CHARACTERISTICS OF PERINATAL COPPER DEFICIENCY

The presence of Cu in animal tissues was recognized during the 19th century, but its essentiality as a nutrient in the diet of mammals was not reported until 1928 by Hart and his associates. The importance of Cu in prenatal development was recognized from studies on the disease "enzootic ataxia" in newborn lambs. This disorder is characterized by spastic paralysis, incoordination of movement, probably due to reduced myelination of the CNS, and anemia. Affected animals usually die within a short time after birth. Copper supplementation of the ewe during pregnancy prevented the disorder.

The teratogenicity of Cu deficiency has been shown in experimental animals. The offspring of guinea pigs fed a Cu deficient diet during pregnancy and lactation have abnormalities of the CNS similar to those found in lambs with enzootic ataxia. The brains of deficient pups are pale and translucent. There is a reduction in myelin content, and that which is present has a low level of phospholipids. Livers are low in Cu, and kidneys are frequently small and immature. Pups that survive birth usually die of aneurysms within 30 days. In rats, newborn pups from Cu deficient dams are hyperirritable and have convulsive seizures after stimulation. The brains of these pups may have pale areas, edema and necrosis; however, unlike lambs with enzootic ataxia, Cu deficient rats do not show nerve fiber degener-
Teratogenic Effects of Copper Deficiency and Excess

Copper deficient rat pups have a low content of myelin and Cu in the brain, but unlike guinea pigs, the composition and amount of brain phospholipids was normal. Mitochondria isolated from the brains of these pups are large and abnormal in shape, with low levels of cytochrome oxidase activity. Interestingly, peroxidation of brain lipids was not increased in spite of the finding of low activity of Cu,Zn superoxide dismutase.

The lesions produced in the CNS by Cu deficiency may be considered as a whole, combining observations from several species. The major effect of Cu deficiency in the brain relates to abnormal myelination. Myelin aplasia, rather than excessive myelin degeneration is apparently the mechanism for the neural lesions. Neural lesions in the Cu deficient fetal lamb are apparent 10 days after the initiation of myelination; at the same time cytochrome oxidase activity increases rapidly in the normal brain. The activity of cytochrome oxidase is lower than normal in brains of ataxic animals, which may lead to tissue anoxia and insufficient production of ATP needed for synthesis of components essential for myelination, such as phospholipids.

Skeletal defects occur as a result of Cu deficiency. Lambs with enzootic ataxia may have poorly developed, light, brittle bones with frequent fractures. Bone abnormalities have been found in Cu deficient calves and fowls. In dogs, and swine it was found that young born to females fed Cu-deficient diets had deformed leg bones. The lesions appeared to be associated with an impairment of osteogenesis, with the resultant thinning of the cortex and trabeculae of the long bones. Copper deficient chicks are different, having severe hypoplasia of the long bones. Amine oxidase and cytochrome oxidase activities are low and there is a high ratio of soluble to insoluble collagen. The increased fragility of Cu deficient bones appears to result from the low number of crosslinkages present in the collagenous matrix.

That dietary Cu deficiency could result in cardiovascular lesions is indicated by reports that cardiac hemorrhages and low tissue Cu levels are characteristic of "falling disease" in cattle. Newborn of Cu deficient rats show signs of cardiovascular problems, with internal hemorrhaging and smaller lesions throughout the cardiovascular system. Similar lesions have been observed in Cu deficient guinea pigs, rabbits, pigs, and chicks. The principle biochemical lesion is thought to be a decreased activity of the enzyme lysyl oxidase. Thus, in deficient animals,