Cardiodepressive Effects of Mercurial Diuretics. Cardioprotective Value of BAL, Ascorbic Acid and Thiamin.* (17504)

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The use of mercurial diuretics is attended by cardiac abnormalities. The more serious, and even fatal, immediate reactions are ventricular fibrillation, preceded by ventricular tachycardia and ectopic beats, or, infrequently, cardiac asystole.(1) Elevation and other deformations of the S-T and T segments, notching of the QRS, prolongation of the P-R and QRS intervals up to alternating bundle branch block, auricular fibrillation and flutter, also occur, in human cases and in animal experiments.(1-3) BAL is conceded to be the most effective dithiol compound in combatting the toxicity of mercurial compounds, as well as neutralizing their diuretic effects.(4) Ascorbic acid likewise reputedly has antitoxic as well as synergistic diuretic effects when administered with mercurials.(1) Thiamin, reported beneficial in arsenical poisoning,(5) has not been used to counteract mercurial toxicity. Neither thiamin nor ascorbic acid have known direct cardiac effects, except that the T wave may become inverted after thiamin.(6) BAL has been observed to cause, beyond slowed cardiac rates, elevated S-T segments and deep S waves.(7)

The purposes of this study were to obtain specific conductive and electrical systole effects of, particularly, mercuhydrin in the isolated rabbit heart; to compare its myocardial toxicity with that of other organic mercurials; and to evaluate the detoxifying effects of BAL, ascorbic acid and thiamin used before and after the mercurial compounds.

Methods. As in our previous investigations(8,9) with the isolated rabbit hearts, they were perfused per aorta and coronary arteries with a solution kept at 37°C, pH 7.4, and oxygenated with 5% CO_2 in oxygen. Electrocardiograms corresponding to lead I were obtained, as the auricles, or ventricles with the auricles cut off, were driven at various rates by means of a thyratron-type stimulator. The P-R, QRS and Q-T intervals were measured at various rates of stimulation with a Cambridge measuring instrument and graphed against the R-R intervals as curves of recovery (relative refractoriness). Control tracings were followed by the injections of the drugs in appropriate dosage, mercurials followed by the supposed antagonists, or vice versa. Ten minute intervals between doses of the same or different drugs allowed records of the maximum effects, and, together with rest periods between salvos of stimuli, elminated the noxae of fatigue. The pH of the perfusate was not altered more than 0.5 unit by any of the drugs added, so that the acids (thiamin hydrochloride, ascorbic acid) administered needed no buffering. Moreover, our own studies(11) indicate that a pH range of 6.5-8.0 of the perfusate is unaccompanied by marked changes of the electrocardiographic intervals measured. A total of 52 experiments, 6 dealing with salyrgan-theo-

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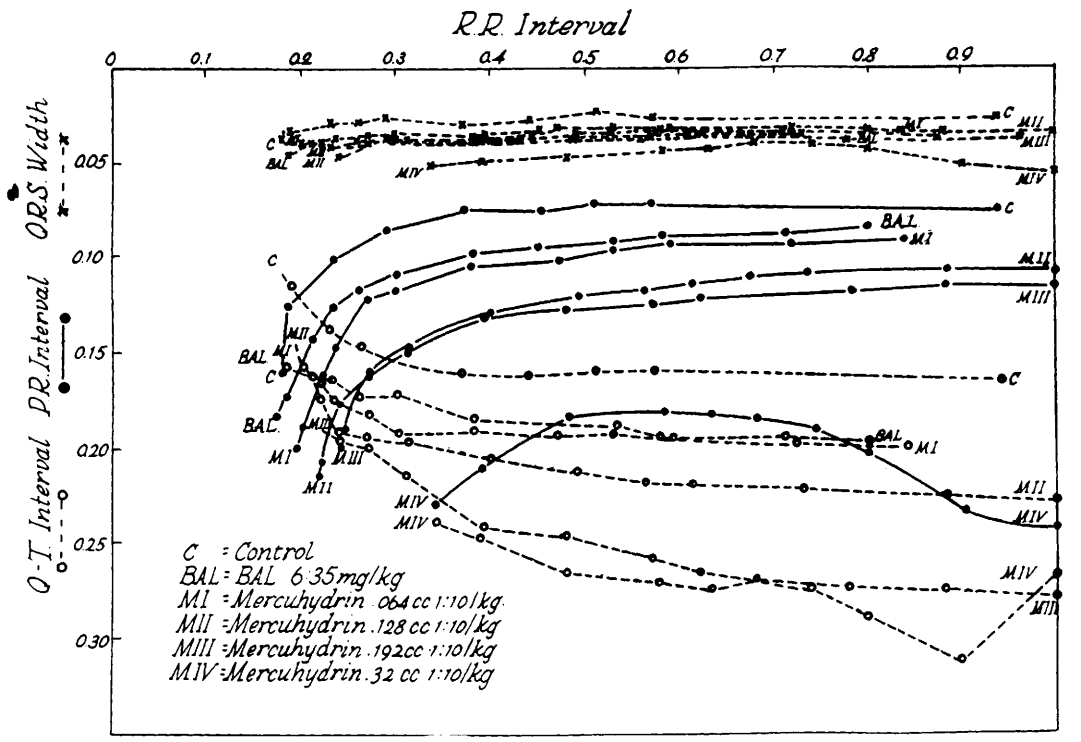

