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REPORT

Few people understand the multiple roles that copper plays in regulating life processes. Too little copper can be lethal, whereas excess amounts can cause serious disease. Copper is required for bone strength, blood cell maturation, iron transport, glucose metabolism, heart muscle contraction, host defense mechanisms and brain development. The dilemma is that while ingesting large amounts of copper is unsafe, avoiding copper deficiency is a must. Here, balance and education are key.

The Copper Dilemma

Copper is a catalyst that facilitates the action of a number of important proteins and enzymes. For example, a key copper-containing enzyme is superoxide dismutase (SOD), which keeps undue oxidation in check by scavenging for free radicals and destroying them. Copper is also necessary to support the function of ceruloplasmin (CP), a major copper-carrying protein that is present in many tissues including the liver and lungs, where it plays a critical antioxidant role. Some studies that have looked at rats, mice and baboons demonstrate that CP aids in lung development and is essential to host defense against pulmonary oxidative damage and infection.(1,2) Ongoing research from the University of California B Davis Clinical Nutrition Research Unit has found that the ability of lysyl oxidase, a copper-containing enzyme, to do its job relates directly to tissue copper levels. The enzyme plays a pivotal role in the cross-linking and regulation of extracellular matrix production and maturation, namely connective tissue remodeling and wound repair. Copper also plays a role in the cross-linking of collagen and elastin fibers, which aids in rebuilding tissue, such as in wound repair. The metal is also vital for arterial integrity by the same token, since such fibers surround them.

