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Further Studies on the Acute Toxicity of Mercurial Diuretics.*

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A number of reports have appeared concerning a serious and sometimes fatal reaction which has been observed following intravenous injection of therapeutic doses of mercurial diuretics.[1-3] This has been shown to be due to a direct action on the heart giving rise to a variety of changes in rhythm and conduction[4,5] and a decrease in work capacity.[6] The reaction appears to be characteristic of mercurials in general, whether organic or inorganic, and not specifically of the diuretic group.

In a previous report, the acute lethal dose was given for the common diuretics as estimated by intravenous injection in intact unanesthetized cats. This work has now been extended to determine the comparative dosages at which cardiac toxicity develops as indicated in the electrocardiogram. The drugs used in the present comparisons were:

Mercuric Chloride: A 5.4% solution in distilled water.

Mercuzanthin: A solution of the sodium salt of N(γ-hydroxymercuri-β-methoxy) propyl camphoramic acid-theophylline (Mercurophylline Injection U.S.P. XIII).

Salyrgan-Theophylline: A solution of the sodium salt of ortho-N(γ-hydroxymercuri-β-methoxy)propyl carbamyl phenoxy acetic acid-theophylline (Mersalyl and Theophylline Injection, U.S.P. XIII).

Mercuhydrin: A solution of the sodium salt of N(γ-hydroxymercuri-β-methoxy) propyl N'(succinyl)urea and theophylline.

MT6: A solution of the disodium salt of N(γ - carboxymethylmercaptomercuri - β - methoxy)propyl camphoramic acid. N(γ-hydroxymercuri-β-methoxy)propyl camphoramic acid was synthesized from camphor, allyl amine and mercuric acetate by methods described in the literature. A solution of the sodium salt of this acid was then added to an aqueous solution of sodium thioglycollate. The resulting solution of the mercaptide was brought to pH 7 to 8 by addition of sodium hydroxide.

Unless otherwise stated, all of the above drugs were used at a concentration of approximately 39 mg of mercury per cc.

Procedure. Normal adult cats of both sexes weighing between 2 and 4 kg were used in this study. The animals were anesthetized with 0.5 cc per kg of dial (10%) with urethane (40%) half of which was given intramuscularly and half intraperitoneally. When necessary, anesthesia was completed by cautious intravenous injection of pentobarbital sodium solution. Electrocardiograms were recorded from lead II. A control tracing was taken and the undiluted solution of the mercurial was immediately injected into the saphenous vein. The total volume was injected over 30 seconds in the case of vol-

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1 DeGraff, A. C., and Nadler, J. E., *J. Am. Med. Assn.*, 1942, **119**, 1006.

2 Wexler, J., and Ellis, L. B., *Am. Heart J.*, 1944, **27**, 86.

3 Pines, I., Sanabria, A., and Arriens, R. T. H., *Brit. Heart J.*, 1944, **6**, 197.

4 Volini, I. F., Levitt, R. O., and Martin, R. J., *J. Am. Med. Assn.*, 1945, **128**, 12.

5 DeGraff, A. C., and Lehman, R. A., *J. Am. Med. Assn.*, 1942, **119**, 998.

6 Long, W. K., and Farah, A., *J. Pharmacol. Exp. Therap.*, 1946, **88**, 388.

TABLE I.
Effect of Intravenous Injection of Mercurial Diuretics on the QRS Interval.

Mercuzanthin			Salyrgan-Theophylline			Mercuhydrin			Mercurie Chloride		
Dose in cc per kg	Control QRS sec.	Maximum QRS observed sec.	Dose in cc per kg	Control QRS sec.	Maximum QRS observed sec.	Dose in cc per kg	Control QRS sec.	Maximum QRS observed sec.	Dose in cc per kg	Control QRS sec.	Maximum QRS observed sec.
.035	.03	NC	.058	.04	NC	.05	.02	NC	.01*	.03	NC
.035	.03	NC	.058	.04	NC	.05	.03	NC	.04*	.03	NC
.071	.03	NC	.117	.03	.12	.1	.03	NC	.05	.03	.08
.071	.02	.04	.117	.03	.05	.1	.03	NC	.1	.03	.16
.142	.03	.20	.233	.03	.16	.2	.03	.06	.2	.02	.05
.142	.03	.14	.233	.02	.14	.2	.02	.10			
.283	.06	.34	.456	.03	.08	.4	.02	.12			
.283	.03	.10	.456	.03	.10	.4	.02	.14			
.566	.02	.12				.8	.03	.12			
.566	.03	.14				.8	.04	.10			