FIG. 1.

BAL (0.22 cc saturated aqueous soln.) prolongs A-V and I-V conduction times and Q-T intervals at all rates of stimulation (R-R intervals). Despite these deleterious effects, the total mercuhydrin tolerated thereafter amounts to 780 mg of mercury/kg of heart weight, or more than 10 times the usual cardiolethal dose of the mercurial. Times—sec.

phylline, 6 with mercuzanthin, and 40 with mercuhydrin, constitute the basis of the following data. The rabbits weighed 1.5 to 2 kg and the hearts 4 to 6 g. The perfusate volume was 1 liter. Hence, to translate dosages of mg/kg of heart weight into concentrations of mg % of perfusate, one need only divide by the factor 20 (*i.e.* $\frac{1000}{5 \times 10}$). Dosages on figures per kg of body weight must be multiplied by the factor 200 to get approximate values per kg of heart weight.

Results 1. *Effects of Mercurials.* Salyrgan-theophylline and mercuzanthin were usually rapidly (within 10 minutes) fatal to the rabbit hearts at doses of 30 mg of mercury/kg of heart weight, or above. Block of severe degree, A-V nodal or intraventricular (QRS widening of 50 to 150%), generally occurred at a dosage of 7.5 mg of mercury/kg or above. That mercuhydrin was less toxic, as noted by previous investigators,(10) was emphasized by its cardiolethal dosage of 75 mg of mercury/kg or over, and the occurence of marked impairment of conduction following doses of 36 mg of mercury/kg or over (Fig. 2, 4, and 6; Table I).

2. *BAL and Mercuhydrin. BAL* in saturated aqueous solution (4.5%), administered in a dosage of 1800 mg/kg of heart weight caused some impairment of conduction and lengthened the Q-T interval. The dosage of mercuhydrin tolerated thereafter, however, increased up to 780 mg of mercury/kg without immediately killing the heart, although further deleterious changes in conduction and refractory period followed (Fig. 1). When conduction impairing doses of mercuhydrin (*e.g.* 36 mg of mercury/kg) were followed by BAL 1800 mg/kg), there resulted a marked re-

