TABLE II. Renal Clearances During Maximal Ephedrine Effect.

Subject	Control values* Filtration rate, cc/min	Control values* Renal plasma flow, cc/min	Period of maximal ephedrine effect† Filtration rate, cc/min	Period of maximal ephedrine effect† Renal plasma flow, cc/min	Change in mean blood pressure, mm Hg	Change in pulse rate per min
Mc.	110	530	114	542	+22	+12
V.	65	383	65	390	+10	+ 5
H.	149	580	144	620	+ 8	+ 4
P.	148	797	155	773	+14	0
E.	111	695	97	580	+26	0
S.	85	542	93	539	+16	+16
W.	140	580	127	616	+43	+ 9
K.	84	435	83	410	+21	+ 2

* Avg of 3 control periods.
† Value for single period of max ephedrine effect, as judged by increase in blood pressure and pulse rate.

Table II. Even these maximal effects show no consistent increase or decrease in renal plasma flow or filtration rate.

E_{PAH} and renal arterial-venous oxygen difference, measured in one subject (W.I.), remained constant at normal values of 94% and 1.2 cc/100 cc, respectively, throughout the course of the experiment, demonstrating that ephedrine does not inhibit tubular excretion of PAH or cause diversion of renal blood through arterial-venous channels.

Summary. Ephedrine in therapeutic doses (35 to 75 mg) administered intramuscularly to 7 subjects and intravenously to one failed to cause any consistent or significant change in renal plasma flow, filtration rate, PAH extraction ratio, or renal arterial-venous oxygen difference, despite an increase in mean blood pressure and pulse rate. These results are in agreement with the conclusion of Chasis, Goldring, and Smith(1) that, in marked contrast to adrenaline, ephedrine in therapeutic doses has no or a negligible effect on the renal circulation.

Received June 18, 1951. P.S.E.B.M., 1951, v77.

Potentiating Effect of Tetraethylammonium on Pressor Response to Epinephrine and Nor-Epinephrine.* (18842)

W. ROY ST. CLAIR AND CLEMENT A. STONE. (Introduced by E. R. Loew.)
From Department of Physiology, Boston University School of Medicine, Boston.

The property of tetraethylammonium (TEA) of potentiating the pressor response to epinephrine and other pressor agents has been attributed(1) to the elimination of homeostatic blood pressure reflexes by this ganglionic blocking agent. In this connection, it is important to discover whether or not TEA has any direct potentiating effect on the action of epinephrine and it was the purpose of this investigation to attempt to shed some light on this aspect of the problem.

Methods. Twelve cats, weighing 2.23-5.57 kg, were anesthetized with ether after premedication with atropine sulphate 1.0 mg/kg. Both vagus nerves were divided and the spinal cord was then pithed in 10 animals after cervical laminectomy; in the remaining 2 animals the probe was passed through the orbit. The preparation was then left for an hour, body temperature being maintained constant by means of a warming device. Carotid blood pressure was recorded on a kymograph by

* This study was supported by a grant from Parke, Davis Co.

1. Moe, G. K., Rennick, B. R., Capo, L. R., and Marshall, M. R., *Am. J. Physiol.*, 1949, v157, 158

TABLE I. Effect of Tetraethylammonium Chloride (TEAC) on the Hypertensive Response to 1-epinephrine and 1-nor-epinephrine. Pressor responses in mm mercury; mean ± S. D.*

	Control group		Test group		Difference	Significance†
1-epinephrine	Before saline	59.2 ± 3.9	Before TEAC	58.8 ± 8.7	.4	P <.5
	After 2 ml saline	62.7 ± 13.1	After 5 mg/kg TEAC	87.8 ± 18.1	25.1	P <.01
	Difference	3.5		29		
	Significance†	.5>P>.4‡		P <.01		
1-nor-epinephrine	Before saline	56.9 ± 10.8	Before TEAC	56.5 ± 6.4	.4	P >.5
	After 2 ml saline	62.9 ± 10.8	After 5 mg/kg TEAC	73.2 ± 11.8	10.3	P <.01
	Difference	6		16.7		
	Significance†	.2>P>.1§		P <.01		

* Computed from 2-4 pressor responses in each of 6 cats.

† "P" calculated by the *t* test of unpaired variates (2).

‡ When calculated by the *t* test of paired variates using the mean of 2 to 4 responses before and after saline, .5>P>.4.

