Augmentation of Vasoactive Substances by Tetraethylammonium Chloride

By Irvine H. Page, M.D., and Robert D. Taylor, M.D.

This investigation attempts to demonstrate the mechanism by which substances that block autonomic ganglionic transmission increase the pressor and depressor activities of a variety of drugs. Short-lived hypertension and a high degree of vascular responsiveness is induced by combining cord destruction, inactivation of the carotid sinus mechanism and nephrectomy. The increased responsiveness is found to be due to removal of the compensatory nervous mechanisms which tend to oppose changes in blood pressure. It may be reduced or abolished by hepatectomy, severe hypotension and shock.

BLOCKADE of transmission of nerve impulses within autonomic ganglia by tetraethylammonium chloride (TEAC) is now recognized as the chief action of this drug, as shown by the several penetrating investigations of Acheson, Moe, Hoobler and Lyons.1, 2, 3, 4, 5 This blockade, as we have demonstrated,6, 7 results in augmentation of the cardiovascular pressor and depressor responses to a variety of substances. Such increased responsiveness contrasts sharply with the refractory state of the vascular system in shock8, 9 and may have important significance because of the probability that disease of the heart and blood vessels may result from specific changes in responsiveness to stimulation. The reasons for failure of TEAC to duplicate surgical sympathectomy is also worthy of investigation.10

The effects of TEAC, however, are not limited to blockade of autonomic transmission. The initial depressor response is due to blockade, but, as more and more of the drug is given, the depressor response gives way to a pressor one, caused by liberation from the liver of a noradrenaline-like substance.11 At this stage of TEAC treatment, responses to many other drugs are greatly heightened. Since the mechanism by which increase in responsiveness occurs is not known, we have studied it; and the results are recorded in this paper.

The broad problem which is our concern is the factors which determine the responsiveness of the blood vessels in health and disease. First, it will be shown that in dogs, cat, rats and human beings, substances such as adrenaline and angiotonin are augmented in their pressor action while others such as pituitrin are not. The mechanism of augmentation is shown to be due chiefly to loss of inhibitory or compensatory nervous mechanisms elicited by the autonomic blockade. Proof of this depends on the experiments encompassing total sympathectomy, cord destruction and inactivation of the carotid sinus mechanism. A number of factors can influence the degree of augmentation, the chief of which, in our experience, are loss of the liver and terminal shock state.

Another means we have found of increasing vascular responsiveness, and hence the extent of the augmentation, is removal of both kidneys; other methods, such as injection of cocaine, methylene blue, tetramethylammonium chloride, and Dibutoln have also been tried. Decreased responsiveness has been
sought by injection of Dibenamine, Benzo-
dioxane and dihydroergocornine. These pro-
cedures in combinations can widely alter
pressor-depressor responses.

If in such experiments as these, responses
to the same dose of vasoactive drugs can be
widely varied, similar variations may well
occur in the course of normal physiologic
adaptation. We have indeed found that,
under conditions as rigidly controlled as we
know, the variations in response of supposedly
normal dogs to standard doses of adrenaline
were adrenaline, U.S.P., 20 γ; 1-noradrenaline (1-Ar-
terenol*) 25 γ; barium chloride, 9 mg.; angiotonin,
5 cat units; renin, 0.1 cc.; and tetraethylammonium
chloride, 5 mg./Kg.; nicotine, 0.15 cc. 1:1000 dilution;
histamine, 40 γ. The details of the experimental
method have previously been described.19

RESULTS

Substances Showing Augmentation

Both adrenaline and 1-noradrenaline are
among the easiest substances to augment with
TEAC. Doses of 5 mg. TEAC per Kg. body

![Graph](image-url)

**Fig. 1.**—Responses of a normal dog (No. 929) under pentobarbital anesthesia showing augmenta-
tion by TEAC. (1) Noradrenaline, (2) adrenaline, (3) barium chloride, (4–6) TEAC, (7) adrenaline,
(8) noradrenaline, (9–10) TEAC, (11) barium chloride, (12) TEAC, (13) noradrenaline, (14) TEAC,
(15) adrenaline, (16–17) TEAC, (18) noradrenaline, (19) adrenaline, (20) barium chloride, (21) TEAC,
(22) adrenaline.

and 1-noradrenaline ranged from zero to
110 mm. Hg.

METHODS

Mongrel dogs of from 6 to 15 kilograms of body
weight were given 35 mg./Kg. of pentobarbital intraperitoneally or intravenously, and the experiments
started within one to one and one-half hours. A
continuous slow drip of saline was given into one
femoral vein and the opposite one used for injections.
Arterial pressure was recorded from a femoral artery
connected to a mercury manometer by polythene
tubing which contained heparin solution. If the re-
spiratory passage was not clear, a tracheal cannula
was inserted. In most cases, the order in which the
test drugs were given was the same. These drugs
weight were given intravenously and often after
the first injection some slight increase in re-
sponse to pressor drugs was observed. Maxi-
mum augmentation often required 20 to 40
mg./Kg. when given in single doses of 5 mg./
Kg. About the same amount was needed when
given by infusion. The rate at which pressor
responses increase above the control levels
roughly parallels the conversion of responses
to TEAC from depressor to pressor. The two
rates are, however, independent of one another
because slight augmentation is usually ob-

* The 1-Arterenol was kindly supplied by Dr.
M. L. Tainter, Sterling-Winthrop Research Institute.
served before the TEAC effect becomes significantly pressor.