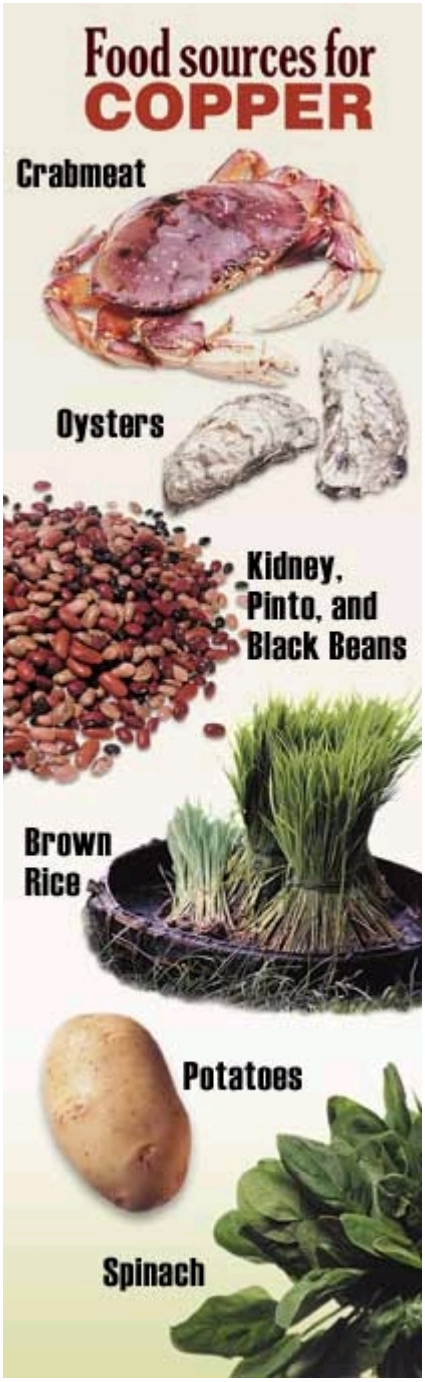
Getting our fill

In a normal body, suggests research from the US Department of Agriculture (USDA), when dietary copper is high and more gets absorbed, any excess gets excreted into the gastrointestinal tract to prevent the mineral from accumulating in the body. Contrarily, if copper intake is low, the body releases less of the mineral to protect against deficiency.(3) But the regulatory mechanism has its limits too, in that the body can't take something from nothing. A study at the Western Human Nutrition Center in San Francisco concluded that, despite the body's innate ability to prevent deficiency through regulating absorption and excretion of copper, it can't maintain a sufficient copper status at low dietary copper intakes. They found this out by testing out varying amounts of dietary copper intake on 11 young men over a 90-day period. The study was divided into three periods, whereby the men received 0.38 mg/d for 42 days, 0.66 mg/d for 24 days, and 2.49 mg/d for 24 days. While copper absorption and excretion fluctuated in response to the intake amount, researchers found that it was difficult for the body to maintain copper homeostasis at the lowest intake (0.38 mg/d).(4)

Meanwhile, other factors relate to the intake of other micronutrients, such as zinc, carbohydrate, iron and vitamin C, which affect

copper bioavailability. Ascorbic acid (vitamin C) has been found to antagonize the absorption of copper intestinally, and can impede the binding of copper to copper-zinc superoxide dismutase (Cu,Zn)SOD.(5) Likewise, zinc opposes the absorption of copper. In an animal study that examined the intestines of various animals that had been fed different amounts of zinc, researchers found that those animals that exhibited a lower zinc intake transferred more copper from a nutrient medium across the mucosal cells. Basically, it's because zinc induces the synthesis of a copper-binding ligand, which sequesters copper content and keeps it from transferring out of the digestive tract mucosal cells.(6) In addition, people whose diets are high in zinc and low in protein seem to be at risk for copper deficiency.(7) The rule of thumb is to counter every 10 mg of supplemental zinc with 1 mg of copper, although that raises the concern of copper excess.

A 1988 study from the Department of Foods and Nutrition at the University of Georgia also found that after feeding male rats various amounts of copper, iron and vitamin C for 20 days, high intakes of iron and/or vitamin C dramatically reduced copper levels. Results showed that high iron intake decreased copper absorption in copper-deficient rats, high vitamin C intake significantly decreased tissue copper levels in rats with adequate copper intake, and high iron plus high vitamin C caused severe anemia in copper-deficient rats, while dropping ceruloplasmin levels in copper-adequate rats by 44%.(8)



Benefits of copper supplementation

So how much copper is enough to maintain optimal health, and what amounts to metal toxicity? You might as well be asking the Phoenix a riddle, experts would say. The main difficulty with establishing an acceptable amount for daily intake has been that there have not yet been any clear markers for measuring copper content in the body.(9) Currently, measurement tools include serum copper levels and ceruloplasmin concentrations. According to SS Percival, Ph.D., a researcher at the University of Florida's Food Science and Human Nutrition Department, although it is tough to standardize among individuals, the best way of assessing copper status so far may be red blood cell SOD, since "if there's no copper, then there is less enzyme activity."

Another confounding factor is that individuals may exhibit different rates of absorption and excretion, due to genetics, malfunctions and disease conditions that may warrant a copper-restricted diet or inherently cause huge losses or excessive retention of copper within the body. Besides which, just because we eat copper-rich foods doesn't automatically translate into getting enough copper into our bodies. In fact, we only absorb 30% to 40% of the amount of copper that we consume in food, suggests research from Cornell University.(10) The authors write that, on the contrary, "Protein and soluble carbohydrates tend to improve copper absorption and bioavailability by enhancing its solubility and intestinal bulk flow. Organic acids, other than ascorbic acid, or agents that form low-molecular-weight chelates, are likely to have a positive effect on overall copper absorption."