NC—No change.
* 0.4% solution.

umes up to 0.8 cc per kg. For the large volumes required in the case of MT6, a burette was used and the solution injected at approximately 2 cc per kg per minute. Tracings were then taken at intervals of 1, 2, 3, 5, 10, 15, 20, 30, 40, 50 and 60 minutes after injection. In some cases this series was extended up to 6 hours at 15-minute intervals.

Results. The observations have been summarized in Table I. In every case the initial dose was low enough so that no change in the electrocardiogram occurred within an hour after injection. This was then increased by a factor of 2 until a lethal or severely toxic level was reached. In the case of Salyrgan-Theophylline, Mercuhydrin, Mercuzanthin and mercuric chloride, the sequence of events following injection of a toxic dose was quite similar. The most significant changes appeared immediately after injection and could for the most part be attributed to depression of conduction. They usually consisted of atrioventricular dissociation or ventricular tachycardia and were invariably accompanied by a marked increase in the QRS interval. In some cases ventricular fibrillation and death ensued. Occasionally the ventricular rate progressively slowed until complete arrest. Usually, however, the electrocardiogram reverted in less than 30 minutes to a more or less regular sinus rhythm (Fig. 1 and 2). These phenomena are in general agreement with those reported by Volini[4] for 2 patients on whom electrocardiograms were taken during the acute episode following the injection of a mercurial diuretic. Furthermore, the literature[1-4] indicates that the typical reaction in man comes on immediately after the injection. Therefore, in the absence of direct evidence, it will be assumed that the action of these drugs in the anesthetized cat is qualitatively the same as in man. In the case of MT6 no significant changes in the tracing were observed immediately in any dose used. The highest doses gave rise to a gradual depression of conduction and rate leading to cardiac arrest after a variable period. These changes are illustrated in Fig. 3. In Table II the

