Effect of Chronic Administration of Mercurial Diuretics on Glomerular Filtration in the Dog.* (17378)

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The acute toxic effects of mercurial diuretics on the heart when administered intravenously are well known.[1-4] Recent reports on Thiomerin, the di-sodium salt of N(γ-carboxymethylmercaptomercuri, β-methoxy) propyl camphoramic acid, have stressed the low cardiac[5,6] and local[7] toxicity when this mercurial diuretic is administered subcutaneously. Enthusiastic support has been given by several authors[8-11] for clinical use of this drug on cardiac patients.

In the following report, we have determined the effect of 3 mercurial diuretics, Thiomerin, meralluride (Mercuhydrin), and mersalyl-theophylline (Merthyl) on glomerular filtration rate in the dog when these compounds are administered intravenously in comparable daily doses.

Methods. Control creatinine clearances were determined on each trained unanesthetized adult female dog one hour after hydration with 40 cc/kg of water by stomach tube. Creatinine determinations were performed by the method of Folin and Wu.[12] A series of 10 dogs were tested with Thiomerin, nine with Mercuhydrin, and 5 dogs were given Merthyl. The diuretics were administered intravenously in a dosage of 0.1 cc/kg/day (0.39 mg Hg/kg/day) for a period of 21 to 28 days. Creatinine clearances were determined at weekly intervals during the test period and in some instances were continued for one or two weeks after drug administration had been discontinued. In addition, mercury excretion determinations were made on three dogs of the Thiomerin series.

Results. Comparison was made of weekly changes in creatinine clearances of the dogs in each drug series. These changes were calculated in terms of percentage increase or reduction in the weekly creatinine clearance of each dog as compared to its control clearance level (Fig. 1, 2 and 3). It was observed that the creatinine clearances in many of the test animals were significantly reduced at the end of the third week of drug administration. However, there was noted a distinct trend toward return to the control clearance level during the recovery period in those animals which were followed for one or two weeks after the drug administration was discontinued.

Comparing the mean percentage changes from the control clearances of the dogs in each series indicates that in the third week Thiomerin produced a significantly greater reduction of creatinine clearance than the other mercurial diuretics tested (Fig. 4).

Evidence of toxicity from the mercurial diuretics developed early in some of the test animals. Three dogs in the Thiomerin series

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1 DeGraff, A. C., and Lehman, R. A., *J.A.M.A.*, 1942, **119**, 998.