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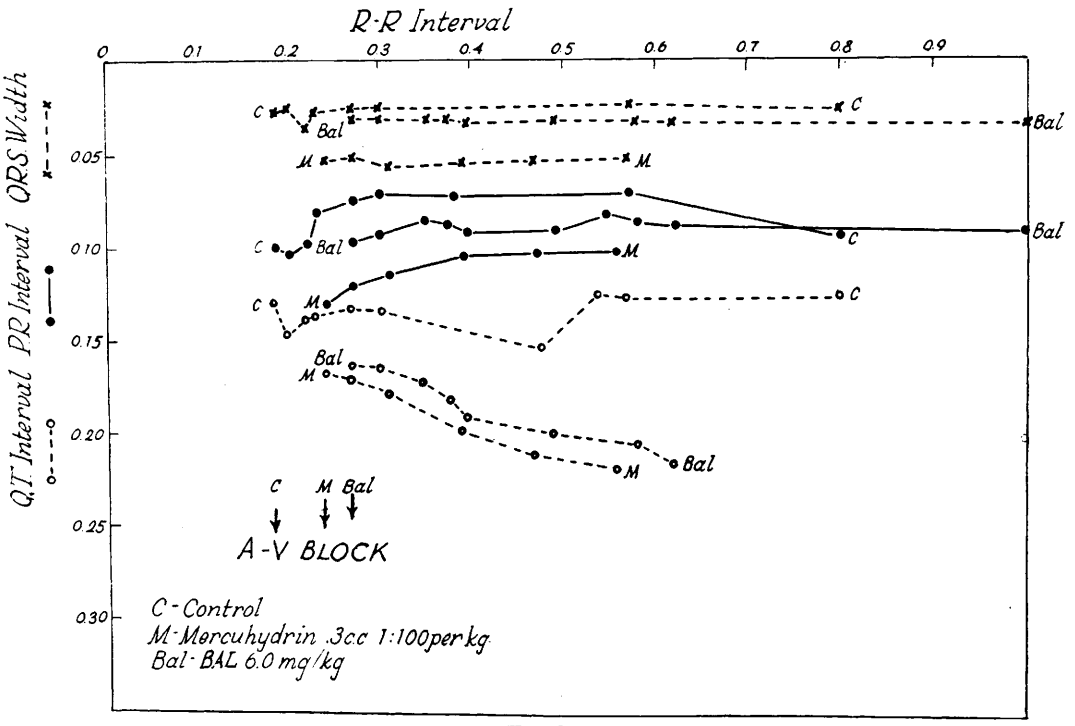

FIG. 2.

The prolongation of QRS, P-R, and Q-T intervals at all rates of stimulation by a blocking dose of mercuhydrin (36 mg of mercury/kg heart weight) is reversed by BAL in that order of decreasing efficacy.

versal of A-V and intraventricular block, though the Q-T interval and the absolute refractory period were further lengthened (Fig. 2). In one instance of complete cardiac asystole after mercuhydrin, BAL caused resumption of idioventricular rhythm, though the heart failed to react to electrical stimulation. S-T changes of monophasic current type and doming or reversals of the T wave frequently followed the exhibition of either mercurials or BAL.

3. *Ascorbic acid and mercuhydrin.* Ascorbic acid in doses corresponding to therapeutic ones in man did not affect the electrocardiogram. Doses of 4500 to 5400 mg/kg at times very slightly impaired conductivity and prolonged the Q-T interval, with minimal S-T and T changes. The maximum tolerated amount of mercuhydrin administered after such doses of ascorbic acid was 570 mg of mercury/kg, although usually only much lower doses could be protected against (Fig. 3, Table I). Ascorbic acid used after blocking doses of mercuhydrin (36 mg of mercury/kg) caused, in general, partial reversal of A-V and possibly I-V block, and not infrequently further slight prolongation of the Q-T interval and the absolute refractory period of the recovery curves of conductivity (Fig. 4). The detoxifying effects were intermediate between those of BAL (supra) and thiamin (infra).

4. *Thiamin and mercuhydrin.* Thiamin in doses corresponding to therapeutic ones in man did not affect the electrocardiogram. Doses of thiamin of 570 to 780 mg/kg of heart weight at times impaired conductivity and prolonged the Q-T interval, with slight S-T and T changes. Mercuhydrin administered after such amounts of thiamin was tolerated up to 196 mg/kg without killing the heart, although increasing block developed (Fig. 5). In one instance a mercuzanthin dose of 105 mg of mercury/kg similarly (Table I) produced A-V dissociation without immediate death of the heart after an apparently protective dose of thiamin (600 mg/kg). Thia-

