

THE CIRCULATORY AND METABOLIC EFFECTS IN MAN OF
HISTAMINE, MECHOLYL®, TETRAETHYLAMMONIUM
AND ATROPINE IN THE PRESENCE OF CIRCULATING
EPINEPHRINE AND NOR-EPINEPHRINE¹

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In pheochromocytoma pharmacologic agents which provoke paroxysms of hypertension [*i.e.*, histamine (1), methacholine chloride (2), and tetraethylammonium chloride (3)] have come to be widely employed as clinical diagnostic tools. Although the usual effects of these drugs, namely fall in blood pressure, tachycardia and vasodilatation, are well recognized, the mechanism by which they induce hypertension in the pheochromocytoma patient remains unclarified.

This study was designed to evaluate the circulatory and metabolic responses induced by histamine, methacholine chloride (hereafter referred to as Mecholyl®) and tetraethylammonium chloride (TEAC) in the presence of measured amounts of circulating epinephrine and nor-epinephrine.

Atropine has been included as a test drug in an effort to determine the role which tachycardia may play in the observed responses, and also because Littman and co-workers (4, 5) have reported augmentation of nor-epinephrine's pressor effects by pretreatment with atropine.

MATERIAL AND METHODS

Blood pressure studies. Fifty-four convalescent hospital patients free of cardiovascular and renal disease were studied during a series of 82 infusion experiments. Twenty patients had paired infusions including both epinephrine and nor-epinephrine.

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The provocative test drugs employed and the dose and volume in which they were administered were:

1. Tetraethylammonium chloride,⁴ 400 mg. (4 ml.) rapidly intravenously.
2. Histamine base, 0.025 mg. as histamine phosphate (0.35 ml.) of a 1:5,000 dilution rapidly intravenously.
3. Mecholyl®,⁵ 10 mg. (1 ml.) subcutaneously.
4. Atropine sulphate,⁶ 1.2 mg. (3 ml.) rapidly intravenously.

Small amounts of normal saline were infused during the initial and terminal control periods and the change to pressor amine was made by way of a three-way stopcock.

All tests were done in the supine position and in the fasting state at least 30 minutes after the intravenous needles and other apparatus had been arranged. Blood pressure was measured by the auscultatory method and pulse was counted every four minutes.

After a 10 minute control period, a control dose of the provocative test drug was given. Blood pressure was then followed at one-half minute intervals for five minutes and at one minute intervals thereafter. Thirty minutes after the control test, the infusion of epinephrine⁷ or of nor-epinephrine⁷ was begun. Fifteen minutes were allowed for stabilization of blood pressure and pulse at new levels; then the test drug was given again and the same observations repeated. Fifteen minutes later the infusion was switched to saline and blood pressure and pulse followed until control levels or a steady state were attained.

⁴ Etamon® chloride, kindly supplied by Dr. E. C. Vonder Heide, Parke Davis and Co.

⁵ Mecholyl®, kindly supplied by Merck and Co., Inc.

⁶ Atropine sulfate, kindly supplied by Eli Lilly and Co.

⁷ Pure synthetic *l*-epinephrine (Suprarenin®) and *l*-norepinephrine (Levophed®) kindly supplied by Dr. M. L. Tainter, Winthrop-Stearns, Inc., were diluted appropriately with saline in sterile volumetric pipettes and were infused at a constant rate of 0.9 ml. per minute by means of a Bowman constant infusion pump. Doses were so calculated that 0.085 µg. per Kg. per minute of epinephrine base or nor-epinephrine base was delivered. In a few early experiments larger doses were employed.

Atropine control tests were done on separate days because of the longer duration of drug action.

Blood samples for glucose and lactic acid were drawn at the following intervals: two control specimens, 15 minutes after the control dose of the provocative test drug, 15 minutes after the infusion of epinephrine or nor-epinephrine was begun, and 15 minutes after the test drug had been given during the infusion. Blood glucose was determined by the method of Nelson (6) and blood lactic acid by a modification of the method of Barker-Summerson (7).

