MASTER

Part A. Amino acid, lipid and red blood cell studies on selenium toxicity with the laboratory rat.

The amino acid and lipid analysis on blood and liver and the amino acid analysis on urine gave irregular values for each determination. Therefore, the average values which were presented in the 1966 Technical Progress report (COO-1449-2) were not considered valid and were not submitted for publication. However, experiments on the *in vivo* conversion of ^{75}Se -labeled selenite-Se to urinary metabolites led to the observance of an unknown metabolite. This metabolite, which was different from the ordinary selenium analogues of sulfur, was designated as "U-1" (COO-1449-3). The use of ^{59}Fe was involved in the study of the anemia of chronic selenium toxicity. The findings because of the labeled iron led to the conclusion that the anemia was from massive hemolysis (COO-1449-3).

PUBLICATIONS: A. W. Halverson, D.-T. Tsay, K. C. Triebwasser and E. I. Whitehead. Development of hemolytic anemia in rats fed selenite. *Toxicol. Appl. Pharmacol.* 17:151 (1970).

GRADUATE STUDENTS TRAINED: Mary Abraham, M.S., 1966

Part B. The nature and importance of selenium metabolites in the animal.

The initial work concerned the isolation-identification of the urinary metabolite of selenite as the trimethylselenonium ion, i.e. $(\text{CH}_3)_3\text{Se}^+$ (COO-1449-4). Other forms of selenium, i.e. selenate, Se-methylselenocysteine, selenomethionine, selenocystine and seleniferous wheat, were then shown to give rise to the metabolite (COO-1449-7). The substance was concluded to be a detoxification

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product of selenium because of its rapid excretion when injected (COO-1449-9), because of its relatively low toxicity when fed or injected (COO-1449-10 and COO-1449-13) and because of its inactivity against the necrogenic syndrome (COO-1449-9).

Additional information on the metabolism and properties of the trimethylselenonium ion in the rat have been obtained. The *in vitro* biosynthesis of the substance was accomplished by incubating ^{75}Se -labeled Na_2SeO_3 with liver or kidney extract in a medium (1) containing S-adenosyl-1-methionine and certain activators (COO-1449-11). Evidence was then obtained that the *in vivo* conversion of selenite-Se to urinary trimethylselenonium ion does not depend on dietary vitamin E (COO-1449-12). Additional results showed that the injection of large doses of trimethylselenonium ion resulted in the exhalation of only small amounts of selenium (COO-1449-13). The exhalation of selenium was increased during a 6-hour period when arsenite was also administered, presumably because of the effect of arsenite in reducing the urinary excretion of trimethylselenonium-Se. In studying the effect of arsenite on trimethylselenonium toxicity, the results indicated little effect when the substances were administered orally (COO-1449-10 and COO-1449-13). When each form was injected, amounts which were non-lethal alone became lethal when administered at the same time (COO-1449-10 and COO-1449-13). The comparable injection of the sulfur analog, i.e. trimethylsulfonium ion, along with arsenite did not appear to result in increased toxicity (COO-1449-13). This

(1) Biochem. 5, 1089 (1966).

indicated that the selenium, and not just the "onium" structure, was important in the synergistic phenomenon. The effect from trimethylselenonium ion and arsenite when administered by injection was in contrast with the known alleviatory effect of arsenite against selenite toxicity (2,3,4).

The results of work on the form of occurrence of selenium in seleniferous wheat were also of interest. Protein-bound selenomethionine accounted for about one-half of the selenium (COO-1449-6). Selenocystine, the seleno-half-cystine moiety and Se-methyl-selenocysteine were not detected in the hydrolysis products or in the water extracts. Selenocysteic acid appeared to be present in significant amount, however.

PUBLICATIONS: I. S. Palmer, D. D. Fischer, A. W. Halverson and

O. E. Olson. Identification of a major selenium excretory product in rat urine. *Biochim. Biophys. Acta* 177:336 (1969).

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Trimethylselenonium ion as a general excretory product from selenium metabolism in the rat. *Biochim. Biophys. Acta* 208:260 (1970).

O. E. Olson, E. J. Novacek, E. I. Whitehead and I. S. Palmer.

Investigations on selenium in wheat. *Phytochem.* 9:1181 (1970).

D.-T. Tsay, A. W. Halverson and I. S. Palmer. Inactivity of dietary trimethylselenonium chloride against the necrogenic syndrome of the rat. *Nutr. Reports Internat.* 2:203 (1970).

(2) *J. Nutr.* 19, 477 (1940).

(3) *J. Pharmacol. Exptl. Therap.* 84, 115 (1945).

(4) *Proc. S. Dak. Acad. Sci.* 32, 72 (1953).

GRADUATE STUDENTS TRAINED: Ding-tsair Tsay, M.S., 1969 and B. D.
Obermeyer, M.S., 1969.