

Letters to the Editor

To the editor:

S.M. Lynch and L.M. Klevay recently reported that copper deficiency has an effect on plasma coagulation factor activities in mice.¹ In their introduction they stated that "elevated plasma activity of certain coagulation factors may be indicative of increased risk of coronary heart disease (CHD)." In a recent article, Salonen et al. showed that an association exists between high levels of tissue iron and the increased risk of CHD.² Other investigators have previously suggested that iron overload may be a major cause of CHD. In 1981 Dr. Jerome L. Sullivan, Director of Clinical Laboratories at the Veterans Affairs Medical Center in Charleston, SC USA, proposed that iron should be considered as a risk factor for heart disease.³ Since that time, other researchers have demonstrated that when tissue iron is chelated by deferoxamine, myocardial reperfusion injury is greatly ameliorated.⁴ Recently we have shown that deferoxamine treatment⁵ and low dietary iron⁶ decreased levels of stored liver iron, which in turn resulted in the prevention of heart pathology in copper-deficient rats. These studies in toto strongly support the concept of a major role for iron in myocardial pathology. Indeed, these findings may challenge current recommendations for dietary intake of iron.

The copper deficient mice of Lynch and Klevay's study¹ were severely anemic. The females were more anemic than the males. The relative size of the heart from the copper-deficient mice was significantly increased compared with the copper-adequate control groups. However, heart size of the females were further increased.

In the description of the composition of the diets, the authors failed to provide specifics regarding the level of the dietary iron. In the discussion the authors stated that the copper-deficient animals exhibited "increased liver iron." Unfortunately, however, data were not shown.

In view of the increased implication that excessive dietary iron intake and iron overload promote heart pathology, it would be helpful to know what the level of dietary iron was and what the levels of liver iron were. It is well established that copper deficiency is associated with elevation of hepatic iron. Increased iron intake aggravates the signs associated with copper deficiency. Were the levels of dietary iron of the present study¹ in excess of the levels recommended for rodents?

Because female mice were more anemic than males, and they exhibited cardiac thrombotic lesions, I hypothesize that the female mice may also exhibit higher hepatic iron concentration than the male mice. If this is so, then the results obtained from the study of Lynch and Klevay¹ may not be simply due to copper deficiency per se, but rather due to the combination of copper deficiency with the elevation of hepatic iron concentration, due to both copper deficiency and high dietary iron intake.

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To the editor:

The diet used in our experiments was introduced nearly 30 years ago¹ and was subsequently modified by Ball et al. as an improvement of the thrombogenic diets then in use. Examination of the diet and the cardiovascular lesions it produced led to the suspicion that copper deficiency, not excessive fat, was responsible. Experiment² confirmed this suspicion and provided further improvement in the diet.

It is quite possible that iron contributes to the cardiovascular pathology. Our diet³ is high in iron (198 mg Fe/kg) in comparison with the amount recommended for rodents (35 mg/kg).⁴ It is well known that liver iron is increased in copper deficiency; in fact, increased liver iron is the most sensitive index of copper deficiency.⁵ The following data on liver iron are offered as an addition to *Table 1*.

It is interesting to note that liver iron was highest in female Cu-deficient mice; a group that experienced extreme cardiac enlargement with thrombotic lesions and death.³ This observation tends to agree with the finding that supplementation of Cu-deficient animals with deferoxamine may partially prevent heart enlargement.⁶ However, it is important to note that while adequate copper nutrition completely prevents heart enlargement,³ treatment with deferoxamine only partially inhibits the heart enlargement resulting from extreme copper deficiency.⁶

The copper deficiency theory⁷⁻¹⁰ on the origin and development of ischemic heart disease is based on experiments with animals and human volunteers, epidemiologic observations, iatrogenic maneuvers, and experiments of nature. Emphasis has been placed on the apparently low copper in the Western diet; the more than sixty anatomical, chemical, and physiological similarities between animals deficient in copper and people with ischemic heart disease; the aggravation of risk factors in men and women depleted of copper; and the

Table 1 Relative heart size in male (M) and female (F) mice fed copper-supplemented (S) or copper-deficient (D)

	M-S	M-D	F-S	F-D	Cu	Sex	Inter
Fe* (mg/g)	0.49 (0.05)	1.88 (0.22)	1.36 (0.16)	2.67 (0.17)	$P < 0.001$	$P < 0.001$	NS

*Reported on dry weight basis as mean (standard error).

dependence on copper of some enzymes affecting the metabolism of lipids and connective tissues and in the defense against free radicals.

The iron hypothesis of Sullivan¹¹ may become incorporated into the copper deficiency theory on further investigation, along with other hypotheses such as hard/soft water, homocysteine, benefits of nuts, and male/female differences, etc. Supplementation of human diets with iron probably is safe if copper intakes are adequate; otherwise, excessive iron may resemble excessive zinc in being potentially hazardous.^{9,12,13}

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Applicants should have a doctoral degree with strong background in phospholipid biochemistry and signal transduction. Research will focus on choline, phosphatidylcholine, and signal transduction in hepatocarcinogenesis. In addition, studies will examine how signal transduction regulates the mammary cell's secretion of lipid into milk. Individual must work with gas-chromatography mass spectrometry, and must be able to develop molecular biologic techniques for use in investigating above problems. The individual will work with the chairman of the department to supervise and develop research programs in the above areas. Position is available May 15, 1993. Minority and women applicants are encouraged to apply. AA/EOE. Send resume to Dr. Dexter Louie, Department of Nutrition, CB #7400 McGavran-Greenberg Building, University of North Carolina, Chapel Hill, NC 27599-7400.