§ When calculated by the *t* test of paired variates using the mean of 2 to 4 responses before and after saline, P >.01.

means of a mercury manometer, and injections were made intravenously into the external jugular vein at 5-minute intervals. Epinephrine and nor-epinephrine were administered alternately in approximately equipressor amounts to produce submaximal response. The doses required were, l-epinephrine,† 0.5-4.0 γ/kg; l-nor-epinephrine, 0.15-3.0 γ/kg. These amounts were made up to a volume of approximately 0.25 ml and were washed in with 0.5 ml of 0.9% saline. The pressor responses to the first 4 to 6 injections increased progressively in size and thereafter became more constant. Then in the test group of 6 cats, 2 to 4 pressor responses to both epinephrine and nor-epinephrine were elicited before, and again after, the administration of tetraethylammonium chloride in a dose of 5.0 mg/kg. Since the responses tended to change with time, a parallel control series of 6 cats was run in exactly similar manner except in that 2.0 ml saline was given in lieu of TEA.

Results. Blood pressure is expressed in terms of mm of mercury and responses as the mean and standard deviation of the absolute rise. After pithing, the baseline blood pressure remained remarkably constant in every cat though there was considerable variation between animals (32-86 mm of mercury). There was a tendency for the level to fall slightly, about 5.0 mm mercury, in some experiments after TEA. Since the potentiation of responses to epinephrine and nor-epinephrine always was much greater than this slight fall of pressure, it indicated not only a greater absolute rise but also a higher peak blood pressure.

Marked augmentation of the pressor response to epinephrine occurred after the administration of TEA (Table I). That this is not due to an increase in sensitivity of the preparation with the passage of time, is seen in the significantly greater response to epinephrine after TEA than after saline. That the test and control groups are comparable is seen in the fact that there was no significant difference between the responses before TEA and those before saline.

Similarly the pressor effect of nor-epinephrine was enhanced by the prior administration of TEA as is shown by a comparison of the responses following TEA with those following saline (Table I).

TEA potentiated the pressor response to epinephrine to a greater extent than that to nor-epinephrine (Table II) for there was no difference between their responses before TEA whereas there was a statistically significant difference after TEA.

The dose of TEA which was employed,

† Pure l-epinephrine supplied by Parke, Davis Co. Dosage of l-epinephrine and l-nor-epinephrine expressed as base.

2. Snedecor, G. W., *Statistical Methods Applied to Experiments in Agriculture and Biology*, 4th edition. The Iowa State College Press, Ames, Iowa, 1946.

TABLE II. Comparison of Responses to Epinephrine and Nor-epinephrine. Pressor responses in mm mercury; mean ± S. D.*

	Epinephrine	Nor-epinephrine	Difference	Significance†
Before TEAC	58.8 ± 8.7	56.5 ± 6.4	2.3	.4 >P >.3
After 5 mg/kg TEAC	87.8 ± 18.1	73.2 ± 11.8	14.6	P <.01

* Computed from 2-4 pressor responses in each of 6 cats.
† "P" calculated by the *t* test of unpaired variates(2).

5.0 mg/kg, was apparently nearly optimal in producing potentiation since the further administration of 10.0 mg/kg did not result in any additional potentiation of pressor responses in the test group when compared with the saline controls.

Discussion. From the results of this investigation one might conclude that TEA, in doses of 5.0 mg/kg intravenously in pithed cats, potentiated the pressor responses to both epinephrine and nor-epinephrine, there being a higher peak response in addition to a greater absolute rise of blood pressure. Since this was demonstrated in vagotomized animals with pithed spinal cords, such potentiation cannot have been due to the modification of cardiovascular reflexes.

Page and Taylor(3) reported the potentiation of the pressor action of epinephrine by tetraethylammonium in intact, anesthetized dogs. The mechanism they postulated was either an explosive manifestation of the sensitization of denervation or the blocking of amine oxidases. Their findings were confirmed subsequently in unanesthetized dogs (4) and by Moe(5). From simultaneous measurements of blood pressure and femoral arterial flow he concluded that the augmentation of pressor responses was due to the elimination of homeostatic cardiovascular reflexes. These are eliminated by virtue of the ganglionic blocking properties of TEA(6). This hypothesis, now supported by Page and Taylor(7), is strengthened by the fact that TEA potentiates the pressor response to other agents(1) and also enhances the fall of pressure produced by depressor substances(5), even that which follows the slow infusion of epinephrine(1). Moe also reported that, in intact anesthetized animals, the absolute rise of pressure in response to epinephrine was greater after TEA, but since the rise began from the hypotensive level established by the agent, the maximum was little greater than before. Stutzman *et al.*(8) report similar findings for phenylephrine after TEA.

