were used in this study on the histochemical specificity of phosphatases. With 18 substrates no indication of the presence in paraffin-embedded mammalian tissues of phosphatases other than the common non-specific alkaline and acid variety was found. With one of the substrates, p-chloranilidophosphonate, a strikingly different picture of enzymatic distribution was observed in the acid range, but otherwise the pattern of distribution of enzymatic activity in any given organ was constant and independent of the substrate used.

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Effect of Tetraethylammonium on Venous and Arterial Pressure in Congestive Heart Failure.

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That widespread vasoconstriction occurs during congestive failure was first proposed many years ago by Starling[1] and by Bolton.[2] Recently, it has been suggested that reflex vasoconstriction contributes to the maintenance of the usually normal arterial pressure[3,4] and the elevated venous pressure[3,5,6] in heart failure. Conversely, the fall in calculated peripheral resistance accompanying the improved output of the digitalized failing heart[7,8] speaks for a release of vasoconstriction. Renin has been found in the renal veins of patients in congestive failure,[3] and the reduction of hepatic and renal blood flows in such cases is further evidence of increased peripheral resistance attributable to vasoconstriction.

Tetraethylammonium chloride is a quaternary ammonium salt which transiently blocks the transmission of impulses through peripheral autonomic ganglia.[9] Hayward[10] has recently observed that tetraethylammonium bromide decreases the venous and arterial pressures in hypertensive patients with compensated or failing circulations. Since peripheral resistance is greatly increased in essential hypertension, it was of interest to observe the effect of this drug on the venous and arterial pressures of normotensive patients with and without failure, in an attempt to delineate the role of vasoconstriction in congestive failure *per se*.

Methods. Venous pressure was measured directly with a No. 18 gauge needle in an antecubital vein, using the sternal angle of the supine patient as a reference point. Arterial blood pressure was measured with a sphygmomanometer and the mean pressure was arbitrarily taken to be the average of the systolic and diastolic pressures. The heart rate was counted at the apex for 30 seconds. After repeated observations of heart rate and pressures had established a constant baseline, tetraethylammonium chloride (TEAC)* in doses of 2 to 6 mg/kg of body

1 Starling, E. H., The Fluids of the Body. W. T. Keener and Co., Chicago, 1909.

2 Bolton, C., *Brit. Med. J.*, 1917, **1**, 642.

3 Merrill, A. J., Morrison, J. L., and Brannon, E. S., *Am. J. Med.*, 1946, **1**, 468.

4 Landis, E. M., Brown, E., Fauteux, M., and Wise, C., *J. Clin. Invest.*, 1946, **25**, 237.

5 Starr, I., and Rawson, A. J., *Am. J. Med. Sci.*, 1940, **199**, 27.

6 Warren, J. V., and Stead, E. A., Jr., *Arch. Int. Med.*, 1944, **73**, 138.

7 Stead, E. A., Jr., Warren, J. V., and Brannon, E. S., *Arch. Int. Med.*, 1948, **81**, 282.

8 Bloomfield, R. A., Rapaport, B., Milnor, J. P., Long, W. K., Mebane, J., and Ellis, L. B., *J. Clin. Invest.*, 1948, **27**, 588.

9 Acheson, G. H., and Moe, G. K., *J. Pharm. and Exp. Therap.*, 1946, **87**, 220.

10 Hayward, G. W., *Lancet*, 1948, **1**, 18.

* Etamon Chloride, Parke-Davis and Company.

weight was injected through a fresh venipuncture over a period of 2 to 4 minutes, and the pertinent observations were continued frequently for 35 to 40 minutes thereafter.

Twenty subjects were studied in the manner described. Group I contained 8 patients with normal arterial and venous pressures, without evidence of cardiovascular disease. Group II included 2 compensated normotensive cardiacs with normal venous pressures and circulation times. Group III consisted of 8 patients with congestive heart failure as evidenced by distended neck veins, basilar rales, enlarged liver, and (except for patient G.H.) edema. None of these patients had a diastolic blood pressure above 90, and all of them, except G.H., were taking digitalis at the time of the study. Group IV consisted of 2 other patients with congestive failure in whom responses were compared before and after effective treatment for congestive failure. One of these patients (W.G.) had slight diastolic hypertension.

Results. The results are summarized in Table I.

Groups I and II. Venous pressures in the normal subjects and compensated cardiacs did not change, or rose slightly. Results were similar when the pressure in the antecubital vein was artificially elevated to levels seen in congestive failure by lowering the arm. Mean arterial blood pressure fell an average of 2.8 mm Hg $\pm$ 10.9 mm and the pulse rate always increased. The results were the same in normal subjects placed in a semi-reclining position 60 degrees from the horizontal.

