [42].

Whilst it is agreed that the intracellular metabolism of copper in Menkes' cells is quite different from that in normal cells [17], there is as yet no consensus on the mechanism involved. The main difference in pathology between genetic and nutritional copper deficiency relates to iron; while anaemia is often observed in nutritional copper deficiency in many species it does not occur in the genetic copper deficiency diseases [42].

Arthritis and Inflammatory Disorders

Copper has been implicated in other disorders; for example, as long ago as 1938 [62] hypercupremia (associated with increased levels of circulating ceruloplasmin) was observed in rheumatoid arthritis, but it was only in 1951 [63] that it was established that copper complexes can be effective in treating arthritis.

The anti-inflammatory activity of copper complexes of various ligands such as amino acids, anthranilic acids and of salicylic acid has been demonstrated and drugs are available in several countries. These copper complexes are known to promote tissue repair [64].

The finding that the copper complexes are always more active than the parent ligand in reducing various kinds of inflammation has prompted the hypothesis, now widely upheld, that the ligands, which may not be antiinflammatory on their own, may well be effective by forming copper complexes in vivo [65].

The copper complexes are thought to operate either as transporters of copper to copper dependent enzymes at the site of inflammation, e.g. Iysyl oxidase or superoxide dismutase or as biochemical agents in their own right [64].

Evidence has been presented to show that metallic copper in the form of copper bracelets can be effective in relieving arthritic discomfort [66]. Whilst much more evidence on efficacy is required, it is now accepted that dissolution of copper in sweat can be followed by absorption through the skin and that this provides a mechanism for direct copper supplementation and thereby a possible explanation of the benefit of copper bracelets [66].

Copper in the Diet

It has been widely accepted for some time, based on work done in the 1940s and 1950s, that copper deficiency in adults is unlikely; it was thought that an adult requirement of between 2 and 3 mg/day copper (30 µg/kg body weight according to WHO), [5] would in all probability, be provided by most diets.

There are now reasons for believing that, whilst adults may actually need less copper than the recommended daily allowance of 2 - 3 mg/day copper [67], many people do not obtain sufficient copper [28]. For example, in the USA a survey indicated that 84% had a dietary intake of less than 1.6 mg/day (an average of 0.82 mg Cu/day) [68]. In New Zealand 79% diets were found to contain less than 2 mg per day. Swedish studies have shown an average intake of 1.6 mg Cu per day [69] and in Denmark of 1.7 mg Cu [21].

In a study over 1972-1978 carried out by the Ministry of Agriculture, Fisheries and Food (1981) [43] in the UK, it was estimated that the average total dietary copper intake by adults was 1.8 mg per day. This estimate was based on Total Diet Studies in which composite samples of most foods in the average diet were analysed (a daily consumption of 1.46 kg food per adult).

Whilst there was no indication of any change in copper intake over the period 1975 to 1977, the 1978 figures showed a slightly lower average intake of 1.6 mg per day, and by 1981 the quantity had fallen to 1.47 mg copper.

Animal liver and various shell fish contain on average more than 20 mg/kg Cu which is the general limit recommended for foods (2 mg/kg for beverages). Meats were found to have an average content of about 2.5 mg/kg Cu.

Overall the percentage contribution of different foods to the dietary copper intake in the UK between 1972 - 1978 was as follows [72]:

	%
Cereals	22 – 30
Meat, and Fish	20 – 30
Fruits and Preserves	11 – 16
Root Vegetables	14 – 17
Other Vegetables	10 – 13
Beverages	9 – 14
Milk	2 – 3

Some attention has been focussed on the value to the national diet of copper intake from drinking water, the copper content of which on occasions can, particularly in the "first draw" water, be high.

Drinking water could make a significant contribution to copper intake if it contains more than 0.25 mg/litre, daily water use in beverages and cooking of 1.5 litres would mean a copper intake of 0.37 mg which is equivalent to that supplied by cereals or by meat. It is argued in some quarters that such copper is sufficient to make up the apparent shortfall between daily intakes in the UK and the WHO and NAC Recommended Dietary Allowance.

However there is little evidence to indicate that drinking water containing more than 0.25 mg/litre Cu is at all common in the UK, water coming out of consumers' taps normally contains less than 0.1 mg/litre. It must therefore be concluded that with the exception of the relatively few areas where the water is cuprosolvent there is little evidence to suggest that the daily intake of copper in drinking water amounts to more the 0.1 mg. Those that receive more should perhaps count themselves fortunate for this inadvertent supplement!

Synthetic Diets

Care has to be taken to ensure that synthetic diets, formulated for the treatment of inherited and acquired metabolic disorders or of food intolerance, contain sufficient copper and other trace elements [28].

Parenteral Nutrition

As with synthetic diets, it is essential that infusion fluids used in long term parenteral nutrition are supplemented with copper; severe hypocuproemia can readily be observed in both infants and adults on prolonged total parenteral nutrition without added copper [28].

Intravenous feeding of children receiving inadequate amounts of copper can lead to severe hypocupraemia, neutropenia and extensive bone changes, all of which can be corrected by the addition of copper [46].

Copper Toxicity

Acute copper poisoning is a rare event, largely restricted to young children who have accidentally drunk solutions of copper sulphate or copper nitrate.

Inorganic copper salts are powerful emetics and inadvertent large doses are rejected by vomiting.

Chronic copper poisoning is also very rare and the only reports refer to patients with liver disease [12].

The capacity of healthy human livers to excrete copper is considerable and it is for this reason, primarily, that no causes of chronic copper poisoning have been reported in healthy humans. Other factors are the homeostatic control of copper absorption at the level of the intestinal mucosa by the formation of copper protein complexes, and the storage of copper on specific protein sites without any harmful effects.

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