amounts or repeated doses of methionine might increase the survival rate.

Summary. A simple and convenient method for producing standardized burn shock in rats is described. Isotonic saline injected intraperitoneally one hour before a standardized burn shock did not increase the survival rate; administration at the time of the burn or one hour following significantly increased the survival rate. Methionine-saline solution given one hour before burning significantly increased the survival rate; given at the time of the burn or one hour following, the effect was the same as with saline alone.

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Enhancement of Epinephrine Induced Cardiac Arrhythmias by Tetraethylammonium Chloride (Etamon).*

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In the experiments to be reported herein tetraethylammonium chloride has been shown to intensify the cardiac arrhythmias occurring in dogs during cyclopropane anesthesia. Secondly, experiments on unanesthetized animals suggest that the choice of a pressor agent for use as an antidote after tetraethylammonium chloride may be critical. After tetraethylammonium injection epinephrine resulted in ventricular tachycardia whereas phenylephrine (Neo-Synephrine) caused no arrhythmias.

Cardiac arrhythmias occurring during cyclopropane anesthesia have been demonstrated experimentally to depend upon reflex sensitization of the heart to epinephrine.[1] Cyclopropane stimulates receptors located in the abdominal viscera, producing afferent impulses which pass to the cord by way of fibers travelling with the splanchnics. The reflex center is located in the brain, presumably in the hypothalamus. Efferent impulses pass to the heart by way of cardiac sympathetics. Since interruption of this pathway at any point has prevented the arrhythmias, the tetraethylammonium ion should theoretically block the reflex sensitization. This agent has been reported to interrupt sympathetic impulses by ganglionic blockade[2] and consequently was expected to block the efferent impulses.

When it was found that tetraethylammonium potentiated the cardiac effects of epinephrine under cyclopropane, the cardiac effects of the ion and epinephrine were also investigated in unanesthetized animals. Epinephrine has been recommended as an antidote for the profound hypotension which may follow the clinical administration of tetraethylammonium.[3]

Cyclopropane-epinephrine ventricular tachycardia was produced in the dog by the method described by Meek *et al.*[4] The only modification of this technic was reduction of the standard test dose of epinephrine in order to lower the mortality from ventricular fibrillation. After the control duration of ventricu-

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1 (a) Allen, C. R., Stutzman, J. W., and Meek, W. J., *Anesthesiology*, 1940, **1**, 158; (b) Stutzman, J. W., Murphy, Q., Allen, C. R., and Meek, W. J., *Anesthesiology*, 1947, **8**, 579; (c) Pettinga, F. L., and Stutzman, J. W., *Fed. Proc.*, 1948, **7**, 93.

2 Acheson, G. H., and Moe, G. K., *J. Pharmacol. and Exp. Therap.*, 1946, **87**, 220.

3 Berry, R. L., Campbell, K. N., Lyons, R. H., Moe, G. K., and Sutler, M. L., *Surgery*, 1946, **20**, 525.

4 Meek, W. J., Hathaway, H. R., and Orth, O. S., *J. Pharmacol. and Exp. Therap.*, 1937, **61**, 240.

TABLE I. Effect of Tetraethylammonium Chloride on Cyclopropane-Epinephrine Cardiac Arrhythmias in 15 Dogs.

Before tetraethylammonium						After tetraethylammonium					
		Duration of arrhythmia, sec		Ventricular rate/min.				Duration of arrhythmia, sec		Ventricular rate/min.	
Cardiac response to epinephrine	No.* of animals	Avg	Range	Avg	Range	Dose, mg/kg	No.* of animals	Avg	Range	Avg	Range
VT	2	22.5	20-25	300	300	—	—	—	—	—	—
VF	—	—	—	—	—	20	2	—	—	—	—
VT	6	47	1-90	304	300-325	10	6	55	5-100	312	250-350
VF	—	—	—	—	—	10	2	—	—	—	—
F VPC	3	15	10-20	200	200	—	—	—	—	—	—
M VPC	2	11.5	3-20	200	200	10	1	30	—	275	275
VT	5	70	25-95	221	200-330	5	4	65	25-95	287	200-325
VF	—	—	—	—	—	5	1	—	—	—	—

VT = Ventricular Tachycardia; VF = Ventricular Fibrillation.
F VPC = Few Ventricular Premature Contractions (Less than 1 VPC to 6 supraventricular beats).
M VPC = Many Ventricular Premature Contractions (More than 1 VPC to 6 supraventricular beats).
Note: The concentration of cyclopropane was controlled at 30% in oxygen. These animals were in Plane 3 to 4 of Stage III.
* Since certain animals had more than one type of arrhythmia total incidence in these columns is in excess of total number of animals which was 15.