Cardiac output studies. In 33 patients, only nor-epinephrine was infused and the responses to either TEAC

or atropine observed. The cardiac output was measured during the infusion of nor-epinephrine and again shortly after the addition of either TEAC or atropine, using Hamilton's dye dilution technique with Evans blue dye. Serial blood samples were collected manually in heparinized tubes at one second intervals from an inlying brachial artery needle. The serum from the centrifuged specimens was transferred directly to microcuvettes and read in a Beckman spectrophotometer at 620 m μ . The results were plotted on semi-logarithmic paper and the cardiac output calculated using the formula of Hamilton and co-workers (8). All curves wherein the point of recirculation could not be definitely found or where

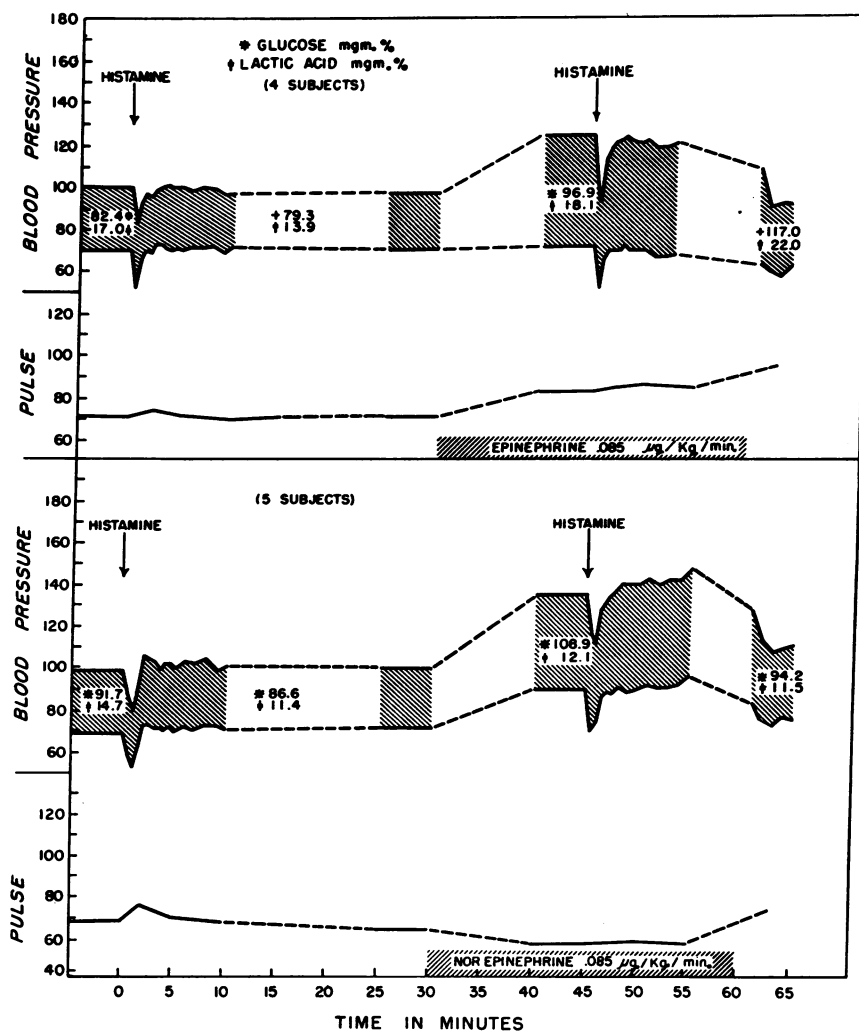


FIG. 1. MEAN RESPONSES TO HISTAMINE BASE (0.025 MG. INTRAVENOUSLY)

Mean blood pressure and pulse responses along with mean glucose and lactic acid values are indicated during control periods (far left) and during epinephrine infusion (upper right) and nor-epinephrine infusion (lower right). The unshaded areas and dotted lines indicate waiting periods during which blood pressure was allowed to stabilize, and do not represent actual values. Note that histamine remains depressor throughout.