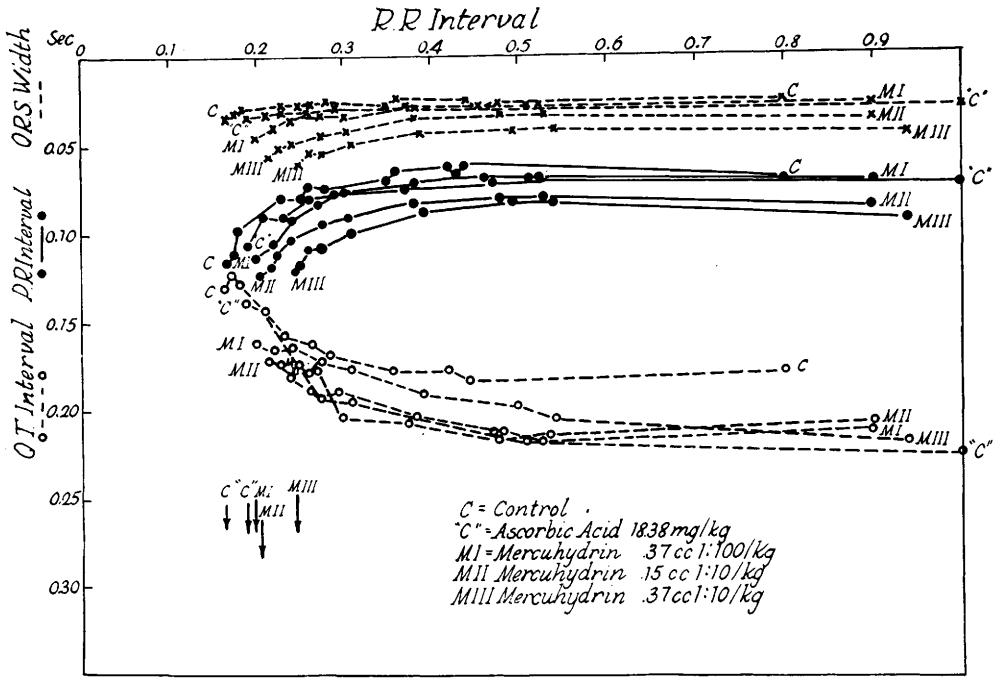

FIG. 3.

Ascorbic acid has practically no effect on this heart preparation except for prolonging the Q-T interval and slightly decreasing the blocking stimulus rate (see arrows). 570 mg of mercury/kg of body weight, or more than 7 times the usual cardiolethal dose, is tolerated thereafter with few further deleterious effects on the measured intervals.

min administered in above doses after blocking doses of mercuhydrin caused partial reversal of the prolonged P-R and QRS intervals, while prolonging the Q-T intervals further (Fig. 6). This action was similar to but less marked than that of BAL and ascorbic acid under similar conditions (supra).

5. *Other drugs and mercurials.* Theophylline ethylene diamine in doses of 3600 mg/kg apparently increased the tolerance of the isolated rabbit heart to mercuhydrin (*e.g.* 120 mg of mercury/kg with non-lethal A-V dissociation, Table I), while itself causing some block and particularly prolongation of the electrical systole.(11) The protective effects of theophylline have been previously reported,(2) associated, perhaps, with the increased absorptive and diuretic results of its combinations with mercurials,(2,12) as well as coronary dilation since pitressin had the opposite effect (Table I). Epinephrine, 6 mg/kg, partially reversed the effects of blocking doses (36 mg of mercury/kg) of mercurials on the P-R, QRS and Q-T intervals, without causing ventricular fibrillation.(11) DeGraff and Lehman(2) had previously reported "improvement" in hearts poisoned by mercurials following ephedrine. Since magnesium sulphate has been reported to have detoxifying value against mercurial diuretics,(13) doses up to 45 to 120 g/kg were employed before and after mercuhydrin with failure to demonstrate any protective or beneficial effects. Marked A-V (not I-V) block and prolongation of the Q-T interval were produced following $MgSO_4$ both before and after mercuhydrin, and the cardiolethal dose of the latter was still 75 to 125 mg of mercury/kg after $MgSO_4$. Niacin likewise failed to increase the tolerance of the isolated rabbit heart to mercurials, and in doses much larger than the corresponding therapeutic ones in man, *e.g.* up to 9000 mg/kg, caused slight impairment of conduction (A-V, rather than I-V), and prolongation of

