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 treatment[5] and low dietary iron[6] 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 study[1] 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 study[1] 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 Klevay[1] 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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References

1 Lynch, S.M. and Klevay, L.M. (1992). Effects of a dietary copper deficiency on plasma coagulation factor activities in male and female mice. *J. Nutr. Biochem.* **3,** 387–391
2 Salonen, J.T., Nyyssonen, K., Korpola, H., Tuomillehto, J., Seppanen, R., and Salonen, R. (1992). High stored iron levels are associated with excess risk of myocardial infarction in Eastern Finnish Men. *Circulation* **86,** 803–811
3 Sullivan, J.L. (1981). Iron and the sex difference in heart disease risk. *Lancet* **1,** 1293–1294
4 Reddy, B.R., Kloner, R.A., and Przyklenk, K. (1989). Early treatment with deferoxamine limits myocardial ischemic/reperfusion injury. *Free Radic. Biol. Med.* **7,** 45–52
5 Fields, M., Lewis, C.G., Lure, M.D., Burns, W.A., and Antholine, W.E. (1991). The severity of copper deficiency can be ameliorated by deferoxamine. *Metabolism* **40,** 105–109
6 Fields, M., Lewis, C.G., Lure, M.D., Burns, W.A., and Antholine, W.E. (1993). Low dietary iron prevents both free radical formation and heart pathology of copper deficient rats fed fructose. *Proc. Soc. Exp. Biol. Med.* **202,** 225–232

To the editor:

The diet used in our experiments was introduced nearly 30 years ago[1] 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. Experiment[2] confirmed this suspicion and provided further improvement in the diet.

It is quite possible that iron contributes to the cardiovascular pathology. Our diet[3] 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 nutriture completely prevents heart enlargement,[3] treatment with deferoxamine only partially inhibits the heart enlargement resulting from extreme copper deficiency.[6]

The copper deficiency theory[7–10] 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