TABLE II.
Effect of Tetraethylammonium Chloride on the Cardiac Response to Epinephrine in 20 Unanesthetized Dogs.

Before tetraethylammonium						After tetraethylammonium chloride 10 mg/kg				
		Duration of arrhythmia in sec.		Ventricular rate/min.			Duration of arrhythmia in sec.		Ventricular rate/min.	
Cardiac response to epinephrine	No. of animals*	Avg	Range	Avg	Range	No. of animals*	Avg	Range	Avg	Range
SA Brady.	3	—	—	61	60-63	1	—	—	125	—
AV N Brady.	3	—	—	62	45-95	—	—	—	—	—
F VPC	8	29	10-45	83	45-115	—	—	—	—	—
M VPC	1	20	—	70	—	6	46	30-75	210	136-250
VR	5	22	10-55	54	45-60	—	—	—	—	—
Bigem	—	—	—	—	—	9	43	15-70	170	125-215
VT	4	9	3-15	161	150-167	19	78	25-160	296	214-375

SA Brady. = Sino-auricular bradycardia; AV N Brady. = Auriculo-ventricular nodal bradycardia; F VPC = Few ventricular premature contractions (less than 1 VPC to 6 supraventricular beats); M VPC = Many ventricular premature contractions (more than 1 VPC to 6 supraventricular beats); Bigem = Bigeminal rhythm (SA-V); VR = Ventricular rhythm; VT = Ventricular tachycardia.
* Since certain animals showed more than one type of arrhythmia the total incidence in these columns is in excess of the total number of animals which was 20.

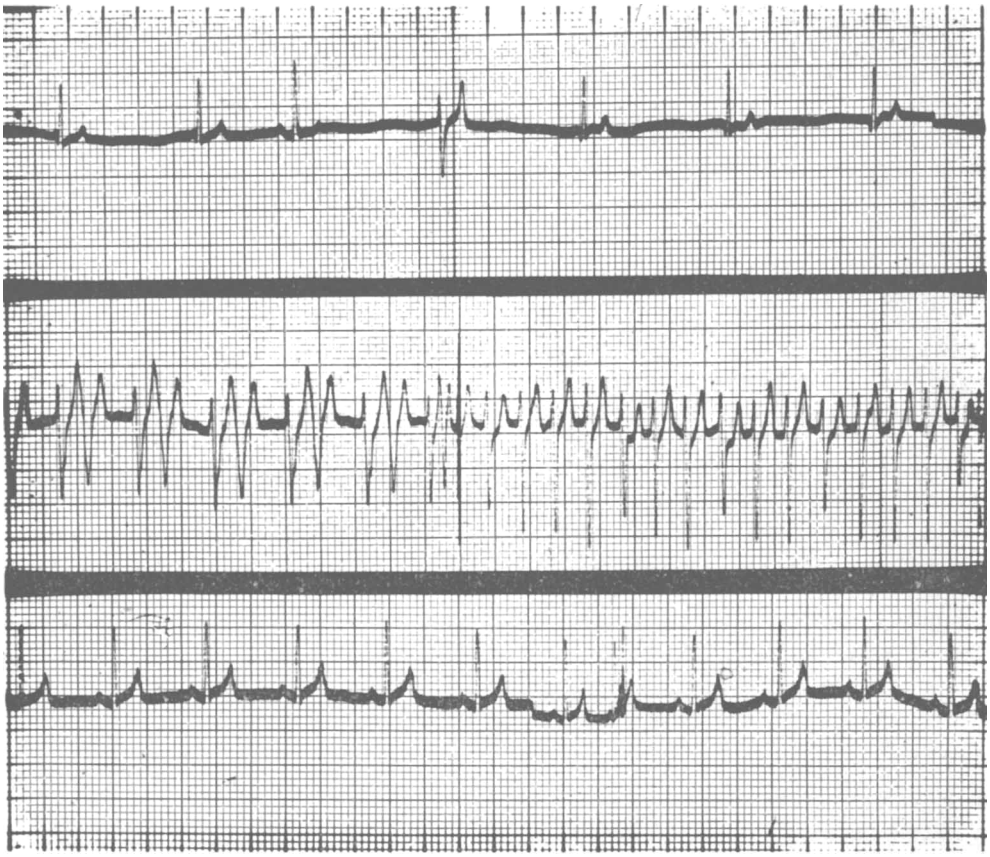

FIG. 1.

All electrocardiograms are from the same unanesthetized dog.

Upper tracing: Response to intravenous injection of 0.01 mg/kg of epinephrine; interpreted as auriculo-ventricular nodal rhythm with 1 sino-auricular and 1 ventricular premature contraction.

Middle tracing: Response to same dose of epinephrine 5 minutes after the intravenous administration of 10 mg/kg of tetraethylammonium chloride; interpreted as ventricular tachycardia.