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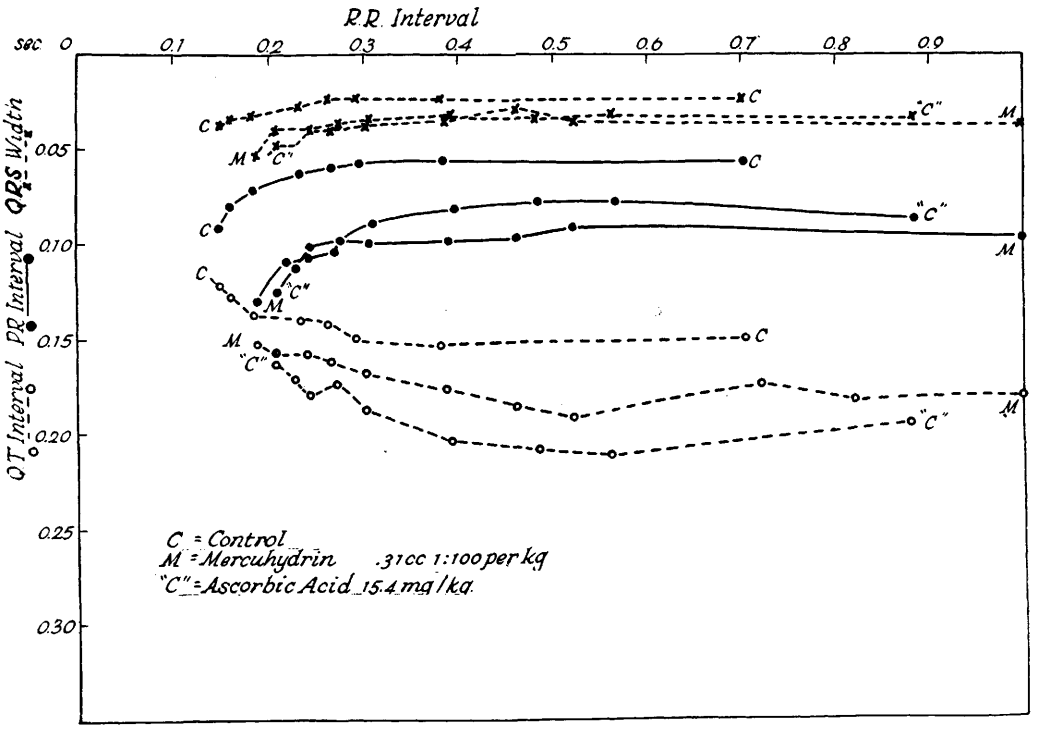

FIG. 4.

The usual effects of a blocking dose of mercuhydrin (36 mg of mercury/kg of heart weight) are reversed as regards A-V and I-V conduction only slightly, and at lower rates of stimulation, by ascorbic acid in this preparation; the electrical systole is further prolonged.

the Q-T interval and the absolute refractory period of conductivity.(11)

Comment. Since the lethal effects of intravenous mercurial diuretics result primarily from cardiac toxicity,(2) it is pertinent to compare the doses of mercurials fatal for the isolated rabbit hearts with the known M.L.D.'s of these drugs in intact animals. In terms of mercury content, mercuhydrin was fatal in dogs in a dose of 45-61 mg/kg of body weight,(1) and salyrgan-theophylline in cats at 35 mg/kg.(2) Our corresponding figures for the two drugs are 75 mg/kg and 30 mg/kg of heart weight respectively. These doses of mercurials produce rapid cessation of cardiac activity as compared with the slower cumulative effects of the M.L.D.'s as defined for intact animals. Although our results are not quantitative, it appears that BAL, ascorbic acid and thiamin offered, in that order, significant protection to the heart against mercurial toxic and lethal effects. *The maximum tolerated (sublethal) doses of mercuhydrin following BAL, ascorbic acid, and thiamin, were 10.0, 7.6, and 2.6 times the previously noted M.L.D. of the mercurial alone in our preparation of the perfused isolated rabbit heart, respectively.* Each of them, likewise, showed definite reversal of mercury-induced conduction defects and, usually, electrical systole prolongation.