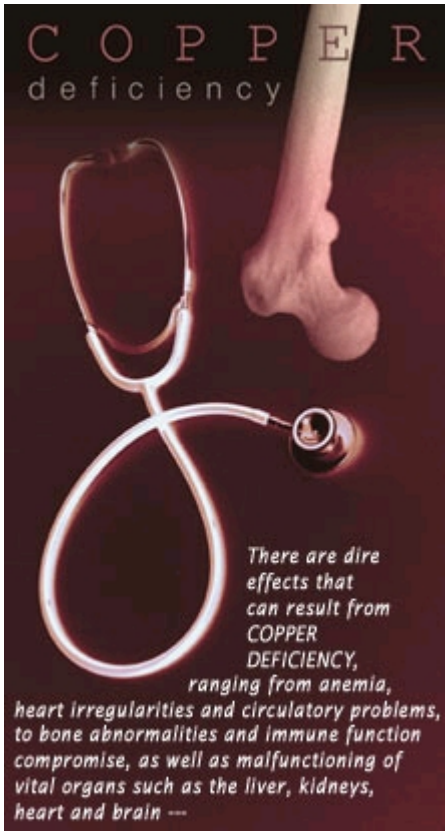
For that matter, there's variability in absorption of the mineral because certain organs store and release copper at different rates. For example, copper concentrations are highest in the brain and liver, while about 50% of copper content in the human body is within the bones and muscles. In addition, researchers at Florida State University have found that, in response to dietary copper restriction, organs such as the brain and heart are highly efficient at conserving copper stores, but that the liver will only restrict the excretion of copper after substantial loss occurs.(11) So it can be misleading to assess general copper status by measuring the copper level in a particular organ. Moreover, a USDA study examining 127 men and women ages 20-83, looking at age and sex with regards to copper intake and absorption, found that copper absorption was greater in women (71%) than in men (64%) aged 20-59 years but was no different among those aged 60-83 years. Copper intake from dietary means varied too, since intake levels were 0.9-1.2 mg/d for women and 1.2-2.3 mg/d for men, yet absorption levels did not differ. The authors concluded that dietary intake requirements might be different among the sexes.(12) So the fact is that, while copper's myriad of health benefits are well documented, little is still known about the mechanisms regulating the body's store of the essential metal.

One area that is clear is that there is a tendency to marginal deficiency in industrialized countries, despite our full bellies. According to scientists at the USDA's Agricultural Research Service (ARS), who examined data from 849 diets in the US, Canada, Great Britain and Belgium, 61% of them contained less than 1.5 mg/d, and almost one third fell below the 1 mg/d mark. The RDA, which is a range rather than a specific number, suggests that the daily intake range be 1.5-3 mg/day. USDA figures reveal that the typical US diet contains no more than 1.2 mg/d of copper, and women average 1 mg/day. Generally, vegetarian diets are more copper-rich than non vegetarian diets because they include nuts, seeds, mushrooms, whole grains and legumes. The irony is that animal sources are the richest in copper, but choices such as oysters, crabs and liver don't make their way to the table very often.

Moreover, some likely sources of copper may not actually pack as much metal as we think. According to a study from the University of Georgia's Department of Foods and Nutrition that reviewed dietary supplements, infant formulas and ready-to-eat cereal products, they either didn't contain a sufficient amount or the copper content was blocked by other nutrients on the ingredient list. According to the researchers, "High intakes of iron, zinc or manganese can interfere with copper absorption."(13) Over 25% of the 18 vitamin and mineral supplements examined contained no copper, 40% contained cupric oxide, a form that has low absorption, and under 30% contained a highly bioavailable form, namely cupric sulfate or cupric chloride. Nearly 40% of the 8 prenatal supplements examined contained iron and zinc without enough copper. Over 65% of 12 infant formulas had ratios of iron to copper exceeding 20:1 (10-17:1 is recommended). None of the 42 ready-to-eat cereal products were fortified with copper or manganese, although they did include less than or about 25% of the daily requirement of iron and zinc. Therefore, copper availability by means of these food sources is actually limited, and impedes the ability of people to achieve a sufficient daily intake of copper through strictly dietary means.

