# Copper: The Maligned Mineral

*by A.S. Gissen*

Few dietary components are more misunderstood than copper. Although copper is the third most abundant essential trace mineral in the body, after iron and zinc, most people consider it unimportant. Even worse, many people have actually taken steps to exclude it from their diets and dietary supplements, believing it to be nothing more than a cause of free radical reactions. This is surprising, because copper has been recognized as an essential nutrient since the 1920's.[1] In the past seventy years, much has been learned about the important biological roles of copper and the copper-dependent enzymes. In fact, copper is emerging as one of the most important minerals in our diet. While unbound, free copper does generate free radicals in vitro, the relevance of this in the body has been called more imaginary than real.[2] In fact, copper has an entirely different role in the body, being a component of two of our most important antioxidant enzymes, copper-zinc superoxide dismutase and ceruloplasmin.[3]

Copper Biochemistry

Unbound, free copper is not found in large quantities in the human body. Instead, almost all of the copper in our bodies is bound to either transport proteins (ceruloplasmin and copper-albumin), storage proteins (metallothioneins), or copper containing enzymes.[4] A substantial number of copper metalloenzymes have been found in the human body. Copper is essential for the proper functioning of these copper-dependent enzymes, including cytochrome C oxidase (energy production), superoxide dismutase (antioxidant protection), tyrosinase (pigmentation), dopamine hydroxylase (catecholamine production), lysyl oxidase (collagen and elastin formation), clotting factor V (blood clotting), and ceruloplasmin (antioxidant protection, iron metabolism, and copper transport).[5] Most features of severe copper deficiency can be explained by a failure of one or more of these copper-dependent enzymes. For instance, depigmentation can be explained by a tyrosinase deficiency, and the defects of collagen and elastin causing abnormalities in the connective tissue and vascular system can be explained by a lysyl oxidase deficiency.

Unfortunately, most research into copper deficiency has focused on acute, severe deficiency. This is relatively rare in humans and animals on typical, varied diets. Marginal, chronic deficiency, however, is much more common. The determination of copper needs and marginal deficiency is complicated by the fact that while copper deficiency doesn't necessarily lower the level of copper-dependent enzymes, it does significantly lower their activity.[6] As an example lets look at lysyl oxidase, one of the most important and best understood roles of copper in the body. This is the main enzyme involved in the necessary cross-linking of connective tissue. Optimal functioning of lysyl oxidase ensures the proper cross-linking of collagen and elastin, vital for the strength and flexibility of our connective tissue. A reduction in lysyl oxidase activity affects the integrity of numerous tissues, including our skin, bones, and blood vessels. In copper deficiency the level of lysyl oxidase isn't altered, but the activity of the enzyme can be reduced by more than fifty percent.[7] Not surprisingly,

some of the hallmarks of copper deficiency are connective tissue disorders, osteoporosis, and blood vessel damage.

Copper Metabolism

The adult human body contains between 80 and 150 milligrams of copper.[8] The liver is the major location of stored copper, containing about 10 percent of the total-body content.[9] Maintaining a steady level of copper in the body depends upon a balance between intestinal absorption and biliary excretion. Biliary excretion of copper is capable of substantially increasing when excess copper is ingested.[10] The exception to this is in persons with the genetic defect causing Wilson's Disease (hepatolenticular degeneration). This genetic disease, affecting approximately 1500 Americans, is characterized by a lack of circulating ceruloplasmin, low serum copper levels, and copper accumulation in the liver.[11] This disease is characterized by an inability of the liver to normally transport copper, leading to copper overload. In most animals and humans, however, copper is essentially non -toxic.

Dietary copper is distributed in many foods. Dried beans and nuts are exceptional sources, while milk and dairy products are poor sources.[12] Studies have found a wide range of intake among different population groups. In the United States, intakes range from .76 to 3.36 milligrams daily.[13] The National Research Council has established a tentative safe and adequate daily intake for copper, which for adults is 2-3 milligrams daily.[13] Numerous studies have shown average copper intake to be well below the recommended allowances, with intakes of less than 1 milligram daily being very common.[14]