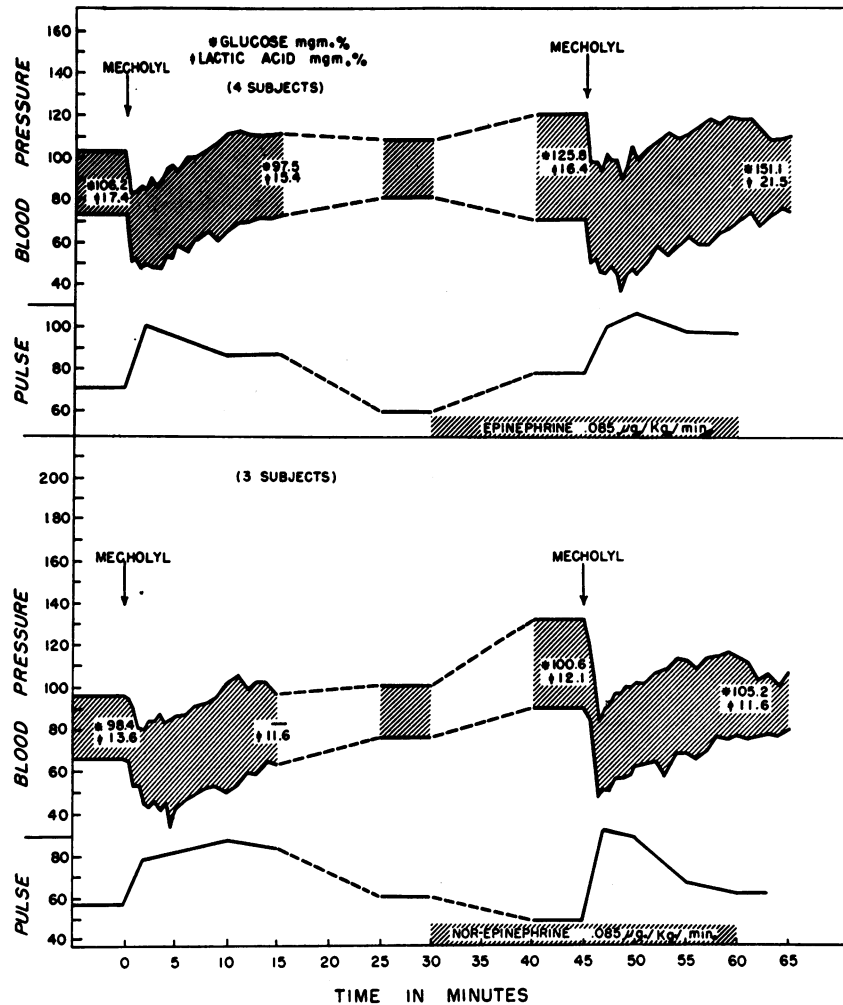


FIG. 2. MEAN RESPONSES TO MECHOLYL® (10 MG. SUBCUTANEOUSLY)

The data have been charted in the same manner as in Figure 1. As with histamine, MecholyL® is consistently depressor.

hemolysis distorted the spectrophotometer values were discarded.

RESULTS

A. Effects of epinephrine and nor-epinephrine

Epinephrine infusion produced systolic blood pressure elevation and usually a fall in the diastolic pressure. Even in the small dose employed in this study, subjects complained of a feeling of uneasiness, anxiety or nervousness. Many patients complained of palpitations and nearly all were aware of tachycardia. Pallor, cold sweat, and apprehension were frequently noted. Because of these unpleasant effects, higher infusion doses of epi-

nephrine attempted during early studies were reduced.

Nor-epinephrine infusion uniformly produced a rise of systolic and diastolic blood pressure and fall in pulse rate with minimal subjective response. Patients appeared comfortable and relaxed even when the blood pressure was markedly elevated. Skin pallor was slight although constriction of the vein into which the infusion was running was usually apparent. Doses of nor-epinephrine two to three times greater than 0.085 μg . per Kg. per minute could be given with no discomfort if the dosage was increased gradually. When high doses were begun abruptly and blood pressure rose

sharply, severe headache was produced in several cases.

B. Blood pressure and pulse responses

Histamine. The effects of histamine were observed during nine infusions, eight of which were paired epinephrine and nor-epinephrine infusions in the same four subjects (see Figure 1). Histamine responses were consistently depressor during control periods ($-20/-20$ mm. Hg), during epinephrine infusion ($-30/-20$ mm. Hg), and also during nor-epinephrine infusion ($-25/-20$ mm. Hg). Pulse rate rose only slightly

during controls (plus 5 beats per minute), during epinephrine (plus 3 beats per minute), and during nor-epinephrine infusion (plus 0.7 beats per minute). A slight flush followed by a moderately severe headache occurred regularly. These effects also were not significantly modified by epinephrine or nor-epinephrine infusion.

Mecholyl®. Mecholyl® effects were observed during seven infusions, six of which were paired epinephrine and nor-epinephrine infusions in the same three subjects (see Figure 2). Within 30 seconds after the drug was given subcutaneously, control pressures fell ($-20/-25$ mm. Hg) and