Barium chloride is augmented often but irregularly, and its augmentation does not parallel that of adrenaline and noradrenaline. Tyramine is easily augmented; 2-aminooctane less easily, while the pressor effects of pituitrin, ephedrine and Paredrine are changed little if any. Depressor substances such as histamine, choline and acetylbetamethyleholine exhibit the phenomenon only moderately. Renin and angiotonin are both augmented and renin tachyphylaxis under certain circumstances is overcome. The action of renin and angiotonin will be the subject of a more detailed communication.

Thus substances of varied chemical structure exhibit the phenomenon, and some vasoactive substances, notably pituitrin, Paredrine and ephedrine, fail to show it.

Mechanism of Augmentation

Sympathectomy and Spinal Cord Destruction.

A variety of mechanisms could account for augmentation. The most likely is concerned with blockade of autonomic ganglionic transmission. This follows from the experiments illustrated in Table 1 in which it is shown that no further augmentation occurred following injection of TEAC into animals subjected to total lumbodorsal surgical sympathectomy plus inactivation of the carotid sinus mechanism. In short, if most of the autonomic ganglia regulating vasmotor responses have already been removed, TEAC has little or no augmenting action. On the other hand, in three experiments total lumbodorsal sympathectomy with supradiaphragmatic vagotomy did not prevent augmentation following TEAC. To preclude augmentation completely, both carotid sinuses and both vagus nerves had to be inactivated.

The view that augmentation is due to removal of compensatory nervous mechanisms was more thoroughly examined in a large number of dogs subjected to progressive removal of various portions of the nervous system. The operations were performed aseptically as neurosurgical procedures. Adequate recovery was allowed between stages to circumvent the profound influence of trauma and shock on vascular reactivity. The so-called “acute” experiments were largely avoided in these studies.

As we have noted elsewhere, total lumbodorsal sympathectomy does not wholly supplant TEAC augmentation although it does so to some undetermined degree. After laminectomy, the anterior nerve roots were sectioned at various levels in 22 dogs to ascertain the minimum denervation compatible with maximum augmentation of vascular responsiveness. Because there was usually some doubt at the operating table as to the precise level at which the roots were being cut, the results were re-examined at autopsy. Since this group of experiments confirm those in which the spinal cord was destroyed, details of the results will not be given. Suffice it to say that preganglionic denervation from C-6 to D-8 in most animals augmented responsiveness as much as when the operation was extended from C-6 to L-3. The augmentation was qualitatively the same after different test drugs as after actual cord destruction.

In four experiments in which dogs were decapitated between the fourth and fifth cervical vertebrae, TEAC augmented responsiveness two to three-fold. Usually destruction of the spinal ganglia alone does not give full augmentation but in the absence of restraint of the remaining nervous system, their loss becomes the more important.

 Destruction of the cord below the level of D-6 does not give maximum augmentation, while progressive destruction up to C-6 causes complete loss of the cord component. Thus the extremes of the area of the cord concerned with the mechanism of augmentation are included within C-6 to D-6. While cord destruction from C-6 caudal significantly augments vascular reactivity, injection of TEAC increases it still further to equal that resulting from the combined operation of inactivation of the carotid sinus mechanism and cord destruction.

Twenty-four experiments were performed in which either the cord was sectioned by the removal of a few millimeters of substance or, after section, the distal cord was destroyed by a pithing rod. We have not obtained con-
AUGMENTATION OF VASOACTIVE SUBSTANCES

Vincing evidence that section of the cord is less effective than section plus distal destruction.

Table 1.—Example of the Effect of Cord Destruction, Nephrectomy, Hepatectomy, Sympathectomy and Carotid Sinus Inactivation

<table>
<thead>
<tr>
<th>No.</th>
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<th>Barium Chloride</th>
<th>Renin</th>
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Cord destroyed C-6 ↓, (11/13/48) nephrectomy 1 day before control injections. Carotid sinus mechanism inactivated.

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Cross transfusion of 2120 cc. blood with normal dog.

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Cord destroyed C-6 ↓ (11/1/48), Hepatectomy 11/2/48. After control injections carotid sinus mechanism inactivated.

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Cord destroyed C-6 ↓ (11/11/48), Hepatectomy (11/19/48). Carotid sinus mechanism destroyed after control injections.

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"Total" sympathectomy

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"Total" sympathectomy

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"Total" sympathectomy and subdiaphragmatic vagotomy.

Inactivation of the Carotid Sinus Mechanism.