Copper is rapidly absorbed from the stomach and small intestine, and this is influenced little by the form of copper ingested.[15] Although the absorption of copper may not sound like an exciting subject, if you take vitamin/mineral supplements containing vitamin C or zinc you should pay close attention. This is because convincing evidence has accumulated suggesting that zinc and vitamin C supplements are strong antagonists of copper status and absorption. In the case of zinc, numerous studies have shown that relatively small increases in dietary zinc significantly lowers copper absorption.[16] This antagonism has been utilized as a treatment of Wilson's Disease, with 50 milligrams of zinc taken with each meal being effective in lowering the abnormal accumulation of copper in people afflicted with this genetic disease of copper metabolism. Much lower levels of zinc supplementation, as little as 50 milligrams a day, has also been shown to antagonize copper status in healthy adults.[17] Numerous cases of zinc-induced copper deficiency have been reported in scientific journals, usually resulting in anemia and blood lipid abnormalities.[18] The use of supplemental vitamin C to lower copper absorption, and hasten copper deficiency, has been well documented in laboratory animals.[19] It has subsequently been shown in several human studies that vitamin C supplements of as little as 1500 milligrams can adversely affect markers of copper status, including copper-zinc superoxide dismutase and ceruloplasmin activity.[20] While the evidence for benefits from taking megadoses of zinc (>50 milligrams daily) and vitamin C (>1000 milligrams daily) are tentative at best, the negative consequences of poor copper status are well documented and certain. There seems little doubt that these interactions will receive increasing attention in the coming years, due to the documented importance of adequate copper intake and the common practice of consuming supplemental vitamin C and zinc without concern or copper supplements.

The long term effects of marginal, subclinical copper deficiency are not well defined. It has been hypothesized that low copper status is not only common, but plays a substantial role in numerous, common degenerative diseases and conditions. If all this has come as a shock to you, that lowly copper could be so vitally important to your health, don't be. Over the years the importance of copper in nutrition has even escaped many of the "so called" experts in the field of nutrition. In the words of one author who reviewed copper's role in human nutrition, " ...but copper has languished as an orphan among human nutritionists because of the obscurity of clinical copper-deficiency states in man. As medical investigators we may have gone down the long road, missing the forest for the trees...But, the influence of subtle differences in dietary intakes of copper on human health may be more important than frank copper depletion."**21** Indeed, in next month's newsletter we will continue our review of copper and nutrition, including copper's role in cardiovascular disease, diabetes, arthritis, osteoporosis, free radical damage, cancer, inflammatory diseases, immune function, blood lipids, and thyroid function. In addition, we will examine the remarkable properties of copper complexes like copper salicylate. These copper complexes have been extensively studied for their anti-inflammatory and antioxidant activity, as well as their ability to mimic the superoxide-radical scavenging activity of superoxide dismutase.

## PART 2
Copper and Cardiovascular Disease
Although the relationship between nutrition and cardiovascular disease is generally accepted by most people, rarely will you hear copper mentioned as a contributing factor in this relationship. Based on the scientific evidence, this is surprising. Almost twenty years ago, it was postulated that there is a direct relationship between the level of copper in the human diet and the incidence of cardiovascular disease.**22** Copper has been known to be associated with lipid metabolism since 1973,**23** and research in numerous animal models, including humans, has shown that copper deficiency can significantly increase the plasma cholesterol concentration.**24** Additionally, this increase in cholesterol results in an increase in LDL-cholesterol and a decrease in HDL -cholesterol, resulting in an increase in cardiovascular disease risk.**25**

It is well documented that animals with copper deficiency often have abnormal electrocardiograms, and die suddenly.**26** In one study that looked at this relationship, it was found that copper deficiency reduced the life -span of rats by almost 75%. People with ischaemic heart disease usually die suddenly, often within one hour of the onset of symptoms. The hearts of people who die of ischaemic heart disease are hypertrophied and fibrotic, with edema, loss of cellular outline, and heart rupture often being found.**27** Interestingly, all of these pathological changes are found in animals deficient in copper. In one human study that compared heart copper levels in heart attack victims and controls that died of other causes, it was found that the hearts of people that died of myocardial infarction were low in copper.**28** Atherosclerotic arteries in humans have degenerative changes similar to those found in the arteries of copper deficient animals.**29** It has also been demonstrated that copper deficiency significantly increases the susceptibility of lipoproteins and cardiovascular tissues to lipid peroxidation, thus increasing the risk of cardiovascular disease.**30**
While the role of adequate copper levels in maintaining cardiovascular health is well established, it is not entirely surprising that copper's importance has been overlooked. One of the laboratory findings often found in cardiovascular disease is increased