Group III. Following injection of TEAC, venous pressure of patients in congestive failure promptly dropped 35 to 80 mm below the baseline. The effect began one to 2 minutes after injection was started, when 100 to 200 mg of the drug had entered the circulation, and was maximal in 5 to 7 minutes. The pressure then started to rise slowly, but usually had not reached its pre-injection level at the end of half an hour. Although there was some overlapping, the average drop in mean arterial blood pressure (24.6 mm Hg $\pm$ 5.6 mm) in Group III was significantly greater than the change seen in Groups I and II ("t" equals 4.25; "P" equals < 0.01). In contrast to the normals, 5 of the 8 patients in Group III had no change in heart rate, 2 slowed slightly, and only one (E.B.) developed a tachycardia. In this patient, a young man with calcified constrictive pericarditis, a tachycardia of the same degree was produced by 1 mg of atropine intravenously, without any change in venous pressure.

Group IV. Two patients in congestive failure were studied before and after digitalization. Before treatment, the injection of TEAC was followed by a sharp fall in venous pressure and a drop in mean arterial pressure. Several days later, when both patients had recovered considerably, the experiment was repeated. In W.G., who had become free of congestive signs and symptoms, TEAC caused no fall in venous pressure. In patient A. H., who still had dyspnea on exertion and basal pulmonary rales, TEAC caused a slight fall in venous pressure. In both patients, the percentile drop in mean arterial pressure was equivalent to that before digitalization.

Arm-to-tongue circulation times, measured with Decholin in 5 subjects before and immediately after injection of TEAC, did not change consistently. No untoward reactions to TEAC were observed, and no change in the degree of the cardiac patients' dyspnea was apparent.

Discussion. In high concentrations, tetraethylammonium increases the cardiac output in a failing heart-lung preparation.[11] However, the drug does not increase the output in dogs under barbiturate anesthesia, and it increases the human cardiac output only slightly or not at all.[12] Moe believes that any increases in output are probably attributable to the tachycardia.

Because the action of TEAC is chiefly on the peripheral autonomic ganglia, the data here presented imply the existence of an increased autonomic vascular tone in congestive failure which contributes to the elevation of venous pressure as well as the maintenance of arterial pressure. Almost the entire peripheral

[11] Acheson, G. H., and Moe, G. K., *J. Pharm. and Exp. Therap.*, 1945, **84**, 189.

[12] Moe, G. K., personal communication.

TABLE I.

Pt., age and sex			Diagnosis*	Dose TEAC, mg/kg	Venous pressure, mm 5% glucose: Baseline corrected to sternal angle	Venous pressure, mm 5% glucose: Max. change	Arterial pressure, mm Hg: Baseline B.P.	Arterial pressure, mm Hg: Mean B.P.	Arterial pressure, mm Hg: Max. change in mean B.P.	Heart rate, per min.: Baseline	Heart rate, per min.: Max. change
Group I											
F.E.	24	M	Normal	6	300†	0	120/72	96	+ 3	74	+ 6
G.G.	25	M	”	6	0	0	128/83	106	0	70	+36
D.F.	24	M	”	6	0	+ 10	110/75	93	— 8	80	+32
M.W.	18	F	Latent syphilis	4	80	0	130/82	106	—16	100	+12
D.B.	48	M	Peptic ulcer	6	78	+ 10	142/84	113	— 5	80	+16
V.C.	29	F	Hemorrhoids	6	135	+ 10	116/76	96	— 4	112	+32
A.Mc.	31	M	Early syphilis	6	30	+ 10	118/72	95	+16	62	+52
O.B.‡	21	M	” ”	6	10	+ 5	158/66	112	0	80	+60
Group II											
M.C.	18	M	RHD, MS, AS, AI	6	35	0	120/36	78	+ 7	76	+24
G.F.	75	M	ASHD, AF	6	95	+ 15	148/64	106	—21	74	+14
				Mean:	51.5 ± 38.8	+6.6 ± 5.8		100.1 ± 10.4	—2.8 ± 10.9		
Group III											
G.H.	54	M	ASHD, My	2	110	— 55	96/60	78	—10	98	— 8
E.B.	24	M	CP, AF	3	165	— 65	110/80	95	—21	84	+22
J.Y.	58	M	CP, AF	6	200	— 70	126/68	97	—27	74	0
W.H.	64	M	SA, AI	4	25	— 35	180/87	134	—19	80	0
M.M.	61	M	RHD, MS, MI, AI, TI, AF	6	80	— 80	128/65	97	—25	62	0
J.W.	49	M	ASHD, AF, ?RHD, ?TI	6	195	— 75	100/76	88	—18	90	0
A.E.	47	M	RHD, MS, AS, AI, AF	6	80	— 45	170/60	115	—31	68	—10
J.D.	65	M	ASHD, ?CP	6	65	— 70	110/78	94	—46	92	0
				Mean:	115 ± 64.5	—61.9 ± 15.6		99.8 ± 17.2	—24.6 ± 10.7		
Group IV											
W.G.	31	M	HHD, ASHD (before digitalis)	3.6	240	—120	146/120	133	—29	130	+36
W.G.			(After digitalis)	4.2	60	+ 25	130/96	113	—21	98	0
A.H.	66	M	ASHD (before digitalis)	4.5	155	— 90	134/82	108	—60	112	0
A.H.			(After digitalis)	5.4	—25	— 20	118/80	99	—53	108	0