The enhancement of epinephrine pressor effects by the blocking of compensatory reflexes, as is suggested by the evidence from the reports which have been cited, leaves unexplained however the potentiation of "Isuprel" (N-isopropyl homologues of epinephrine) tachycardia by TEA which at the same time augments the depressor response to the drug(4); nor does it explain the finding that hepatectomy abolished the augmenting action of TEA(3). There are few reports concerning the possibility of an additional direct mechanism although Moe(5) makes the statement, unsupported by published data, that, in the pithed cat, TEA does not appreciably alter the pressor action of epinephrine. This is at variance with the findings herein shown which would indicate that TEA does possess the property of potentiating the pressor actions of epinephrine and of nor-epinephrine independently of the central nervous system.

A peripheral effect of TEA in modifying responsiveness to various substances has been demonstrated by Collins(9). Using isolated intestine he reported augmentation of re-

3. Page, I. H. and Taylor, R. D., *J.A.M.A.*, 1947, v135, 348.

4. Corcoran, A. C. and Page, I. H., PROC. SOC. EXP. BIOL. AND MED., 1947, v66, 148.

5. Moe, G. K., *J.A.M.A.*, 1948, v137, 1115.

6. Acheson, G. H. and Moe, G. K., *J. Pharm. and Exp. Therap.*, 1946, v87, 220.

7. Page, I. H. and Taylor, R. D., *Circulation*, 1950, v1, 1233.

8. Stutzman, J. W., Pettinga, F. L., Fruggiero, E. J. and Maison, G. L., PROC. SOC. EXP. BIOL. AND MED., 1948, v68, 686.

9. Collins, D. A., *J. Pharmacol. Exp. Therap.*, 1948, v94, 244.

sponses to angiotonin and histamine and variable results with barium chloride and acetylcholine. Stone(10) found that TEA potentiated the motor effect of epinephrine on the seminal vesicle of the guinea pig. Finally, suggestive evidence was presented by Stutzman *et al.*(8), who reported that epinephrine-induced ventricular tachycardia was enhanced by tetraethylammonium chloride, even in spite of effective sympathetic block, and supradiaphragmatic splanchnicectomy.

Summary. 1. The potentiation by TEA of the pressor responses to epinephrine and nor-epinephrine has been demonstrated in cats with spinal cord pithed. 2. The effect of epinephrine was enhanced to a greater extent than that of nor-epinephrine. 3. This potentiation was not due to the modification of homeostatic cardiovascular reflexes.

Received June 18, 1951. P.S.E.B.M., 1951, v77.

10. Stone, C. A., 1951, unpublished data.

Effects of a Pancreatic Preparation (Viokase) in Depancreatized Cats. (18843)

W. J. TUDDENHAM AND A. E. MILMAN.* (Introduced by F. D. W. Lukens.)

From the George S. Cox Medical Research Institute, University of Pennsylvania, Philadelphia, Pa.

Substitution therapy for patients or animals which are deficient in the external secretion of the pancreas is still unsatisfactory. The various pancreatic preparations have afforded only limited replacement. Depancreatized carnivorous animals have usually been fed raw pancreas for its digestive and lipotropic effect. Even this falls far short of the normal external secretion. Recently a desiccated, defatted pancreatic powder (Viokase)† has been tried in depancreatized cats in this laboratory. The effect of this powder on the mass and fat content of the stools has been examined. Its influence on the insulin requirement has been observed because of Machella's unpublished report that the insulin requirement of a depancreatized man was increased during its administration.

Methods. Cats were depancreatized under nembutal anesthesia and the completeness of the operation confirmed by the amount of glucose excreted during fasting on the first one or 2 post-operative days. After this, a few days on insulin and penicillin put the animals in excellent condition. They were kept in metabolism cages. The daily excretion of glucose was determined and the dose of insulin adjusted accordingly. The stools of each cat were collected daily before the cages were cleaned, and were pooled for each metabolic period; the pooled samples were then dried to constant weight in a hood and analyzed for total fat by the method of Fowweather(1) adapted for use on the dried stool. Duplicate or triplicate analyses were performed on each sample.

The diet for all animals during all periods used for fat analyses (Tables I and II) was 150 g of raw horse meat daily. The studies on insulin requirement included some animals on 150 and some on 200 g of meat. The meat was quite constant in its composition. Analyses of different lots showed that it contained 73% water; 27% solids (dry weight); 20.8 g of protein per 100 g meat based on the determination of nitrogen. This means that the 150 g diet contained 31 g of protein, and 41 g dry weight. Two fat analyses showed 0.082 and 0.093 g of fat per gram dry weight of food. Based on the average of these measurements, the daily fat intake was 3.57 g per day. During the periods on Viokase, 2 level teaspoonfuls (about 3 g) of this powdered pancreas was mixed with the meat. Because of its small

* National Institutes of Health Postdoctorate Research Fellow, 1949-50.

† Manufactured by the Viobin Corp., Monticello, Ill.

1. Fowweather, F. S., *Brit. J. Exp. Path.*, 1926, v7, 7.