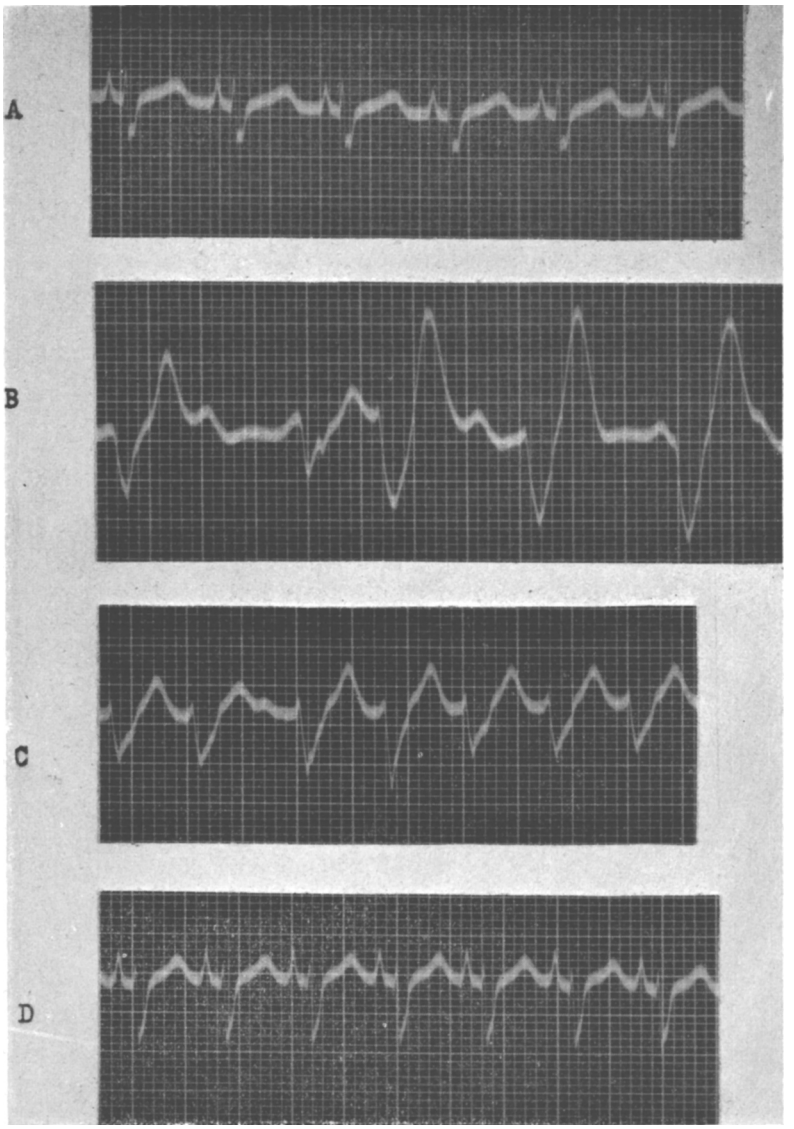


Fig. 1.
Effect of intravenous injection of 0.283 cc per kg of Mercuzanthin solution on the electrocardiogram of the anesthetized cat. A, control tracing; B, one minute after injection; C, 10 minutes after injection; D, 50 minutes after injection.

time of onset of marked electrocardiographic changes due to MT6 is given as a function of dosage. It is evident that the higher the dose the more rapidly the cardiac effects appear. However, at 4 cc per kg no cardiac toxicity appeared within 6 hours after injection. It is not to be inferred, however, that MT6 or indeed any of the mercurials used in this study can be tolerated indefinitely at these large doses. The majority of the animals died, or were expected to die, after several days due to mercury intoxication.

Quantitatively, the toxic effect of the first 4 mercurials is most consistently reflected in the electrocardiogram in an increase in the QRS interval. Using this as a criterion, the maximum tolerated dose for each drug has been roughly estimated and is given in Ta-

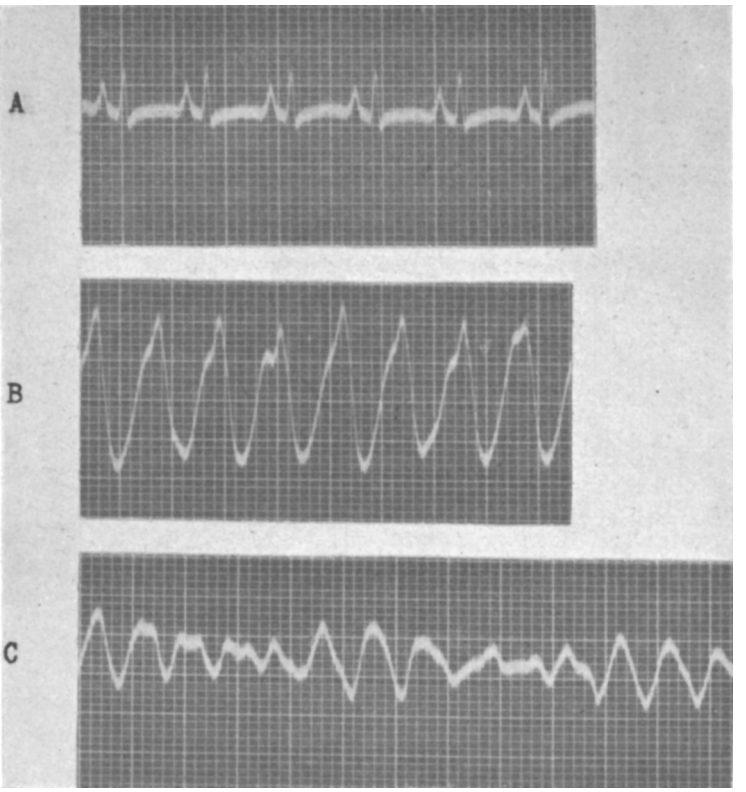


Fig. 2.
Effect of intravenous injection of 0.233 cc per kg of Salyrgan-theophylline solution on the electrocardiogram of the anesthetized cat. A, control tracing; B, one minute after injection; C, 3 minutes after injection. Death ensued shortly after C.