* RHD—Rheumatic Heart Disease. ASHD—Arteriosclerotic Heart Disease. HHD—Hypertensive Heart Disease. SA—Syphilitic Aortitis. MS—Mitral Stenosis. AS—Aortic Stenosis. AI—Aortic Insufficiency. TI—Tricuspid Insufficiency. CP—Constrictive Pericarditis. My—Myocardial Infarction.

† The arm was lowered far below the level of the heart, but no correction to the level of the sternal angle was made. This value is not included in the calculation of the mean.

‡ This patient had received 0.5 mg of adrenalin subcutaneously 40 minutes before these observations.

vascular bed is under active vasomotor control.[13] A reduction in the amount of blood pumped from the venous to the arterial side of the circulation would lower arterial pressure while tending to elevate venous pressure.[1,2,5] It seems possible, therefore, that whenever cardiac output is inadequate, reflex peripheral autonomic mechanisms are called into play. These would maintain arterial pressure by arteriolar constriction and tend to increase cardiac output by further increasing the venous filling pressure. Venous filling pressure might be elevated by an increased tone in the large veins or by a redistribution of blood resulting from constriction of smaller peripheral vessels. These experiments do not exclude the possibility that other factors such as increased blood volume or tissue fluid pressure may also play major roles in the maintenance of the elevated venous pressure of congestive failure.

Finally, it should be pointed out that only the peripheral venous pressure was measured in these experiments. It is possible, particularly in subjects without venous hypertension, that pressure changes in the central veins and right atrium were not closely reflected by changes in the peripheral venous pressure.

Summary. Tetraethylammonium chloride given intravenously to 9 normotensive patients in congestive failure caused a precipitous fall in venous pressure and a significant decrease in arterial pressure in every case. Compensated cardiacs and non-cardiac normotensive controls showed no fall in venous pressure and a much smaller change in arterial pressure. Following digitalization, 2 cardiac subjects in failure lost some of their initial responsiveness to TEAC.

[13] McDowall, R. J. S., *Phys. Rev.*, 1935, **15**, 98.

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Survival of Rats After Temporary Complete Renal Ischemia.*

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It has been shown that rats generally survive bilateral interruption of the renal circulation for periods lasting up to one hour.[1] With longer intervals of complete ischemia, the mortality rises sharply. Cessation of blood flow to both kidneys for two hours is uniformly fatal; there is progressive elevation of BUN and death occurs in uremia within a few days.

The principal lesion produced by temporary periods of complete renal ischemia is necrosis of the proximal convoluted tubules.[1] In rats with a one hour period of bilateral ischemia, the necrosis is followed by repair and survival of the animals. Rats with a 2 hour period of ischemia evidently die in uremia before regeneration is effective.

In order to determine whether the renal lesion produced by periods of ischemia longer than those in the preceding experiments was subject to repair and would permit survival of the rats, unilateral ischemia was produced. The left main renal artery and vein of 50 adult white rats were occluded with a bulldog clamp for periods ranging from 2 to 4 hours. A 5 hour period was unsatisfactory because of the frequent occurrence of renal infarction. Heparin was given intravenously before clamping, and in some instances during clamping, to retard intrarenal thrombosis. The right kidney was intact. The animals were sacrificed at various intervals up to 5 months after removal of the clamps.

Results. Tubular necrosis was followed by

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1 Koletsky, Simon and Gustafson, G. E., *J. Clin. Invest.*, 1947, **26**, 1072.