Oversupplementing, however, can tax the appropriate levels of other nutrients such as zinc and iron. A recent study published in Free Radical Biology and Medicine(14) suggested that ingesting up to 7 mg/d of copper was safe, since its findings demonstrated that such a dose of copper didn't promote oxidative damage. In fact, the study authors suggest that consuming this higher dose of copper may actually protect red blood cells against free radical damage. The researchers tested the effects of higher copper supplementation in 26 healthy subjects, aged 50-70, over three six-week test intervals. Each of them received a certain amount and form of copper for a six-week period, but they didn't take any copper supplements during the six-week period before and after each of the three supplementation periods. The first amount of copper they received during the first six-week test phase was 3 mg/d CuSO(4); they took 3 mg/d Cu glycine chelate (CuG) during the second test phase; and 8 mg/d CuG was given during the final study period. Results showed that an intake of copper as high as 7 mg/d didn't seem to increase the levels of copper-zinc (Cu,Zn) SOD activity in red blood cells that usually occurs in response to the presence of free radicals, which are formed by oxidation. Findings also revealed that blood cells showed increased resistance to rupturing, suggesting that the elevated copper intake might actually have protected the blood cells against the destructive oxidation.

Dangers of excess



Copper could be called a nutritive paradox, since its merit also forms the basis of its detriment. When it comes to helping or hindering health, the metal's equivocal nature lies in the fact that copper is a pro-oxidant. That means that its good reputation for doing good deeds—aiding the transport of iron, preventing the transformation of good fat into bad fat (lipid peroxidation), helping wounds to heal—is sullied by its association with spurring on free radical activity and its subsequent oxidative damage at the cellular, tissue and organ levels.(15) Oxidative damage has been implicated in aging, as well as the development of cancer, heart disease and many other diseases. Some evidence points to patients with Wilson's disease (an inherited genetic defect that causes a buildup of copper and the inability to release the metal), have signs of lipid peroxidation in their livers. Wilson's disease can result in damage to the liver, kidneys, brain and eyes, as well as anemia (due to compromised iron absorption), jaundice and softening of the bones. Some patients have also been known to develop cirrhosis of the liver as a result of the copper-mediated oxidative damage. Myocardial infarction (MI) patients have been found to have high levels of plasma copper too.(16) It seems that copper may heighten the inflammatory response through oxidation that may lead to atherosclerosis. Meanwhile, other evidence, such as a study from the University of Heidelberg, Germany, suggests that copper-induced oxidation may play a role in the development of Alzheimer's disease. That's because copper-mediated oxidative damage has been implicated in promoting the toxicity of beta A4 (A beta) and the metabolization of amyloid precursor protein (APP), two contributing factors to the neurodegenerative pathology.(17)

Copper excess has been implicated in liver and other forms of cancer. The cause is supposedly linked to the action of a cytoplasmic copper-binding protein. When researchers at the Sapporo Medical University, Japan studied the role of copper accumulation in liver cancer, they found that it might produce a "selective growth environment" for cancer lesions.(18) Similarly, researchers at the University of Pittsburgh concluded that excess copper could result in cellular damage and hepatocellular carcinomas (HCC). They basically found that copper levels were 2.2-fold higher in tumors and 1.7-fold higher in liver surrounding tumors. The reason appears to be that copper excess lowers serum ceruloplasmin (CP) oxidase activity, which results in compromised free radical scavenging capacity and potentially an increase in oxidative damage.(19)

Meanwhile, researchers at the University of Michigan published a study earlier this year in the journal Clinical Cancer Research(20) that complement these other findings. They showed how lowering overall copper content in the bodies of cancer patients could effectively arrest the growth of tumors. The idea stemmed from other study findings that point to copper's role in causing angiogenesis (the process of growing new blood vessels). Likewise, tumor growth seems to be fueled by copper, since they use copper to build tiny blood vessels that feed their development. Administering a drug called tetrathiomolybate (TM), which has been used to treat patients with Wilson's disease, researchers found that five out of six patients had tumor growth stop. And even the

