Editorial

Copper in Health and Disease

One "trace" element which, until recently, has received comparatively little attention in relation to human disease is copper. This substance is found widely distributed in nature and is present in foodstuffs and water, the quantity depending on the soil content of copper. Foods known for their high copper content include nuts, dried legumes, cereals, dried fruits, poultry, fish, and animal tissues. The normal diet contains at least 2.5 to 5 mg of copper per day. The exact daily requirement for copper is unknown but it is of the order of 2 to 3 mg per day in adults. There are approximately 100 to 150 mg copper in the human body. Almost half of this is present in muscles; the bones and liver also contain substantial proportions.

The full significance of the functional role of copper is obscure, but it is known that this metal is concerned in erythropoiesis and that it is important in the formation of bone as well as in maintaining the myelin of the nervous system.[1] Copper deficiency, experimentally produced, results in the development of a severe anemia which, in swine, is microcytic and hypochromic in type and is accompanied by a profound disturbance in iron metabolism. Thus, there is marked hypoferremia, the absorption of iron is impaired and the production of red corpuscles is disturbed. Furthermore, it has been found that in deficient animals a marked reduction in osteoblastic activity takes place. Bone is not deposited on the calcified cartilagenous matrix and deformities develop.[2] Finally, in the syndrome of "enzootic ataxia," which has been described in lambs feeding on a soil deficient in copper in Australia, degenerative changes are found in the corpus callosum, in the internal capsules and in the white matter of the frontal lobes as well as in the motor pathways of the spinal cord.[1]

Copper is also known to be essential for maintaining the color of fur and for the production of "ink" in the squid and octopus. In addition, it is necessary for the folding of the keratin molecule and is thus essential in maintaining the normal structure of wool.[3] Copper is a constituent of certain enzymes and its importance in metabolism is attributable in part to this fact.

In man, considerable interest has been directed recently to the measurement of serum copper and to the variations which occur in health and disease.[4] The serum copper consists of two fractions. One of these, which reacts promptly with diethyldithiocarbamate and is therefore known as the "direct-reacting" fraction, consists of copper loosely bound to albumin and is probably copper in transport. This fraction represents very little of the serum copper. The major fraction, as much as 96 per cent in man, is firmly bound to an alpha$_2$-globulin and consists mainly of the blue copper compound, *ceruloplasmin*. This substance has been shown to possess enzymatic activity as a polyphenyl oxidase. There is good correlation between the oxidase activity of plasma and the ceruloplasmin level but whether or not this is of physiologic significance is unknown. In blood, copper is also found in the red cells. A colorless copper compound which has been named "erythrocuprein" has been isolated recently.[5]

The serum copper is increased under a great variety of circumstances.[1] An increase occurs in pregnancy and is observed also in association with many infectious diseases, when tissue destruction is taking place, in acute leukemia and in many other disorders, including even cases of schizophrenia. It would appear that hypercupremia is a rather nonspecific reaction and therefore, the finding of hypercupremia is of little use as an aid in differential diagnosis.

Hypocupremia, on the other hand, is uncommon. Best known is the hypocupremia of Wilson's disease.[6] In this condition there is a

marked reduction in the ceruloplasmin level. It is not always appreciated, however, that the direct-reacting fraction of the serum copper is not reduced in Wilson's disease and often it is substantially increased in amount. Thus, although in most patients with Wilson's disease hypocupremia is present, the *total* serum copper may, in some cases, be little or not at all reduced.

Hypocupremia has not been observed in human nutritional deficiencies and, in fact, nutritional deficiency of copper has, so far, not been recorded in man. Hypocupremia has been observed, however, in some cases of sprue and it is frequently found in association with the nephrotic syndrome.[7] In the latter condition, the excretion of copper in the urine is correlated with the proteinuria characteristic of this disorder.

Of special interest are the recent reports describing infants who have been observed to have hypocupremia in addition to hypoferremia, hypoproteinemia, edema and hypochromic microcytic anemia.[8,9] The cause of this striking syndrome is obscure. Dietary deficiency of copper and abnormality of protein metabolism at the cellular level have been suggested as the underlying causes. The condition has been corrected rather easily with iron therapy and "spontaneous" cure has also been observed.

Further studies of the role of copper in human metabolism as well as elucidation of the manner in which copper functions in the mammalian organism should be both interesting and fruitful. —M. M. WINTROBE, M.D.

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