serum levels of copper. While this may sound confusing, recent research has helped to explain this paradox. It has been suggested, for instance, that an elevated serum copper level is an independent risk factor for heart disease.**29** Many researchers have considered this elevation of serum copper to play a role in the pathogenesis of cardiovascular disease, although other researchers have strongly disagreed with this hypothesis. A recent animal study, however, seems to have explained this relationship between copper levels and cardiovascular disease. This study examined the effects of diet-induced atherosclerosis on the copper levels and status of numerous tissues.**30** It was found that serum copper levels increase significantly, while aorta and liver copper levels decrease significantly, in rats with experimental atherosclerosis. Instead of assuming that these elevated copper levels contribute to the formation of atherosclerosis, these researchers examined the effects of increasing the dietary copper levels in these animals. Administration of additional copper resulted in a further increase in serum copper, a significant decrease in serum cholesterol, and an increase and normalization in aorta and liver copper levels. However, instead of increasing the incidence of atherosclerosis, additional copper significantly decreased the incidence of atherosclerosis in the aorta and coronary arteries. Further, it has been shown that excess dietary cholesterol causes cardiovascular disease by lowering the absorption of copper, an effect that is preventable by increasing the copper level in the diet.**31**

Taken as a whole, the role of copper in maintaining cardiovascular health is well established. Copper is essential both for its role in antioxidant enzymes, like Cu-Zn Superoxide Dismutase and Ceruloplasmin, as well as its role in Lysyl Oxidase, essential for the strength and integrity of the heart and blood vessels. With such a central role in cardiovascular health, it is disappointing that copper has been generally overlooked in the debate over improving our cardiovascular health. Copper deficiency has produced many of the same abnormalities present in cardiovascular disease. It seems almost certain that copper plays a large role in the development of this killer disease, not because of its excess in the diet, but rather its deficiency.


## PART 3
### Copper and Free Radicals

The function of copper as an integral component of Cu-Zn Superoxide Dismutase (SOD) and Ceruloplasmin is well established. Cu-Zn SOD, for example, performs antioxidant functions in varied tissues and fluids, and is indispensable to oxygen-metabolizing organisms.**32** In addition, it has been demonstrated that most copper containing enzymes, including CuZn-SOD, are produced at a similar rate regardless of copper status, although their function is significantly impaired by copper deficiency.**33** Thus, the activity of these enzymes are significantly lessened in spite of no decrease in their production.

Copper deficiency has been shown to result in a 2-fold increase in the level of lipid hydroperoxides in liver mitochondria.**34** However, an interesting finding was that while the specific activity of Cu-Zn SOD decreased significantly, so did the activity of catalase and glutathione peroxidase, two other important antioxidant enzymes that don't require copper for their activity. Other research has shown that copper deficiency induces an increase in intracellular and extracellular glutathione levels, which the authors ascribed to a compensatory adaptive response to the negative effect of copper deficiency on glutathione peroxidase and Cu-Zn SOD activity.**35** It appears clear that the decrease in antioxidant protection caused by copper deficiency goes

beyond a decrease in the activity of copper-dependent antioxidant enzymes by inducing a wide range of disturbances in other antioxidant enzyme systems. Additionally, copper deficiency depresses Cu-Zn SOD activity and prostacyclin synthesis in the aorta.[36] as well as increases the susceptibility of lipoproteins and heart tissue to peroxidation, providing strong evidence that copper plays a vital role in the protection of the cardiovascular system from free -radical mediated damage and disease.[37] Thus, it appears clear that adequate copper is vital for optimal functioning of many antioxidant enzymes, both copper dependent and otherwise, in varied organs and tissues.

## Copper and Osteoporosis

Almost two hundred years ago, the German physician Rademacher empirically established that broken bones healed faster when the patient was given copper supplements.[38] In the years that have followed, compelling evidence has established a vital role for copper in the biosynthesis of bone and connective tissues and their maintenance.

