Comments (43630A)

Medeiros, Davidson, and Jenkins, *Proceedings of the Society for Experimental Biology and Medicine,* **203**:262–273, 1993, are to be complemented on their timely Minireview on cardiomyopathy related to consumption of a diet inadequate in copper. It was also gratifying to see the inclusion of a tentative working model to explain the events leading to cardiac failure in copper deficiency. However, the Minireview and the model have a basic flaw which should be addressed. The purpose of a review is to provide a historical account of all of the relevant experiments related to the specific topic of the review. A more difficult step is to attempt to make "sense" out of all of the information, and the inclusion of a hypothetical model is a bonus and provides food for thought. The Minireview by Medeiros *et al.* nearly provided an excellent historical account of all of the relevant references, with the exception of the exclusion of data that have been generated over the past decade at the Human Nutrition Research Center in Beltsville, MD. This is not necessarily a trivial comment because consideration of the excluded information forces one to reconsider the model proposed by Mederios *et al.* We have shown repeatedly for over a decade that if you provide male weanling rats with a diet that is deficient in copper and contains sucrose or fructose as its carbohydrate, the rats develop cardiac lesions, hypertrophy, altered biochemical function, and pathology as described by Medeiros *et al.* However, this outcome occurs only under specific dietary conditions. The carbohydrate of the diet must contain sucrose or fructose. If the carbohydrate of the diet is starch and the diet is deficient in copper, organ copper concentrations will be low and the activity of copper-dependent enzymes will be low or nondetectable, but there will be only mild cardiac lesions, mild hypertrophy, little pathology, and the rats can eat the copper-deficient diet indefinitely without death by hemothorax or aneurysms. The conclusion that one is forced to come to is that in the rat copper deficiency by itself is not sufficient to produce the cardiomyopathy of copper deficiency! There is an interaction between dietary fructose and copper that results in the cardiomyopathy of copper deficiency. If Medeiros *et al.* had not excluded this information from their Minireview, then their model for cardiac failure in copper deficiency would have looked considerably different. The model must take into consideration all the known observations. Interactions are common in biology and they are not easy to decipher. It would be difficult to include information from the observation on the dietary fructose and copper interaction in the scenario proposed by Medeiros *et al.* It is much easier to say that one is working with main effects of copper. If the authors come to this conclusion, then they owe it to their readers to inform them that the proposed model was designed for very restricted conditions and that the model does not explain all the known observations.

In view of this exclusion of publications from the Beltsville Human Nutrition Research Center from the Minireview of Medeiros *et al.*, we can only conclude that this Minireview is misleading to the scientific community and it is gross negligence or deliberate omission of certain data on the part of the reviewers. Medeiros *et al.* have ignored a segment of the scientific literature on the topic of cardiomyopathy.

We interpret our collective data as strongly suggesting that copper deficiency does not result in cardiomyopathy, nor does consuming fructose as the dietary carbohydrate result in cardiomyopathy. Rather, it is an interaction between copper and fructose that leads to the cardiomyopathy. The model proposed by Medeiros *et al.* considered changes in metabolic events to a single dietary component and does not consider the multiple changes in dietary components that are known to be required to produce the cardiomyopathy.

We have included a list of 13 publications from the Beltsville Human Nutrition Research Center that point out the complexity of developing the cardiomyopathy of copper deficiency. The other 150 publications that are not included herein also provide evidence that the type of dietary carbohydrate, dietary protein, age, and sex of the rat greatly play a role in the pathologic consequences and mortality of copper deficiency.

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1. Fields M, Ferretti RJ, Smith JC, Reiser S. Effect of copper deficiency on metabolism and mortality in rats fed sucrose or starch diet. J Nutr **113**:1335–1345, 1983.
2. Reiser S, Ferretti RJ, Fields M, Smith JC. Role of dietary fructose in the enhancement of mortality and biochemical changes associated with copper deficiency in rats. Am J Clin Nutr **38**:214–222, 1983.
3. Fields M, Ferretti RJ, Smith JC, Reiser S. Effect of dietary

carbohydrate and copper status on blood pressure in rats. Life Sci **34**:763–769, 1984.
4. Fields M, Lewis CG, Scholfield D, Powel A, Rose AJ, Reiser S, Smith JC. Female rats are protected against the fructose induced mortality of copper deficiency. Proc Soc Exp Biol Med **183**:145–149, 1986.
5. Fields M, Lewis CG, Beal T, Scholfield D, Patterson K, Smith JC, Reiser S. Sexual differences in the expression of copper deficiency in rats. Proc Soc Exp Biol Med **186**:183–187, 1987.
6. Bhathena SJ, Kennedy BW, Marsh P, Fields M, Zamir N. Differential effect on copper deficiency on plasma atrial natriuretic peptides in male and female rats. In: Hurley LS, Keen CL, Lonnerdal B, Rucker RB, Eds. Trace Elements in Man and Animals 6. pp115–116, 1988.
7. Bhathena SJ, Kennedy BW, Marsh PA, Fields M, Zamir N. Increased circulating atrial natriuretic peptides in copper deficient male rats. In: Brenner BM, Laragh JH, Eds. Advances in Atrial Peptide Research. Vol **2**: pp319–322, 1988.
8. Bhathena SJ, Kennedy BW, Smith JC, Fields M, Zamir N. Role of atrial natriuretic peptides in cardiac hypertrophy of copper-deficient male and female rats. J Trace Elem Exp Med **1**:199–208, 1988.
9. Redman RS, Fields M, Reiser S, Smith JC. Dietary fructose exacerbates the cardiac abnormalities of copper deficiency in rats. Atherosclerosis **74**:203–214, 1988.
10. Fields M, Ferretti RJ, Reiser S, Smith JC. The severity of copper deficiency in rats is determined by the type of dietary carbohydrate. Proc Soc Exp Biol Med **175**:530–537, 1989.
11. Burns WA, Fields M, Smith JC, Reiser S. Myocardial lesions in copper deficiency modified by dietary carbohydrate. J Trace Elem Exp Med **3**:67–77, 1990.
12. Scholfield DJ, Reiser S, Fields M, Steele NC, Smith JC, Darcey S, Ono K. Dietary copper, simple sugars and metabolic changes in pigs. J Nutr Biochem **1**:362–368, 1990.
13. Fields M, Lewis CG, Lure MD. Anemia plays a major role in myocardial hypertrophy of copper deficiency. Metabolism **40**:1–3, 1991.