sixth patient in this Phase I study, all but one of several tumors stopped growing. In a previous study, explains lead researcher Dr. George Brewer, professor of human genetics and internal medicine at the university, they tested the copper-lowering drug's ability to prevent cancer development. The researchers examined its effects in 37 mice carrying the breast cancer gene (BRAC), by giving TM to 22 of the mice for 275 days, while comparing them to 15 controls. Results indicate that while TM didn't destroy the cancer cells, which still appeared in clusters, they didn't proceed to form tumors. The amount of copper reduction that Brewer is referring to, however, doesn't result in outright deficiency. He says, "Cells have a lower copper requirement than tumors, so what we're talking about is a chemical copper deficiency as opposed to a clinical copper deficiency."

The deficiency dilemma

While severe deficiency isn't believed to be a widespread public problem, marginal deficiency is prevalent, given the typical North American diet. As far as the general population, though, copper deficiency is most often the result of "decreased copper stores at birth, inadequate dietary copper intake, poor absorption, elevated requirements induced by rapid growth or increased copper losses," suggest researchers at the Institute of Nutrition and Food Technology, University of Chile, Santiago.(21) However, some health conditions may predispose certain individuals to deficiency, such as in prematurity, malabsorption syndromes, and conditions predisposing to excessive copper losses.(22) In Menkes disease, for example, the rare syndrome is characterized by the inability to store copper. After countless data to understand this condition, which can't be helped by mere supplementation, the latest evidence from the National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH) suggests that those suffering from Menkes disease may be deficient in the copper enzyme, dopamine-beta-monooxygenase.(23) And there are dire effects that can result from copper deficiency, ranging from anemia, heart irregularities and circulatory problems, to bone abnormalities and immune function compromise, as well as malfunctioning of vital organs such as the liver, kidneys, heart and brain.(24)

New research from the Grand Forks Human Nutrition Center in North Dakota has uncovered a link between copper deficiency in pregnancy and neurological defects in the offspring of laboratory animals, which may have huge implications for humans. During pregnancy, sufficient copper intake is essential for normal neurological growth of the fetus. Consider, says lead author and research chemist at the ARS, Tom Johnson, Ph.D., that, "A sizeable reserve of copper is built up in the liver during fetal development that helps satisfy the requirement of the newborn for copper. Thus, adequate copper intake during pregnancy is important to ensure the fetus acquires sufficient copper to fill this reserve. However, for the health of the mother, she should have a copper intake of 1.5-3.0 mg/d postpartum and during lactation." The need for copper in neurological development comes down to copper-containing and copper-dependent enzymes in the brain.

Protein kinase C (PKC) for one is a copper-dependent enzyme that is crucial in helping to develop the nervous system. Researchers studied the PKC levels in the brains of rat pups whose mothers had been fed a copper-deficient diet during and for a few weeks after pregnancy. The diet was defined as 1 mcg/d for one group and 2 mcg/d for a second group of rats (one third of the recommended level), while a third group got sufficient dietary copper intake. Results showed that while PKC levels rose in all the rat groups during the three weeks after birth, the increase was only half as much in the group whose moms got 1 mcg/d, and 25% less in the 2mcg/d group. Moreover, at 2 mcg/d, one form of PKC was off by 50% in the cerebellum, which happens to be the control center for motor function. In baby animals, copper deficiency usually results in poor muscle coordination.

A similar study from the University of California at Davis revealed that copper deficiency during pregnancy can result in "Numerous gross structural and biochemical abnormalities," which seem to stem from copper deficiency-induced changes in free radical defense mechanisms, connective tissue metabolism and energy production. Another observation by the same researchers was that copper is better absorbed from breast milk than from infant formula.(25)

Other research suggests that people with rheumatoid arthritis (RA) tend toward copper deficiency. A study in the Journal of Rheumatology(26) showed that patients with rheumatoid arthritis had low levels of several micronutrients, including copper, compared to the typical American diet. Consequently, the authors suggest that, "routine dietary supplementation with multivitamins and trace elements is appropriate in this population." A deficiency may also explain why copper, which is an anti-inflammatory agent, is useful in the treatment of (RA) and other inflammatory conditions. A study(27) showed that copper supplementation surpassed aspirin in terms of anti-inflammatory action B boasting 130% the activity of cortisone.

