Lack of Correlation Between Zinc, Copper and C-Reactive Protein in Human Serum.* (27546)

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The appearance in serum of the acute-phase or C-reactive protein (CRP) is accepted as a reliable index of inflammation or tissue destruction(1). The cuproprotein, ceruloplasmin, also responds similarly to inflammation as another of the numerous known acute-phase reactants(2). Hence, elevated serum ceruloplasmin (copper) levels occur in a variety of conditions such as myocardial infarction, cirrhosis, rheumatoid arthritis, rheumatoid heart disease, and most acute and chronic infections. The rise of serum copper seen in pregnancy, and with administration of certain hormones such as testosterone and estrogen, is quite striking(3).

In contrast to the situation with copper, relatively little is known concerning factors which affect serum zinc levels. Johnson(4) recently reported that total serum zinc concentration declines with parenteral administration of testosterone propionate and estradiol benzoate in non-pregnant subjects and also that there is a decrease in total serum zinc content during normal pregnancy. A 20-25% lowering of serum zinc during pregnancy has been noted by various investigators (5-7). Both the rise in serum copper and the fall in serum zinc of the mother are attributed to the continuous elaboration of estrogen(4).

Variations in serum zinc under pathological conditions have been examined especially by Vikbladh(7) and values obtained showed rather marked uniformity. Patients with acute infectious diseases had a decrease in serum zinc values during the febrile stage, which became rapidly normal upon recovery. Uncomplicated cases with hemorrhagic anemia and essential iron deficiency anemia showed only a slight decrease in serum zinc content, which was not significant in comparison with normal controls. Low serum zinc values, on the other hand, were usually encountered in untreated cases of pernicious anemia. A significant decrease in zinc content was also found in patients with leukemias, malignant tumors, hepatic disease, chronic polyarthritis and chronic nephritis. Cases of acute rheumatic fever in the afebrile stage, acute nephritis, gastric ulcers, and diabetes mellitus did not show any particular deviation from the normal distribution. Elevated serum zinc values, with the exception of newborn infants, were rarely encountered.

Since these investigations seem to indicate that serum zinc may vary in inflammatory conditions, the present study was undertaken to investigate more fully the concentration of zinc in serum with reference to copper and particularly to presence or absence of CRP.

Methods. The blood was collected randomly from non-pregnant hospital patients with "B-D Vacutainer" apparatus using "No. L-3200 tubes for blood lead determination" and disposable needles. Most samples were taken 3 hours or more after meals, although no special effort was made to use only "fasting" subjects. Medications were not recorded. Serum was separated promptly from the cells and analyzed the same day. A total of 100 sera were analyzed for zinc(8), copper(9), and C-reactive protein by the capillary precipitin method employing commercially available CRP anti-serum.

Results and discussion. The "normal" values adopted in the present study are as follows: zinc, 80-160 μg/100 ml serum; copper, 70-140 μg/100 ml serum; CRP, absent. (In samples showing a positive CRP reaction, the millimeters of precipitate determined the degree of positive reaction. For example, a 2-mm precipitate is referred to as a 2+ CRP reaction, etc.)

A summary of the data (Table I) shows that the concentration of serum zinc tends to be depressed slightly in presence of CRP,

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TABLE I. Zinc and Copper Content of 100 Sera in Relation to CRP Reaction.

No. of sera	CRP	Zn* Mean	Zn* Range	Cu† Mean	Cu† Range
		(μg/100 ml)			
55	0	126	(48-167)	123	(65-197)
19	1+	109	(56-160)	144	(91-206)
7	2+	117	(60-148)	189	(152-269)
5	3+	117	(87-150)	179	(151-208)
14	4+	117	(77-154)	176	(106-256)
100					

* Duplicate determinations
† Single "

but that the decrease does not appear to depend upon the intensity of the CRP reaction. In agreement with previous findings(10) serum copper generally increases with the CRP reaction, indicating that it responds more typically as an acute-phase reactant. The data in Table I can be further summarized by stating that the mean concentration of zinc of the 55 sera with negative CRP reactions is 126 μg/100 ml as compared with a mean of 113 μg for the 45 sera showing positive CRP reactions. In contrast, the corresponding concentrations of serum copper are 123 and 165 μg/100 ml.

The results of the zinc and copper levels were compared with each other irrespective of their relations with the CRP test. There were 56 sera which had a "normal" copper level, *i.e.*, less than 140 μg/100 ml and 44 sera with copper concentrations greater than this value. The mean concentration of zinc in the former group is 122 μg/100 ml, while the mean concentration in the latter "abnormal" group is 118 μg, again indicating that the level of zinc in the serum is not influenced markedly by inflammatory processes. The *relative* constancy of the serum zinc levels in contrast to the larger variations in copper indicates that serum zinc and copper concentrations are independent variables. In this regard, one should note that there is similarly no evidence of a correlation between serum copper and iron levels in any healthy or diseased individual(11). However, the serum iron levels are well below "normal" in infections.

The present study confirms earlier findings (7) that while zinc normally occurs in serum in about the same concentrations as copper (and iron) it varies less in pathological conditions than the later metals. Changes in the serum zinc level in disease states are evidenced almost always through a reduction in serum zinc concentration. Such changes are shown herein to bear no overt relationship to acute-phase phenomena. Apparently there are factors such as pregnancy(4-7) which may affect more noticeably than inflammation or tissue destruction the zinc-copper relations in serum.

Summary. The concentrations of total zinc and copper in sera from 100 non-pregnant hospital patients were examined particularly in relation to the CRP reaction. Although the concentration of serum zinc tends to be slightly lower in the presence of CRP, the decrease does not correlate with the intensity of the CRP reaction and/or with the degree of hypercupremia. The data demonstrate that serum zinc and copper concentrations are independent variables.

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