Further studies indicate that mercaptomerin (the disodium salt of N (γ-carboxymethyl-mercaptomercuri-β-methoxy)propyl camphoramic acid, thiomerin-Campbell Products) is less than 1/200 as cardiotoxic as mercuhydrin. Slight cardioprotective effects also result from the exhibition, before or after thiomerin, of BAL, but not of thiamin or ascorbic acid.(14) The mechanism of BAL detoxication of mercury has been adequately discussed elsewhere.(4) We can offer no explanation of the actions of thiamin and ascorbic acid, other than possible

14. Ruskin, A., and Johnson, J. E., to be published.

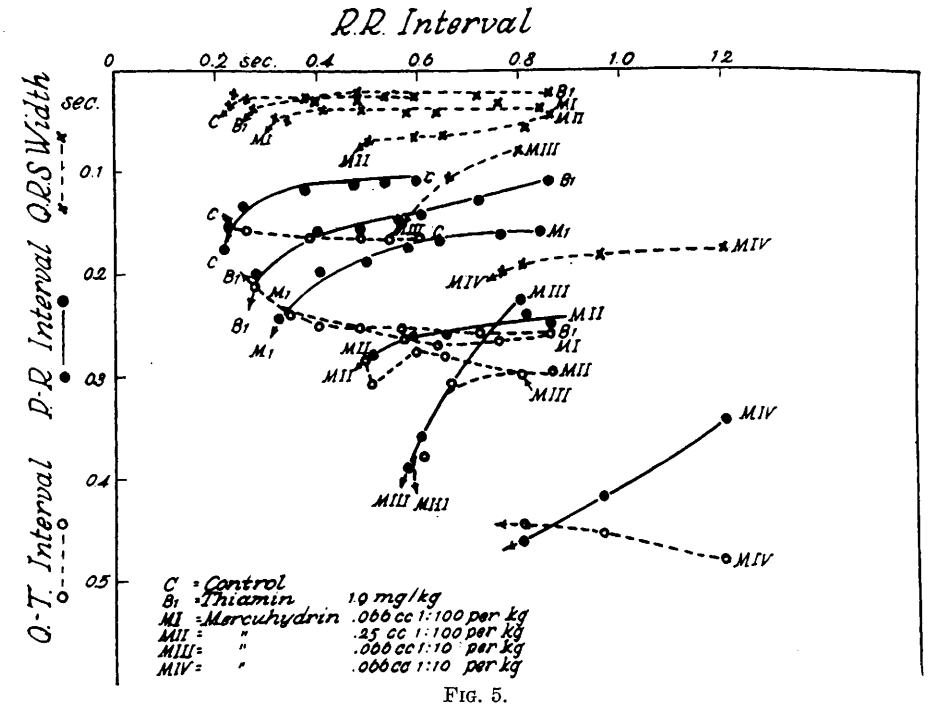

FIG. 5.

The large dose of thiamin has increased A-V conduction time and the Q-T intervals at all rates of stimulation in this heart. Nevertheless, mercuhydrin is tolerated, thereafter, though with markedly deleterious effects, up to 195 mg of mercury/kg of heart weight, or almost 2 times the usual cardiolethal dose of mercuhydrin alone.