Lower tracing: Response to the intravenous injection of 0.05 mg/kg of phenylephrine 5 minutes after 10 mg/kg of tetraethylammonium chloride on a subsequent day; interpreted as sino-auricular rhythm.

lar tachycardia had been determined, tetraethylammonium chloride§ was administered intravenously over a period of 60 seconds in doses of 5 to 20 mg/kg. Ten minutes later the test dose of epinephrine§ was repeated. The results of experiments on 15 animals are summarized in Table I. Tetraethylammonium not only afforded no protection in any dosage tested but with doses of 10 or more mg/kg actually increased the duration of epinephrine induced ventricular arrhythmias. Bilateral supradiaphragmatic splanchnicectomy and sympathetic chain section at T-10 were performed on 4 dogs and prevented cyclopropane-epinephrine ventricular tachycardia by interrupting the afferent limb of the reflex arc. In these animals 10 mg/kg of tetraethylammonium chloride followed in 10 minutes by epinephrine resulted in ventricular tachy-

§ Tetraethylammonium chloride (Etamon) and epinephrine (Adrenalin HCl) were kindly furnished by Parke, Davis & Co., Detroit; phenylephrine HCl (Neo-Synephrine) by the Department of Medical Research, Winthrop-Stearns, Inc., Boston; and pentobarbital sodium by Eli Lilly & Co., Indianapolis.

cardia of longer duration than the control. This dose of tetraethylammonium was found to be effective in blocking the cardiac acceleration from electrical stimulation of the preganglionic fibers to the stellate.

Since the above experiments suggested that tetraethylammonium was sensitizing the heart to epinephrine in spite of effective sympathetic block, the response was studied on 20 unanesthetized dogs. Epinephrine in doses of 0.003 to 0.01 mg/kg was administered intravenously at a constant rate over 50 seconds. The effects on cardiac rhythm were determined by electrocardiographic tracings (Lead II). The results of epinephrine before and 5 minutes after 10 mg/kg tetraethylammonium chloride are compared in Table II. In 19 of the 20 animals the cardiac arrhythmias were definitely more severe and of longer duration after tetraethylammonium. In 10 animals the response to phenylephrine hydrochloride (Neo-Synephrine)§ after tetraethylammonium was tested. In each case the sino-auricular node remained the pacemaker, and the only electrocardiographic evidence of phenylephrine injection was a slight decrease in rate. Fig. 1 shows electrocardiograms from a typical experiment.‖ The dosage of phenylephrine was 0.05 mg/kg which has a pressor effect equivalent to 0.01 mg/kg of epinephrine in unpremedicated dogs.

The mechanism by which the tetraethylammonium ion potentiates the cardiac effects of epinephrine has not been elucidated. That the arrhythmias are simply the result of epinephrine stimulating a heart freed of vagal control is unlikely in view of the work of Wilburne, Surtshin, Rodbard and Katz who reported that atropine prevented ventricular tachycardia resulting from injection of large doses of epinephrine in the unanesthetized dog.[5]

Corcoran and Page reported that tetraethylammonium chloride potentiated the pressor effects of epinephrine in the unanesthetized dog.[6] In extending the pressor potentiation observation in animals anesthetized with pentobarbital Page and Taylor[7] warned of the possibility that a safe antidotal dose of epinephrine for pressor effect may be much less than usual after tetraethylammonium has been administered. In the present investigation it was found in 6 dogs that the maximum level of mean blood pressure with phenylephrine was not altered significantly by previous injection of tetraethylammonium chloride. The total change in blood pressure was greater with phenylephrine after tetraethylammonium, but this was the result of hypotension from tetraethylammonium. Blood pressure was recorded by cannulation of the femoral artery under local anesthesia in lightly morphinized dogs and also in animals anesthetized with pentobarbital sodium.§

From the results of our experiments it is concluded that:

1. Epinephrine is contraindicated as a pressor agent after tetraethylammonium chloride.

2. Phenylephrine (Neo-Synephrine) is a satisfactory pressor agent after tetraethylammonium chloride.

3. Tetraethylammonium chloride is contraindicated for the prophylaxis or treatment of cardiac arrhythmias during cyclopropane anesthesia.

‖ Electrocardiograms were recorded with a Sanborn Viso-Cardiette made available through the kindness of Mr. J. L. Jenks, Jr., of the Sanborn Co., Cambridge, Mass.

5 Wilburne, M., Surtshin, A., Rodbard, S., and Katz, L. N., *Am. Heart J.*, 1947, **34**, 860.

6 Corcoran, A. C., and Page, I. H., PROC. SOC. EXP. BIOL. AND MED., 1947, **66**, 148.

7 Page, I. H., and Taylor, R. D., *J. A. M. A.*, 1947, **135**, 348.