TABLE II.
Onset of Electrocardiographic Changes After MT6.

Dose in cc per kg	Time in minutes for onset of major E.K.G. changes (other than alterations in rate or amplitude of deflections.)	Period of observation in min
2	none	60
2	"	60
4	"	90
4	"	60
4	"	360
8	75	75
8	none	60
8	105	120
16	10	30
16	50	50
16	90	90
16	60	75

ble III. It will be noted that there is comparatively little difference in toxicity among the 3 commonly used mercurial diuretics. Furthermore, mercuric chloride, while clearly the most toxic substance studied, is closer to the diuretics than might have been anticipated. The toxicity of MT6 when judged in terms of the immediate electrocardiographic changes described above is less than 1/400 that of mercuric chloride or 1/160 that of Mercuhydrin, which is otherwise the least toxic of the group.

Discussion. Johnston[7] showed that sodium thiosulfate could restore the normal force and rhythm of the isolated turtle heart poisoned with Salyrgan or Mercuzanthin. In a previous report from this laboratory[5] it was indicated that thiosulfate exerts a similar action in the intact cat. More recently Long and Farah[6] have investigated the prophylactic and therapeutic action of 2 monothiols

[7] Johnston, R. L., *J. Lab. Clin. Med.*, 1941, **27**, 303.

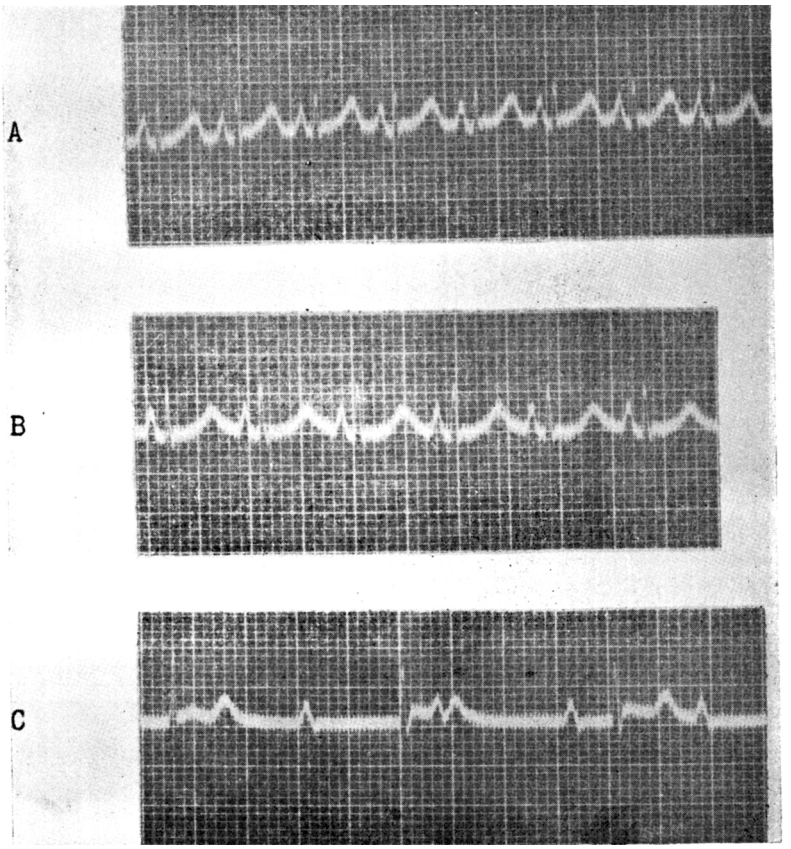


Fig. 3.
Effect of intravenous injection of 16 cc per kg of MT6 solution on the electrocardiogram of the anesthetized cat. A, control tracing; B, 40 minutes after injection; C, 50 minutes after injection. The animal died shortly after tracing C.

TABLE III.
Comparative Acute Cardiac Toxicity of Mercurials.