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Response to Letter by Lewis, Fields, and Lure

Lewis *et al.* claim that the "Minireview is misleading to the scientific community and it is gross negligence or deliberate omission of certain data on part of the reviewers" because the Minireview did not, in their view, adequately address the role of fructose in exacerbating the copper deficiency signs. We contend that we were not negligent. The charge that we deliberately omitted references to many of the Beltsville group's papers is not entirely correct. Apparently, these scientists thought we should have focused only on their fructose-copper research at the expense of the fine research of other laboratories. On page 263, first column we discussed the role of fructose in Reiser's (*American Journal of Clinical Nutrition* **42**:242–251, 1985) classic paper. Other Beltsville researchers (Schoenemann *et al.*) are also cited.

The Minireview, as opposed to a full-length review, was intended to focus on a potential mechanism that may be responsible for the cardiomyopathy in copper deficiency, not the descriptive studies pertaining to fructose/sucrose effects upon copper deficiency. We did not mislead since we acknowledge a role of fructose in the paper. To contend that the cardiomyopathy occurs only when fructose and/or sucrose are fed in combination with a copper-deficient diet cannot be stated conclusively, since many of the studies, but not all, cited by Lewis *et al.* used relatively insensitive techniques (i.e., heart weight or heart:body weight) when examining cardiac parameters indicative of cardiomyopathy. It can also be argued that many of the studies were not of long enough duration to fully evaluate the influence of dietary corn starch and/or glucose as the primary carbohydrate. Early work conducted by Shields *et al.* (*American Journal of Pathology* **41**:603, 1962) demonstrated significant cardiac lesions and a high rate of mortality in pigs fed a cornstarch-based copper-deficient diet. While it is generally agreed that fructose and/or sucrose feeding in combination with a copper-deficient diet do exacerbate the signs of copper-deficiency when compared with a cornstarch- and/or glucose-based copper-deficient diet, this is in the context that those animals fed fructose and/or sucrose develop the problems in a matter of weeks, at which time many such studies are terminated. An analogous situation can be demonstrated by some of our recent work on post-weanling rats, where copper restriction does produce cardiomyopathy but not hypertrophy. In previous studies, many researchers, including ourselves, thought that cardiac problems as related to copper deficiency were only unique to young, growing animals because of the fact that older rats, when fed a copper-deficient diet, did not develop cardiac hypertrophy. As pointed out in the review, we now know that cardiomyopathy does occur without hypertrophy in older copper-restricted rats. This occurs despite the fact they are of marginal copper status, not deficient. We are also set to begin a study in which we plan to feed marginal copper levels with a sucrose-based diet as a source of carbohydrate and determine the cardiac pathology, function, and molecular aspects over a 12-month period. Length of time may be a critical aspect that many nutrition studies do not take into account. Using a cornstarch or glucose-based diet in combination with copper deficiency over a similar length of time may test whether such conditions may lead to cardiac dysfunction and should be pursued.

We did not intend to offend the Beltsville group when we did not focus our review on the fructose influence of copper deficiency. However, we are disturbed that many researchers tend to focus only on how

many times they are cited in a paper. We are well aware of the Beltsville group's fine contributions to this field. In many of our scientific papers we have referenced their work and in an older review by the senior author, we did review much of the work on sucrose and fructose (*Biochemical Archives* **1**:67–73, 1985). In the Minireview, we did not even mention our recent publication pertaining to the influence of fat type upon alteration of ventricular hypertrophy. In an article published in the June issue of the *Journal of Nutrition* (Jenkins and Medeiros, **123**:1150–1160, 1993), we cited the work of the Beltsville group pertaining to the fructose connection at least four times. It is because of their work that we continue to use a high sucrose diet when studying copper deficiency upon cardiac parameters. Furthermore, it was our assumption that the focus of the Minireview was one of cardiac mechanism(s) as affected by copper deficiency. Lewis *et al.* failed to note that we did not even mention much of the work conducted on lipoproteins as affected by copper deficiency and the elegant work of David Lei's laboratory at the University of Arizona. We believed that the questions of both lipoproteins and fructose/sucrose were not directly related to this Minireview (as opposed to a full-length review) on mechanisms and comparative aspects, especially molecular aspects, of the copper-deficient heart model. This is also apparent from the letter by Lewis *et al.*, which gives us no clue as to the mechanism by which fructose apparently exacerbates the copper deficiency signs, but stresses purely descriptive aspects of their studies. Perhaps a Minireview on the fructose/sucrose and copper connection is in order.

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