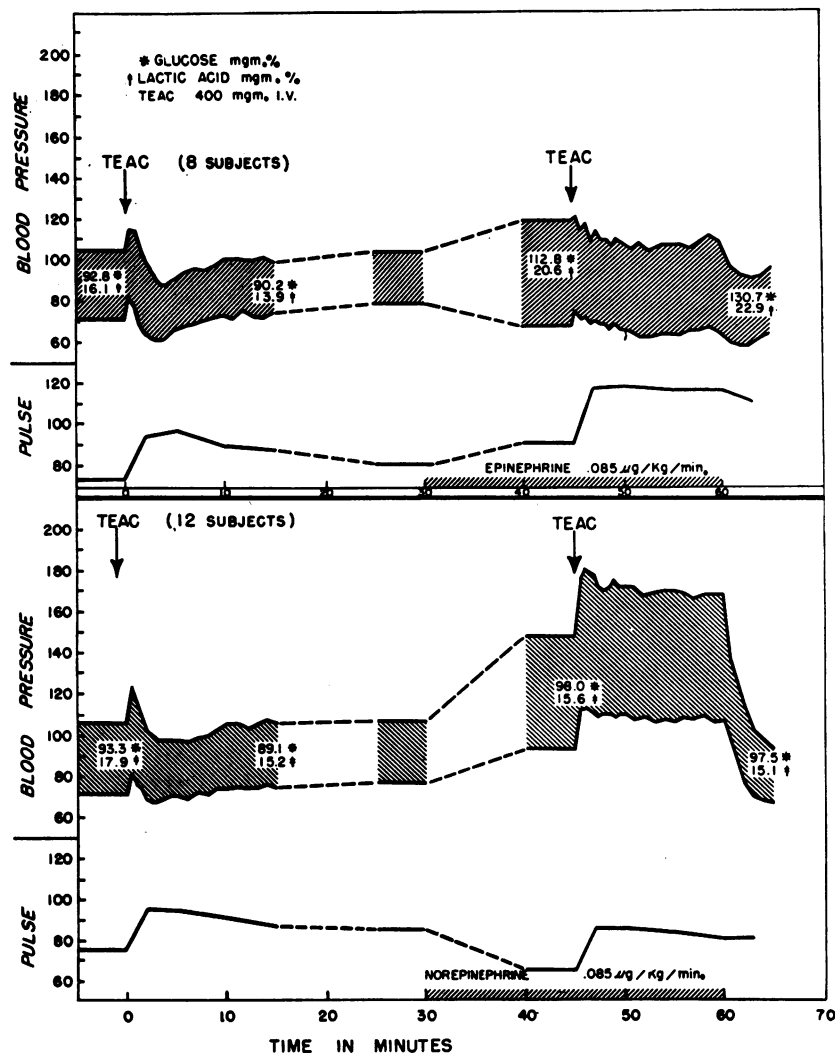


FIG. 3. MEAN RESPONSES TO TETRAETHYLAMMONIUM CHLORIDE (TEAC, 400 MG. INTRAVENOUSLY)

The data have been charted as in Figure 1. Note how the TEAC response becomes strikingly pressor during nor-epinephrine infusion (lower right).