Compound	Max. tolerated intravenous dose in cc per kg based on widening of the QRS interval	Ratio
Mercuric chloride	0.04	1.0
Salyrgan-Theophylline	0.058	1.4
Mercuzanthin	0.071	1.8
Mercuhydrin	0.1	2.5
MT6	>16.0	>400.0

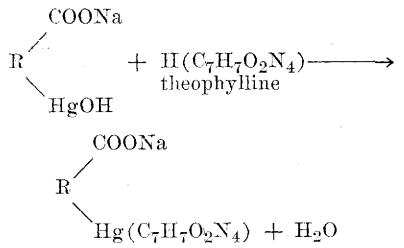
(cysteine and glutathione) and one dithiol (2,3-dimercapto propanol, British Antilewisite) against the acute cardiac effects of Salyrgan. They found that the intravenous LD_{50} of Salyrgan in mice was slightly increased by intravenous injection of a mol equivalent of any of the above compounds one minute before the mercurial. They also reported that arrythmias produced in the isolated heart lung preparation of the dog as well as the intact dog could be successfully treated with these compounds. 2,3-Dimercapto propanol was considerably more effective than monothiols in the intact dog but not in the isolated heart. Apparently no attempt was made to combine the mercurial with the thiol before injection and compare its toxicity with the parent drug.

It has long been known that compounds of the general structure RHgOH will react with many simple salts as follows:

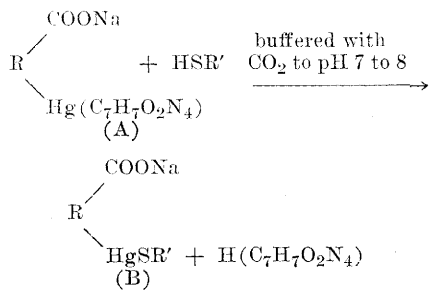
$$RHgOH + KBr \longrightarrow RHgBr + KOH$$

where the base formed may be quantitatively titrated. Presumably such a reaction goes

to completion because of the failure of RHgBr to ionize. The common mercurial diuretics are prepared by a similar reaction:



It has been previously shown[8] that this combination with theophylline results in a decrease in the local toxicity of the mercurial and perhaps a slight improvement in the acute cardiac toxicity.[5] Further experiments showed that the following reaction:



will cause the precipitation of theophylline in practically theoretical yield thus suggesting that the mercaptide is more stable than the theophylline complex. The experiments described above correspondingly demonstrate a very considerable decrease in the cardiac toxicity for a compound of structure B (MT6) as compared with compounds of structure A (Mercuhydrin, Mercuzanthin, Salyrgan-Theophylline). These results are quite out of line with those of Long and Farah[6] in which treatment with the thiol preceeded the injection of the mercurial. This might have been expected, however, because in their experiments the thiol would be required to compete for the mercurial with whatever group the mercurial combines with in the tissues. The difference they observed in the effectiveness of 2,3-dimercapto propanol as compared with simple monothiols may then be caused by a difference in the fate of the detoxifying agent.

A number of reports have recently appeared concerning the general subject of detoxification of heavy metals by formation of mercaptides, especially in connection with the development of British Antilewisite. Most of this work is not relevant to the acute action of mercury on the heart and need not be considered here. Moreover, it should be noted that the magnitude of detoxification demonstrated in the above experiments is not necessarily capable of wide application. Thus the acute intravenous lethal doses of a series of alkyl mercuric thioglycollates (also defined by structure B) reported by Cohen[9] are only slightly greater than the maximum tolerated doses given in Table III for the 3 diuretics.

Clinical studies with MT6 will be reported elsewhere.

Summary. Mercuric chloride, Salyrgan-theophylline, Mercuzanthin, Mercuhydrin and N(γ-carboxymethylmercaptomercuri-β-methoxy)propyl camphoramic acid disodium salt (MT6) have been compared with respect to their ability to cause cardiac toxicity as manifested by changes in the electrocardiogram of the cat. The toxicity has been found to decrease in the order named. Compound MT6 causes no immediate changes in the electrocardiogram in doses up to 160 times the maximum tolerated dose of Mercuhydrin. This improvement appears to be due to the relatively greater stability of the mercaptide as compared with the theophylline complex.

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8 DeGraff, A. C., Batterman, R. C., and Lehman, R. A., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 373.

9 Cohen, S. J., *J. Pharm. Exp. Therap.*, 1929, **35**, 343.