In Parkinson's disease too, researchers at the Parkinson's Disease Society Research Centre, London, UK, found decreased levels of copper and elevated levels of iron. Iron blocks the absorption of copper.(28) And in terms of immune function, a study from the University of Florida, Food Science and Human Nutrition Department explained that interleukin concentrations are reduced in marginal copper deficiency, and that neutrophils are reduced in number and action in severe copper deficiency.(29) By the same token, the author suggests that neutrophils may be useful as a measurement for copper status in humans.

Last but not least, a series of new animal studies from the USDA's Grand Forks Human Nutrition Research Centre suggest that too little copper in the body may be a factor in aging. The reason is that low-copper intake is linked to an increase in protein glycation by which sugar molecules bind to protein molecule. The free ends of the sugar molecules then proceed to attach to other proteins forming cross-links that prove distorting to the protein, eventually bending the protein so out of shape that it begins to malfunction. The real trouble with glycation, though, is that it sets the stage for oxidative damage to cellular lipids, nucleic acids, proteins and carbohydrates. Moreover, this untoward process increases with age and it's also believed to cause much of the tissue

damage in diabetes patients. The researchers already knew that copper-deficient rats typically have high blood sugar levels, but now they were demonstrating that the low copper levels were encouraging the glycation process.(30) The reason, explains Jack T. Saari, Ph.D., lead researcher and a physiologist at the ARS, is that carbohydrate metabolism is altered by copper deficiency. “There is evidence that insulin released by the pancreas is impaired,” he says, “which causes an exaggerated elevation of blood glucose during feeding (reduced glucose tolerance) no matter what the carbohydrate source is. Glucose is not taken up and incorporated by the cells as readily and is thus available for undesirable reactions, such as aberrant binding proteins (glycation).”

As with almost any nutritive element that prove of benefit to human health, though, too much of a good thing can prove bad. But while moderation may be the key to the intake of other essential nutrients such as antioxidant vitamins, calcium, iron, fat, and protein, working out a safe, effective dose for copper intake is as finicky as trying to hang a painting perfectly straight. In the case of copper, too little or too much of the metal in our bodies isn’t just an annoyance or arbitrary calculation. Unlike other micronutrients that we can take in large doses before reaching a toxicity threshold, a minute amount of copper is all that it takes to perform its meticulous tasks that are so essential to human health. That tiny requirement for things to operate correctly within the human body also makes for a delicate equation when it comes to tipping the scales to excess or deficiency and the consequences. As science continues to elucidate the multiple roles of copper in maintaining optimum health, we may yet be able to better gage how much of this miraculous metal is really right for our bodies.

References

1. Yang F, et al. Cellular expression of ceruloplasmin in baboon and mouse lung during development and inflammation. Am J Respir Cell Mol Biol 1996 Feb;14(2):161-9.

2. Fleming RE, et al. Primary structure of rat ceruloplasmin and analysis of tissue-specific gene expression during development. J Biol Chem 1990 May 5;265(13):7701-7.

3. Turnlund JR. Human whole-body copper metabolism. Am J Clin Nutr 1998 May;67(5 Suppl): 960S-964S.

4. Turnlund JR, et al. Copper absorption, excretion, and retention by young men consuming low dietary copper determined by using the stable isotope 65Cu. Am J Clin Nutr 1998 Jun;67(6):1219-25.