2 Volini, I. F., Levitt, R. O., and Martin, R., *J.A.M.A.*, 1945, **128**, 12.

3 Long, W. K., and Farah, A., *J. Pharm. and Exp. Therap.*, 1946, **88**, 388.

4 Lehman, R. A., PROC. SOC. EXP. BIOL. AND MED., 1947, **64**, 428.

5 Lehman, R. A., and King, E. E., *Fed. Proc.*, 1949, **8**, 314.

6 Herrmann, G. R., Chriss, J. W., Schwab, E. H., Hejtmancik, M. R., and Sims, P. M., *Fed. Proc.*, 1949, **8**, 74.

7 Lehman, R. A., Taube, H., and King, E. E., PROC. SOC. EXP. BIOL. AND MED., 1949, **71**, 1.

8 Ruskin, A., Johnson, J. E., and Roddy, W. N., *Fed. Proc.*, 1949, **8**, 329.

9 Grossman, J., Weston, R. E., Edelman, I. S., and Letter, L., *Fed. Proc.*, 1949, **8**, 62.

10 Batterman, R. C., Unterman, D., and DeGraff, A. C., *Fed. Proc.*, 1949, **8**, 272.

11 Herrmann, G. R., *J.A.M.A.*, 1949, **140**, 509.

12 Folin, O., and Wu, H., *J. Biol. Chem.*, 1919, **38**, 81.

THE EFFECTS OF MERCURIAL DIURETICS ON GLOMERULAR FILTRATION

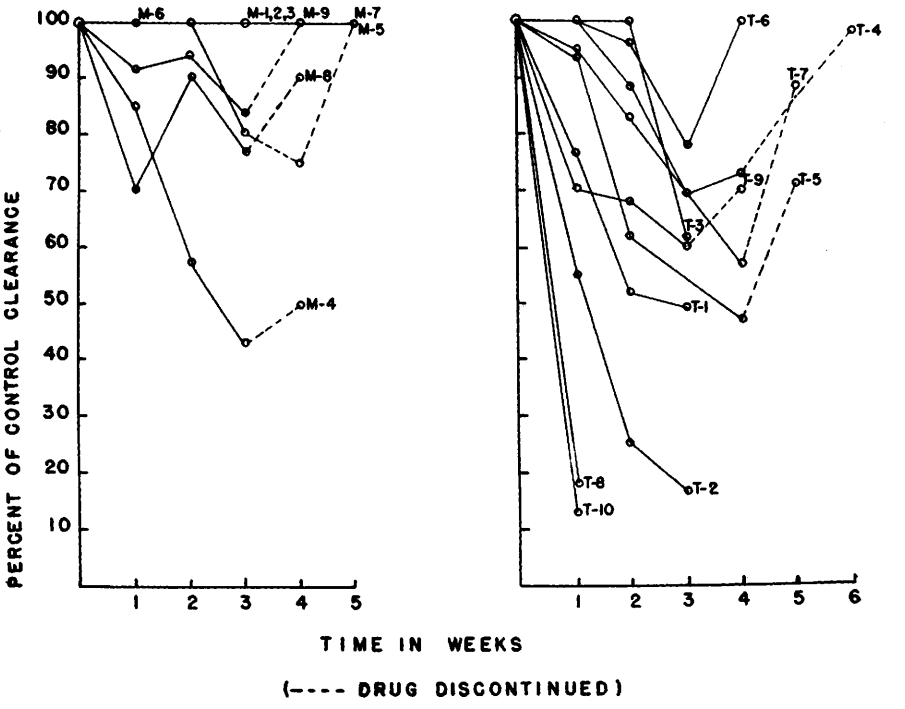

FIGURE 1 MERCUHYDRIN

FIGURE 2 THIOMERIN

(T-3, T-8, and T-10) developed a severe stomatitis in the first week of drug administration. Stomatitis did not occur in the dogs of the Mercuhydrin or Merthyl series. Moderate to severe diarrhea occurred in 4 Thiomerin dogs (T-4, T-5, T-8 and T-10) and none appeared in the Mercuhydrin and Merthyl dogs. Severe dermatitis with generalized loss of hair developed in two Thiomerin dogs (T-6 and T-7) and in one Mercuhydrin dog (M-8). One Thiomerin dog, not included in the series, died on the seventh day and two other Thiomerin dogs (T-8 and T-10) died on the 8th day with evidence of severe mercurial poisoning. A fourth Thiomerin dog (T-6) died with acute pulmonary edema four days after the drug was discontinued. One of the Mercuhydrin dogs (M-6) died on the seventh day of apparent acute cardiac toxicity immediately following intravenous injection of the drug. No deaths occurred in the Merthyl series.

Discussion. The dose employed in these experiments was chosen because it gives satisfactory diuresis in the dog for a period of 4-6 hours. When administered subcutaneously, a variable amount of mercury may be retained at the site of injection by local tissue combination, therefore the diuretics were given intravenously.

In general, evidence of mercurial poisoning was accompanied or heralded by an early reduction of the creatinine clearance. It would appear that the reduction in the glomerular filtration rate is a temporary manifestation if the drug is discontinued before irreparable renal damage is produced. In the dogs that had only mild signs of mercury poisoning, the creatinine clearance returned to normal one or two weeks after discontinuing the drug.

It appears that Thiomerin is more toxic than either Mercuhydrin or Merthyl when tested in this manner. Our opinion is based on the observation of evidence of mercury poisoning such as stomatitis and diarrhea which occurred more frequently in the Thiomerin dogs than

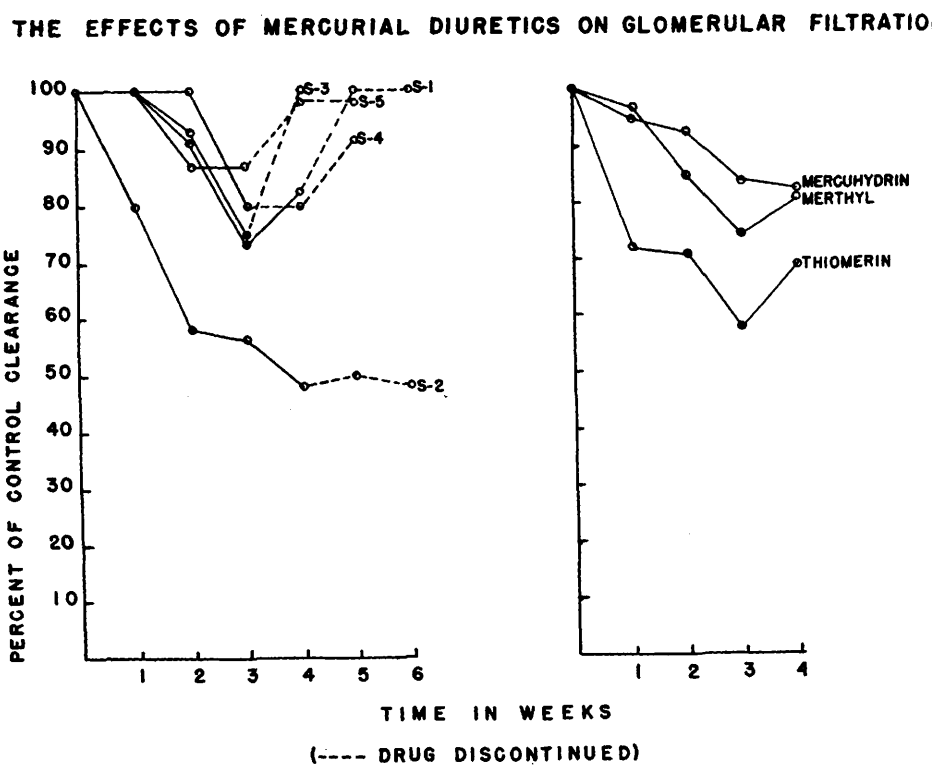

FIGURE 3 MERTHYL

FIGURE 4 MEAN CLEARANCE REDUCTIONS

in the animals given the other two drugs. We also noted that by the third week of drug administration, the creatinine clearances of the Thiomerin dogs were reduced to a greater extent than those of the dogs in the Mercuhydrin and Merthyl series. Special care was taken to use solutions of Thiomerin which were kept refrigerated and not over 4 days old.

Data obtained from mercury excretion determinations of 3 Thiomerin dogs suggested that the excretion of the drug is not as rapid or complete as with other mercurial diuretics. In the few studies conducted, the dogs that showed symptoms of mercury poisoning also showed a delayed excretion of mercury.

Summary. Mercurial diuretics administered intravenously in chronic dosage to dogs reduced the glomerular filtration rate as measured by the creatinine clearance. This reduction in glomerular filtration rate was found to be temporary in most dogs that did not have severe symptoms of mercury poisoning.

Thiomerin, when administered intravenously in comparable chronic dosage to the dog, was found to be of higher toxicity than either Mercuhydrin or Merthyl, as indicated by reduced creatinine clearances, and other signs of mercury poisoning.

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