Lysyl Oxidase, which is involved in the synthesis of the collagen that constitutes much of bone and connective tissue, is a copper dependent enzyme. Like other copper dependent enzymes, synthesis of Lysyl Oxidase is unaffected by copper deficiency, although its activity is significantly impaired.[39] Copper-deficiency induced osteoporosis has been documented in numerous animal species, including humans.[40] While this condition has most often been documented in young, growing animals and children, it has been found in young adults and the elderly.[41] Copper deficiency has even been implicated in the etiology of idiopathic scoliosis.[42] Skeletal abnormalities have often been found concurrently with low copper status, and these have usually been associated with osteoporitic changes and increased susceptibility to fractures.[43] Insufficient copper intake has also been shown to lower bone calcium levels during long-term deficiency.[44]

With the essential role that copper plays in maintaining bone health, it is surprising how little attention has been given to copper's role in bone diseases. Interestingly, estrogens, which have a beneficial effect on preventing post-menopausal bone loss, have been shown to raise the level of ceruloplasmin (the main copper transport protein) two to three fold, providing a possible explanation for how estrogen positively influences bone health, as well as cardiovascular health.[45] Prolonged cortisone treatment, well known for promoting the development and accelerating the progression of osteoporosis, has been shown to increase the body's excretion of copper and lower copper status, providing more evidence of a correlation between copper status and osteoporosis.[46]

## PART 4

### Copper and Immune Function

It has been well documented that adequate copper status is essential for normal functioning of the immune system in laboratory and domestic animals.[47] For instance, not only has it been shown that the functioning of macrophages were decreased in severely copper deficient rats, but even marginally copper-deficient rats had impaired immune functioning.[48] Interestingly, immune function was significantly impaired at dietary copper levels that didn't seem to decrease tissue copper or the activity of red blood cell Cu,Zn-superoxide dismutase (SOD).[49] However, neutrophil SOD-activity and neutrophil function was significantly

diminished, suggesting that immune function may be more sensitive to diets low in copper than standard measures of copper status. It was also found that immune impairment could be detected as soon as one week after the initiation of a diet low or marginal in copper, and the addition of adequate copper reversed the immune suppression within one week of supplementation. The authors concluded that, "...the adverse effects of inadequate copper intake on neutrophil activity occur rapidly and are readily reversed by dietary copper repletion." Additionally, it has been demonstrated that copper deficiency reversibly impairs DNA synthesis in activated T-cells by limiting interleukin 2 activity up to 50%, and this was reversible with copper supplementation.**50** Because of this sensitivity to copper status at levels of intake that have little effect on other indicators of copper status, immune system cells have been suggested to be a readily accessible and copper-status sensitive population of cells for the assessment of copper status.**51**

Copper, Cancer, and Carcinogenesis
The role of copper in the development of cancer is somewhat similar to copper's role in cardiovascular disease. This is because the serum level of copper is often elevated in animals and humans with cancer.**52** Like the elevation of serum copper in cardiovascular disease, it seems that the elevation of serum copper that occurs in conjunction with cancer is part of the bodies biological response to the cancer, rather than its cause. Numerous studies examining varied types of tumors have demonstrated that with remission usually comes a decrease in serum copper levels to normal.**53** Patients who responded to therapy or surgery usually had a return to normal serum copper levels, while nonresponders had a persistently elevated serum copper level. Interestingly, most tumor cells have decreased Cu-Zn SOD activity compared to normal cells,**54** and it has been suggested that the elevation in serum copper is a physiological response designed to activate SOD or other copper enzymes in cancer cells to inhibit their growth. Indeed, numerous copper complexes that demonstrate SOD-mimetic properties, including copper salicylate, have been shown to possess anticancer, anticarcinogenic, and antimutagenic effects both in vitro and in vivo.**55** In fact, there is some experimental evidence that copper complexes can cause established tumor cells to redifferentiate into normal cells,**56** and because of this it has been suggested that, "..the future use of copper complexes to treat neoplastic diseases has some exciting possibilities."**57**

Because copper is an essential component of several endogenous antioxidant enzymes, and free radicals have been proposed to play a role in the process of carcinogenesis, the effects of dietary copper levels on the development of cancer has been investigated. Rats fed low copper diets show a higher incidence of carcinogen - induced colon tumors when compared with rats fed a high copper diet.**58** Another study in rats found similar results, but with the additional finding of a decrease in aortic integrity possibly leading to eventual aneurysm.**59** These findings are especially interesting for two reasons. To begin with, dietary copper has often been incorrectly suggested to be a cause or promoter of cancer. If this was true increased dietary copper would enhance, rather than inhibit, carcinogen-induced gastrointestinal malignancy. Lastly, it has been shown that there is a relationship between aortic aneurysmal disease and malignancy in humans, and this is likely the result of decreased copper status as demonstrated in the animal study mentioned above.**60**