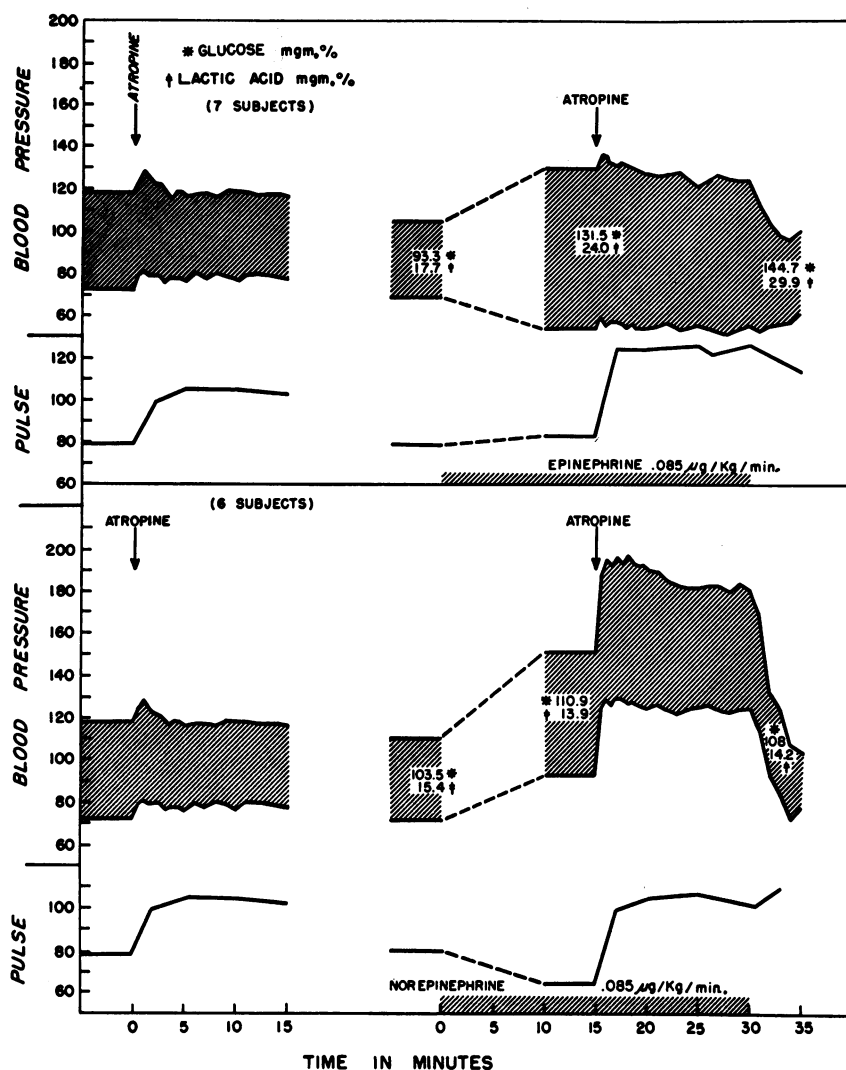


FIG. 4. MEAN RESPONSES TO ATROPINE SULFATE (1.2 MG. INTRAVENOUSLY)
The data are plotted as in Figure 1. As with TEAC, atropine causes marked potentiation of nor-epinephrine hypertension.

these depressor effects were even more prominent during epinephrine infusion ($-30/-34$ mm. Hg) and nor-epinephrine infusion ($-48/-42$ mm. Hg). Increase in pulse rate was more marked with Mecholy1® than with histamine, during control periods (plus 28 beats per minute), with epinephrine (plus 28 beats per minute), and during nor-epinephrine (plus 43 beats per minute). Tachycardia persisted at least 15 minutes. In addition, all patients exhibited the other muscarinic effects of Mecholy1®, such as flush, profuse sweating, salivation and an urge to defecate and urinate. Sweating was less profuse during epinephrine and

nor-epinephrine infusion. There were no untoward side effects such as bronchospasm or cardiac arrhythmias.

TEAC. The response to TEAC was tested during 20 infusions, 8 epinephrine and 12 nor-epinephrine; 7 subjects received both (see Figure 3).

Control TEAC responses were only slightly depressor ($-12/-8$ mm. Hg) after an initial transient pressor rise lasting 30 to 60 seconds. TEAC responses during epinephrine infusions were also depressor ($-15/-5$ mm. Hg). During nor-epinephrine infusion, however, TEAC be-

came dramatically pressor (+33/+20 mm. Hg) and this persisted until the infusion was discontinued. The subjective response to the rapid injection of TEAC was usually a sudden metallic taste, followed by a generalized sensation of coolness and tingling in the hands and feet. Epinephrine and nor-epinephrine did not alter these reactions.

Pulse rate was increased by TEAC during the control periods (plus 23 beats per minute) and also during epinephrine (plus 27 beats per minute) and nor-epinephrine (plus 21 beats per minute).

Atropine. The response to atropine was tested during 13 infusions, 7 epinephrine and 6 nor-epinephrine, 6 subjects receiving both. During control tests with atropine blood pressures were essentially unchanged except for a transient slight increase in systolic and diastolic pressure (see Figure 4). During epinephrine infusion, atropine produced no significant change in blood pressure but during nor-epinephrine infusion blood pressure rose sharply (+45/+35 mm. Hg), and as with TEAC these potentiated pressor effects were sustained until the infusion was discontinued.

Atropine produced very little subjective effect. An occasional patient noted dryness of the mouth or palpitation. The pulse rate uniformly increased during the control test (plus 25 beats per minute), during epinephrine (plus 43 beats

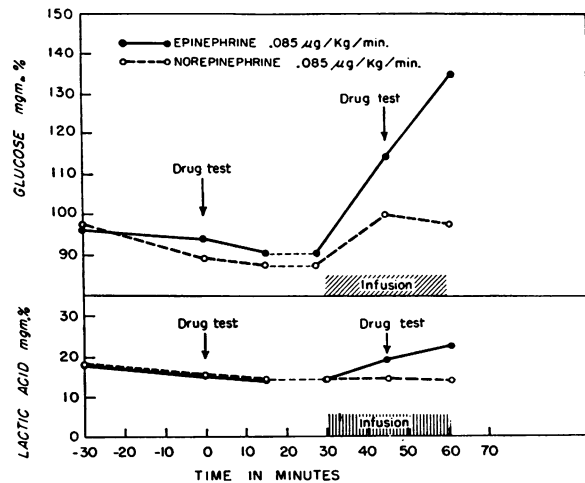


FIG. 5. THE MEAN GLUCOSE AND LACTIC ACID VALUES OBTAINED BEFORE AND AFTER CONTROL TESTS WITH HISTAMINE, MECHOLYL® AND TEAC (FAR LEFT) TOGETHER WITH THE CHANGES INDUCED BY EPINEPHRINE (SOLID LINE) AND NOR-EPINEPHRINE (DOTTED LINE)

It should be noted that these indices of adrenal medullary activity were not altered by the provocative test drugs.

per minute), and during nor-epinephrine infusion (plus 41 beats per minute). In one patient paroxysmal auricular tachycardia was precipitated by atropine given during nor-epinephrine infusion.