5. Harris ED, et al. A role for ascorbic acid in copper transport. Am J Clin Nutr 1991 Dec;54(6 Suppl):1193S-1197S.

6. Fischer PW, et al. The effect of dietary zinc on intestinal copper absorption. Am J Clin Nutr 1981 Sep;34(9):1670-5.

7. Sandstead HH. Copper bioavailability and requirements. Am J Clin Nutr 1982 Apr;35(4):809-14.

8. Johnson MA, et al. Adverse effects of high dietary iron and ascorbic acid on copper status in copper-deficient and copper-adequate rats. Am J Clin Nutr 1988 Jan;47(1):96-101.

9. Percival SS. Copper and immunity. Am J Clin Nutr 1998 May;67:1064-8.

10. Wapnir RA. Copper absorption and bioavailability. Am J Clin Nutr 1998 May;67(5 Suppl):1054S-1060S.

11. Levenson CW. Mechanisms of copper conservation in organs. Am J Clin Nutr 1998 May;67(5 Suppl):978S-981S.

12. Johnson PE, et al. Effects of age and sex on copper absorption, biological half-life, and status in humans. Am J Clin Nutr 1992 Nov;56(5):917-25.

13. Johnson MA, et al. Copper, iron, zinc, and manganese in dietary supplements, infant formulas, and ready-to-eat breakfast cereals. Am J Clin Nutr 1998 May;67 (5 Suppl): 1035S-1040S.

14. Rock E. The effect of copper supplementation on red blood cell oxidizability and plasma antioxidants in middle-aged healthy volunteers. Free Radic Biol Med 2000 Feb 1;28(3):324-9.

15. Dameron CT, et al. Mechanisms for protection against copper toxicity. Am J Clin Nutr 1998 May;67(5 Suppl):1091S-1097S.

16. Trace elements in prognosis of myocardial infarction and sudden coronary death. Journal of Trace Elements in Experimental Medicine (USA), 1996, 9/2(57-62).

17. Multhaup G. Amyloid precursor protein, copper and Alzheimer's disease. Biomed Pharmacother 1997;51(3):105-11.

18. Sawaki M, et al. Role of copper accumulation and metallothionein induction in spontaneous liver cancer development in LEC rats. Carcinogenesis 1994 Sep;15(9):1833-7.

19. Eagon PK, et al. Hepatic hyperplasia and cancer in rats: alterations in copper metabolism. Carcinogenesis 1999 Jun;20 (6):1091-6.

20. Brewer GJ, et al. Treatment of metastatic cancer with tetrathiomolybdate, an anticopper, antiangiogenic agent: Phase I study. Clin Cancer Res 2000 Jan;6(1):1-10.

21. Uauy R, et al. Essentiality of copper in humans. Am J Clin Nutr 1998 May;67(5 Suppl):952S-959S.

22. Beshgetoor D, et al. Clinical conditions altering copper metabolism in humans. Am J Clin Nutr 1998 May;67(5 Suppl):1017S-1021S.

23. Kaler SG. Diagnosis and therapy of Menkes syndrome, a genetic form of copper deficiency. Am J Clin Nutr 1998 May;67(5 Suppl):1029S-1034S.

24. Olivares M, et al. Copper as an essential nutrient. Am J Clin Nutr 1996 May;63(5):791S-6S.

25. Lonnerdal B. Copper nutrition during infancy and childhood. Am J Clin Nutr 1998 May;67(5 Suppl):1046S-1053S.

26. Kremer JM, et al. Nutrient intake of patients with rheumatoid arthritis is deficient in pyridoxine, zinc, copper, and magnesium. J Rheumatol 1996 Jun;23(6):990-4.

27. JAMA, 1974;229:1268-9.

28. Dexter DT, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain 1991 Aug;114 (Pt 4):1953-75.

29. Percival SS. Copper and immunity. Am J Clin Nutr 1998 May;67(5 Suppl): 1064S-1068S.

30. J Nutr Bio. Vol 10, Issue 4;210-214 April 30, 1999 article related at http://www.ars.usda.gov/is/pr/1999/990820.htm.

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