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This Week's Citation Classic®

Klevay L M. Hypercholesterolemia in rats produced by an increase in the ratio of zinc to copper ingested. *Amer. J. Clin. Nutr.* 26:1060-8, 1973.
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An increase in the ratio of zinc to copper ingested produced hypercholesterolemia in rats in five experiments done in three years in two environments. Consonance was established with coronary heart disease epidemiology, for example, risks associated with soft water, diets high in sucrose and low in fiber, and lack of exercise. [The *SCI*® indicates that this paper has been cited in over 170 publications.]

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While writing a thesis on dietary fat and bile acid metabolism at the Harvard School of Public Health in the early 1960s, I gradually became fascinated by the inverse association between the hardness of drinking water and the risk of death from coronary heart disease. I remember discussing the reality of the association with Jane Worcester. I spent three weeks in the geology library, read some geology texts cover to cover, and began a limited experimental search for trace elements that could alter the concentration of cholesterol in blood. Even then it was clear that cholesterol was important in the pathophysiology, if not the etiology, of heart disease.

I then moved to the University of Cincinnati, partly because of a tradition there of research on health effects of metallic elements. At that time few people, besides Henry A. Schroeder and Walter Mertz, knew how to do trace-element experiments and realized their potential importance in medicine. As a means of learning more about trace-element research, I appended measurements of trace elements to a nutritional survey of the Republic of Panama. We designed an environment for trace-element research in which I did some of these experiments.

I was reluctant to attribute my results to copper deficiency since decreases in hematocrit were minimal. I thought I had found a phenomenon analogous to the amino acid imbalances studied by Alfred E. Harper. A dozen chemicals now are known[1] to reciprocally alter copper nutriture and cholesterol in plasma, and it is known that anemia is not a necessary concomitance of deficiency. The induction of copper deficiency by excess zinc is the simplest explanation. The phenomenon has been confirmed in at least eight independent laboratories.

Hans Selye says that scientific results are important if they are true, generalizable, and surprising. The truth of the phenomenon is demonstrated by my five experiments and the eight confirmations. The discussion of results was limited to generalizability in the context of coronary heart disease. Although I was searching for the effect, the results were surprising, as *Nutrition Reviews* had never linked zinc, copper, and cholesterol. I believe the paper is frequently cited because it contains the first data linking copper nutriture and cholesterol metabolism.

These results provide the basis for the theory[2-5] implicating copper metabolism in the origin of ischemic heart disease. Copper deficiency is the only nutritional insult that produces hypercholesterolemia, glucose intolerance, abnormal electrocardiograms, hypertension, and hyperuricemia together. As these characteristics are the major predictors of heart disease risk, and diets[6] in the US seem to be low in copper, copper deficiency may be important in its origin. The theory has been developed in a series of experimental and theoretical papers; I hope it assists in simplifying the explanations of ischemic heart disease.

1. Klevay L M. Aspirin hypocholesterolemia associated with increased microsomal copper in liver. *Nutr. Res.* 6:1281-92, 1986.
2. ———. Coronary heart disease: the zinc/copper hypothesis. *Amer. J. Clin. Nutr.* 28:764-74, 1975. (Cited 135 times.)
3. ———. The influence of copper and zinc on the occurrence of ischemic heart disease. *J. Environ. Pathol. Toxicol.* 4:281-7, 1980.
4. ———. Copper and ischemic heart disease. *Biol. Tr. Elem. Res.* 5:245-55, 1983.
5. ———. The role of copper, zinc, and other chemical elements in ischemic heart disease. (Rennert O M & Chan W-Y, eds.) *Metabolism of trace metals in man. Volume I. Developmental aspects.* Boca Raton, FL: CRC Press, 1984. p. 129-57.
6. ———. An appraisal of current human copper nutriture. (Sorenson J R J, ed.) *Inflammatory diseases and copper: the metabolic and therapeutic roles of copper and other essential metalloelements in humans.* Clifton, NJ: Humana Press, 1982. p. 123-6.

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