C. Metabolic studies

Although the test drugs alone (histamine, Mecholyl®, and TEAC) had no effect on blood

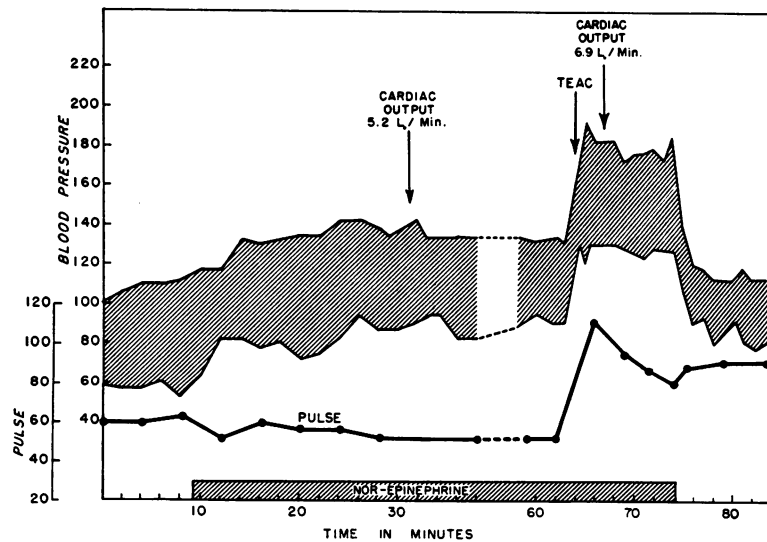


FIG. 6. DETERMINATION OF THE CARDIAC OUTPUT BEFORE AND AFTER POTENTIATION OF NOR-EPINEPHRINE BY TEAC

TABLE I
*Actual cardiac output values (liters per minute) during nor-epinephrine infusion and after blood pressure potentiation by tetraethylammonium chloride (TEAC) or atropine **

Subject	Nor-epinephrine infusion	Blood pressure potentiation	Difference†
TEAC			
K. B.	6.22	8.10	+1.88
E. L. R.	4.60	5.52	+0.92
W. R.	5.16	6.88	+1.72
J. B. M.	6.79	7.32	+0.53
J. L. W.	4.87	6.27	+1.40
G. G.	5.70	6.50	+1.80
	Mean	+1.38 L./min.	
	S.E.	±0.22 L./min.	
		0.01 > p > 0.001	
Atropine			
T. G.	4.59	8.04	+3.45
A. M.	5.99	10.50	+4.51
O. L. B.	4.56	5.76	+1.20
A. S.	4.85	6.66	+1.87
J. W.	5.74	7.10	+1.36
F. W.	5.74	7.79	+2.05
	Mean	+2.40 L./min.	
	S.E.	±0.53 L./min.	
		0.01 > p > 0.001	

* Dye-dilution curve method of Hamilton and coworkers (8).

† Difference due to potentiation.

glucose or lactic acid levels (Figure 5) these were both elevated by epinephrine infusion, glucose rising from a mean of 90 mg. per cent to 114 mg. per cent during the first 15 minutes of infusion and then to a mean of 135 mg. per cent after 30 minutes of epinephrine. Lactic acid similarly rose from a mean of 14 to 19 mg. per cent in 15 minutes and to 22.5 mg. per cent in 30 minutes.

With nor-epinephrine, glucose level rose slightly from a mean of 87.5 to 100 mg. per cent in the first 15 minutes and did not change significantly (mean, 97.5 mg. per cent) in 30 minutes. Lactic acid levels were not changed by nor-epinephrine infusion nor were they affected when TEAC and atropine augmented the nor-epinephrine blood pressure effects.

D. Cardiac output studies

To clarify the mechanism by which TEAC and atropine caused the observed sudden increases in blood pressure (nor-epinephrine potentiation), cardiac output was measured during a series of nor-epinephrine infusions before and approxi-

mately five minutes after potentiation by TEAC (15 subjects) or atropine (18 subjects) (see Figure 6 for a typical experiment).