Copper. Inflammation. and Arthritis

As long ago as 1000 B.C., foods high in copper and copper bracelets were thought to be beneficial in treating arthritic conditions.**61** In 1945, patients with rheumatoid arthritis were shown to exhibit higher than normal serum copper levels.**62** Indeed, the copper content of serum is known to be elevated above normal values in various inflammatory diseases in man and laboratory animals.**63** Despite this seeming contradiction, copper complexes were successfully used from the 1940's to 1970's in the treatment of numerous conditions characterized by arthritic changes and inflammation.**64** Even the time-tested copper bracelet was eventually shown to be an effective anti-inflammatory, due to the absorption of copper through the skin.**65** However, the development of anti-inflammatory steroids and aspirin-like nonsteroidal anti-inflammatory drugs quickly replaced copper compounds in the treatment of these conditions. Numerous researchers have examined the paradoxical role of copper in the process of inflammation, and they have determined that the increase in serum copper is a physiological response to inflammation, rather than a promoter of it.**66** In fact, the main copper containing enzyme, ceruloplasmin, is significantly elevated in inflammatory conditions and has anti -inflammatory activity.**67** Additionally, it has been shown that copper deficiency increases the severity of experimentally-induced inflammation,**68** and that dietary copper must be increased to maintain adequate copper status of animals in an inflammatory state.**69**

With the knowledge that many copper complexes possess anti-inflammatory activity, and the finding that these copper complexes almost always have significantly stronger activity than their parent compounds, it has been hypothesized that the active form of many popular anti-inflammatory drugs are their copper chelates. Interest in copper complexes as anti-inflammatory drugs and antiarthritics is evidenced by the large number of reviews and symposia proceedings published in recent years.**70** The sum of this research has shown that copper chelates of most anti-inflammatory compounds, as well as many other compounds, have strong anti-inflammatory activity in numerous models of inflammation. Also, these copper chelates have lower toxicity and stronger anti -inflammatory activity than their parent compounds.

Copper Complexes

Although most research utilizing copper complexes has been to determine anti-inflammatory activity, copper complexes have shown potential as a physiological approach to the treatment of numerous chronic diseases. This potential has been expanded to include, in addition to inflammatory diseases, gastrointestinal ulcers, cancers, carcinogenesis, and diabetes. In these conditions much of the research interest has centered on the finding that many copper complexes demonstrate superoxide dismutase (SOD) activity. Because of this, many of these compounds have been designated as SOD-mimetics. One of the better recent reviews on this topic of copper complexes is a good example of the breadth of research that has been published on this topic. This review, published in the journal Progress in Medicinal Chemistry, is 110 pages long and contains a bibliography of 736 references.**71** Unfortunately, despite the tremendous promise that copper complexes have in many varied diseases and conditions, clinical interest in these compounds has been almost nonexistent. While copper is slowly becoming less misunderstood, one can only hope that it will eventually be properly utilized in its potential for maintaining health and treating disease.

Copper Supplementation

The importance that adequate copper nutriture plays in ensuring health, coupled with the fact that few of us obtain the recommended 2-3 milligrams daily of copper in a normal diet, makes copper supplementation essential if we are to prevent an inadequate copper intake. Most human supplements of copper contain either copper sulfate or copper gluconate, two well utilized forms of copper. However, because copper outside of biological systems can catalyze oxidation, the preferred type for multivitamin/mineral supplements is a coated form of copper, such as coated copper gluconate. This allows for all the important benefits of copper, without having the copper lower the vitamin/mineral supplements shelf-life. For most of us on average diets that contain 1-2 milligrams of copper, and not consuming large amounts of the copper antagonists vitamin C (>1000 milligrams) and zinc (>30 milligrams) daily, a daily supplement of 1-3 milligrams of copper should be adequate. Consumers of larger amount of vitamin C and zinc would be well advised to supplement with 3 milligrams of copper daily. Additionally, some people may wish to supplement with special forms of copper such as copper salicylate. Total copper supplementation should not exceed 5 milligrams daily, except under a physician's supervision.

No information in this article should be taken as a recommendation. If you have any questions about the relationship between copper and your health, seek the advice of a qualified physician.

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