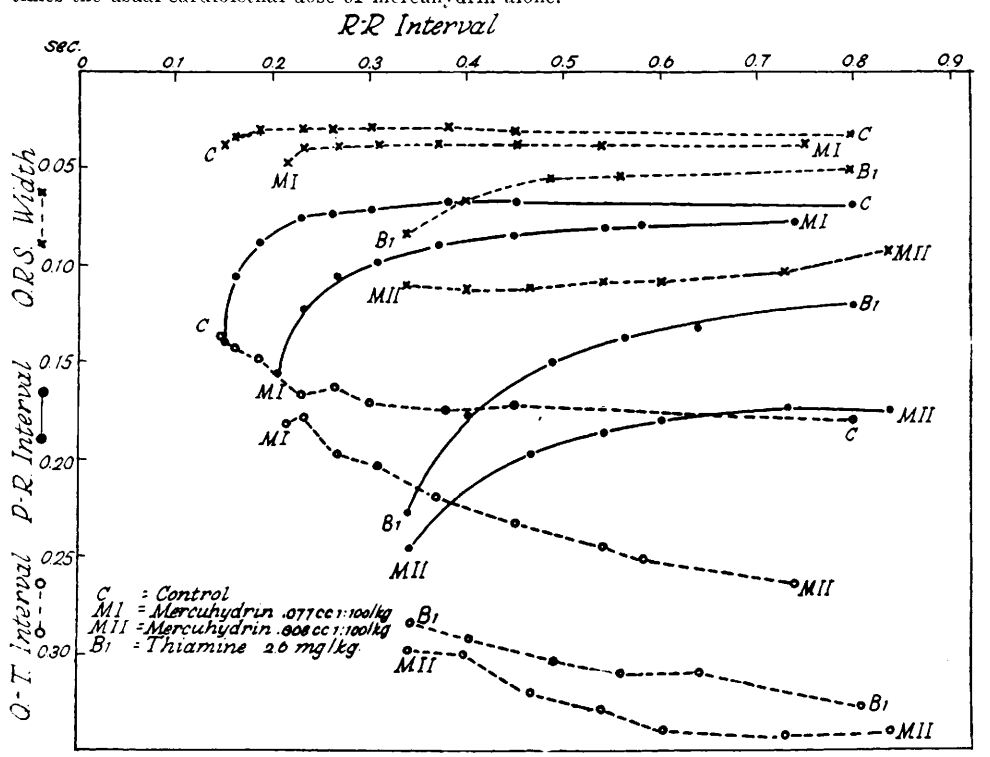

FIG. 6.

A total of 45 mg of mercury/kg of body weight administered in two successive doses of mercuhydrin has caused marked prolongation of A-V and I-V conduction and electrical systole in this preparation. Thiamin then effected marked shortening of conduction times and a slight shortening of Q-T intervals without changing the blocking stimulus rate.

TABLE I.
Representative Doses of Mercuhydrin and Other Mercurials in mg/kg Heart Weight Producing Marked Conduction Delays (50% to 150% in QRS Width at 150 Beats/min.) and Rapid (Within 10 Minutes) Asystole in Isolated Perfused Rabbit Hearts.

Conduction delays mg/kg	Rapid asystole mg/kg
Salyrgan-theophylline	
7.9	29.6
10.8	36.2
11.8	44.1
Mercuzanthin	
7.4	30.8
12.6	46.7
44.2 (after thiamin)	105.4 (after thiamin)
Mercuhydrin	
17.8 (after pitressin)	75.8
29.8	88.2
30.4	95.6
38.8	112.7
40.0	116.2 (after $MgSO_4$)
40.7	118.9
42.1	124.6
44.1	144.4
48.6	148.5
48.8	149.4
53.9	169.4 (after thiamin)
56.1	195.2 (" ")
62.3	356.7 (after ascorbic acid)
66.8	418.8 (" " ")
120.4 (after aminophylline)	570.6 (" " ")
242.6 (after BAL)	696.6 (" BAL)
	780.5 (" ")

potentiation of the cellular enzyme systems incompletely destroyed by mercury. Biochemical studies, utilizing the Warburg technic, now being conducted in our neuro-chemistry laboratory, may substantiate this hypothesis.(15) Other substances concerned with cellular oxidation, such as niacin and riboflavin, are without effect on mercurial toxicity.(11) The favorable effects of theophylline ethylene diamine and epinephrine confirm previous similar observations. Magnesium salts, while apparently stimulating the contractility of the preparation,(11) produce, with mercuhydrin, additional deleterious conduction effects, without changing the cardiolethal dosage of the mercurial compound.

Summary. Mercuhydrin uniformly caused conduction delays in the A-V node and ventricles of the isolated rabbit heart. Electrical systole (Q-T interval) was likewise prolonged, and failure of A-V conduction (dropped beats) produced at lower than usual rates of stimulation—all at doses above 36 mg of mercury/kg of heart weight. Rapid cardiac asystole resulted from doses above 75 mg of mercury/kg of heart weight. Preliminary BAL, ascorbic acid, and thiamin, in descending order of efficacy, raised the blocking and cardiolethal dosages of mercuhydrin, and the same drugs administered following the mercurial compound partially reversed the cardiac effects measured. Theophylline ethylene diamine and epinephrine exhibited lesser cardio-protective activity. Magnesium sulphate and niacin had none.

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