In 12 experiments (6 TEAC and 6 atropine) satisfactorily paired curves were obtained and demonstrated a significant increase in cardiac output during potentiation ($p < 0.01$) (Table I). Potentiation by atropine increased cardiac output an average of 2.4 L. per minute ($p < 0.01$) and TEAC an average of 1.38 L. per minute ($p < 0.1$). Cardiac index (cardiac output divided by surface area in $M.^2$) increased 0.75 L. per minute per $M.^2$ with TEAC ($p < 0.01$) and 1.43 L. per minute per $M.^2$ with atropine ($p < 0.01$).

Pulse rate increased with TEAC (24 beats per minute) and with atropine (44 beats per minute) as in the other nor-epinephrine infusion experiments, and calculated stroke volume fell an average of 7 ml. per beat with TEAC potentiation and 8 ml. per beat with atropine, neither decrease being significant (Figure 7).

Calculated peripheral resistance (mean pressure times 1,332)/cardiac output did not change consistently with TEAC, decreasing in three patients and increasing in three. However, with atropine peripheral resistance fell in all patients (mean fall, 198 units) ($p < 0.01$) (Figure 7).

E. Unusual responses

In 6 of 33 infusions, TEAC failed to potentiate nor-epinephrine. In three of these the dose of nor-epinephrine in itself failed to change the control blood pressure levels. In the other three patients, TEAC in itself did not produce its usual tachycardia.

In 2 of 26 nor-epinephrine infusions atropine failed to potentiate nor-epinephrine. In both of these instances the blood pressure failed to rise with the dose of nor-epinephrine employed. In one of these cases when the dose of nor-epinephrine was doubled (0.170 μ g. per Kg. per minute), the blood pressure rose and atropine then produced potentiation.

In a patient with Hodgkin's disease and a large tumor mass in the region of the right carotid sinus, atropine alone caused a marked, sustained rise in blood pressure and pulse and both epinephrine and nor-epinephrine were potentiated by atropine. This was the only patient in whom epi-

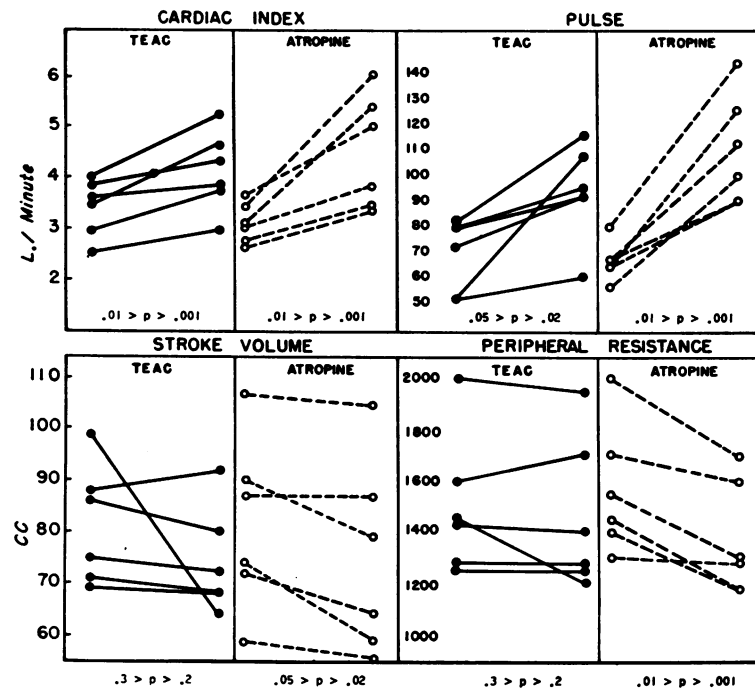


FIG. 7. THE VALUES FOR CARDIAC INDEX, PULSE, STROKE VOLUME AND PERIPHERAL RESISTANCE BEFORE (LEFT-HAND POINTS IN EACH BOX) AND DURING (RIGHT-HAND POINTS IN EACH BOX) NOR-EPINEPHRINE POTENTIATION BY TEAC (SOLID LINES) AND ATROPINE (BROKEN LINES)

nephrine was potentiated. After the tumor was shrunk with X-ray, epinephrine was no longer potentiated.

DISCUSSION

It is apparent that of the several test drugs which induce pressor responses in cases of pheochromocytoma, TEAC must produce its effects by a different mechanism than histamine or Mecholyl®.

In these studies TEAC consistently potentiated the pressor effects of circulating nor-epinephrine. These responses closely resembled the paroxysmal blood pressure rises provoked by TEAC in pheochromocytoma and suggest that a positive provocative test with this drug constitutes an augmentation or potentiation phenomenon specific for circulating nor-epinephrine.

On the other hand, histamine and Mecholyl® were consistently depressor even in the presence of the infused pressor amines. Thus, a mechanism other than potentiation must account for their ability to induce pressor paroxysms.

Although it is speculative to compare our re-

sults in normal subjects during infusions to results in patients with pheochromocytoma, our subjects did resemble such patients in a very important way; namely, they had been made acutely hypertensive by circulating catecholamine.

The pharmacologic similarities of TEAC and atropine in these studies suggest that their ability to induce nor-epinephrine potentiation may be accounted for by a similar mechanism. Our data indicate that blood pressure augmentation is accompanied by an increase in cardiac output rather than by increase in peripheral resistance. This increase in output must be the result of a rise in heart rate, an increase in the force of cardiac contraction or both. Since neither TEAC nor atropine alone significantly increases cardiac output, the increase demonstrated with potentiation must reflect the action of these drugs (9) in speeding heart rate, tachycardia occurring at a time when the peripheral blood vessels are tightly constricted by nor-epinephrine.

This increase in pulse rate by TEAC and atropine almost certainly involves the buffer reflexes of the carotid sinus and the aortic arch, and the

augmented blood pressure responses both qualitatively and quantitatively resemble the acute "de-buffering" effects observed by Kezdi (10) after Novocain® block of the carotid sinuses in man.

In accordance with the mechanism first suggested by Moe (11) and Hoobler, Moe, and Lyons (9), potentiation as observed here might be accounted for in the following manner.

With infusion of nor-epinephrine, peripheral vasoconstriction occurs and the blood pressure rises. The carotid sinus and aortic depressor nerve are stimulated to increase vagal tone, thereby slowing the heart and tending to prevent further rise of the blood pressure. When TEAC or atropine are suddenly introduced during nor-epinephrine infusion, the vagal bradycardia is blocked, heart rate increases and any compensatory change in peripheral resistance is prevented by (nor-epinephrine) vasoconstriction. Therefore the blood pressure must rise.

The failure to produce potentiation of epinephrine suggests a significant difference between man and the experimental animal, since Page and Taylor (12), Moe (11), and Goldblatt (13) have observed potentiated epinephrine responses to TEAC in animals.

Our inability to produce epinephrine potentiation in man may reflect: 1) epinephrine's vasodilating effect in contrast to nor-epinephrine's vasoconstriction (14); 2) that the dose of epinephrine tolerated by man may be too low to permit potentiation; or 3) that the cardiac output may already be maximally increased before the potentiating agent is introduced.

Because of the striking potentiation of nor-epinephrine by atropine in these studies, we have employed this drug as a provocative test for pheochromocytoma four times in three patients with proven tumors. On two occasions the blood pressure rose sharply after 1.2 mg. of intravenous atropine but on the other two the blood pressure remained at control levels in spite of the appearance of marked tachycardia. Since these patients had consistently pressor TEAC responses, it is suggested that other mechanisms beyond simple buffer block may participate in the positive provocative test with TEAC.

The blood sugar and lactic acid data confirm the known differences in the metabolic effects of nor-epinephrine and epinephrine infusion (15). In

the present study, histamine, Mecholyl® or TEAC alone in the doses used did not cause significant increase in blood sugar or lactic acid to indicate firing of the adrenal medulla with elaboration of epinephrine. Since it has been shown (16) that increase in blood sugar and lactic acid can be produced by smaller doses of epinephrine than those required to change the blood pressure, it would seem that histamine, Mecholyl® and TEAC given intravenously in the control studies here did not stimulate the adrenals.

CONCLUSIONS

The results suggest the following conclusions:

1. Since tetraethylammonium chloride (TEAC) consistently augments the hypertension induced by nor-epinephrine infusion a positive provocative test with TEAC in pheochromocytoma may well represent a potentiation phenomenon specific for circulating nor-epinephrine.

2. Since histamine and Mecholyl® remain depressor during epinephrine and nor-epinephrine infusion, a different mechanism must account for the pressor responses which these agents may induce in pheochromocytoma.

3. In contrast to the results in the experimental animal epinephrine potentiation could not be produced in man with TEAC.

4. Atropine, like TEAC, potentiates nor-epinephrine and deserves further evaluation as a screening agent for pheochromocytoma.

5. Pressor potentiation of nor-epinephrine by TEAC and atropine is accompanied by an increase in cardiac output and no significant change in peripheral resistance, probably reflecting blockade of the carotid sinus and aortic arch reflexes which control heart rate.

6. Metabolic studies produced no evidence to suggest that histamine, Mecholyl® or TEAC in the doses employed provoked stimulation of the normal adrenal medulla.

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