When only the carotid sinuses themselves were removed, vascular reactivity was unaltered. Section of vagus and/or aortic depressor nerves after removal of the carotid sinuses was without conspicuous effect in brief experiments. That these operations produced only a partial obliteration of the compensatory nervous mechanism is shown by the fact that TEAC injections augmented responsiveness to a significant, though lesser, degree.
When the cord was destroyed from C-6 caudad a day or two before, and the carotid sinus mechanism was inactivated, no further augmentation could be induced in 26 dogs (Table 1) by injection of large amounts of TEAC. In short, this extensive surgical destruction reproduced the augmentation resulting from TEAC injections into the intact animal.

Some of our experiments suggest that carotid sinus reactivity is increased by cord destruction. The Effect of the Removal of the Liver, Kidneys and Adrenal Glands on Augmentation

The Effect of Hepatectomy.—The role of the liver in the control of vascular reactivity has been dealt with in another paper. We shall consider here only the alterations resulting from its removal on the augmenting effect of TEAC. Its depressor action was much increased several hours after hepatectomy, doses of 2.5 mg. Kg, producing almost fatal falls in arterial pressure in some cases. The response of these animals to adrenaline, noradrenaline, barium chloride and angiotonin was poor before TEAC and improved little, if at all, after it. Indeed, for a long time in the early experiments, we saw no augmentation in the hepatectomized animals and we were almost ready to conclude that there was none. Extension of the experiments to well over a hundred made it possible to demonstrate occasional definite augmentation.

Fig. 2.—Demonstration of the moderate augmenting effect of TEA in a sympathectomized dog treated with a small dose of atropine (No. 498). The initial responses are already greater than normal. (1) Adrenaline, (2) barium chloride, (3) angiotonin, (4) renin, (5) atropine 1/100 gr., (6) TEA 5 mg./Kg., (7) adrenaline, (8) barium chloride, (9) angiotonin, (10) TEA, (11) adrenaline, (12) serotonin, (10) TEA, (11) adrenaline, (12) serotonin, (13) renin, (14) nicotine, (15) barium chloride, (16) saline 120 cc.
tion after repeated doses of TEAC. This occurred more often in animals in which nephrectomy was performed just prior to hepatectomy.

In some animals augmentation appeared so long after injection of TEAC (several hours later) that the responsibility of TEAC was questionable. The relationship between the appearance of augmentation and the dose of TEAC was difficult to determine because it was necessary to administer the drug with such care in these animals. As long as an hour might be required to introduce 10 mg./Kg., which is not ordinarily a full augmenting dose. While adrenaline and noradrenaline were, on occasion, apparently augmented by action of TEAC, renin never was and angiotonin seldom was.

When the cord had been destroyed from C-6 caudad several days before hepatectomy, injection of TEAC elicited almost no vascular response, pressor or depressor. The usual rise in arterial pressure noted in dogs after cord destruction was absent, as was the pronounced fall customary after hepatectomy alone. It was as though the two had cancelled each other out. In such animals slight, if any, augmentation to adrenaline, noradrenaline or barium chloride occurred (Table 1, experiments Nos. 774, 756). Thus, hepatectomy alone seriously reduces or abolishes the effectiveness of TEAC as an augmenting agent.

<table>
<thead>
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<th>BaCl</th>
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</table>

**Table 2.—Examples of Effect of Cord Destruction, Renal Hypertension and Nephrectomy on Vascular Reactivity**

AC was difficult to determine because it was necessary to administer the drug with such care in these animals. As long as an hour might be required to introduce 10 mg./Kg., which is not ordinarily a full augmenting dose. While adrenaline and noradrenaline were, on occasion, apparently augmented by action of TEAC, renin never was and angiotonin seldom was.

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**Nephrectomy and Adrenalectomy.**—TEAC caused augmentation with or without anesthesia in dogs nephrectomized one to three days before. Nephrectomy alone increased the responses especially to renin and angiotonin and, with the addition of TEAC, the animals exhibited a heightened degree of sensitivity to adrenaline, noradrenaline and barium chloride as well.

We have observed that the initial responses to TEAC in nephrectomized dogs were pressor, as though they had already received TEAC. This suggests that nephrectomy may cause the retention of substances able to institute
autonomic ganglionic blockade. However, the mechanism may be entirely different.

When bilateral adrenalectomy was performed almost an hour before the experiment and the animals allowed either to recover from ether anesthesia or to continue anesthetized with
pentobarbital, no significant change in vascular reactivity was detected. The long term effects of adrenalectomy in relationship to salt and steroid administration will be considered in another communication. We were also unable to detect an adrenal participation in the responsiveness of nephrectomized dogs and in 3 animals in which the cord had been destroyed and the kidneys removed.

The carotid sinuses of dogs subjected to nephrectomy and cord destruction from C-6 caudad were highly sensitive. Cardiac arrest occurred when the sinus was approached surgically unless the vagus nerves had been previously cut. The same phenomenon occurred in three of the dogs with the adrenal glands removed as well.

Augmentation occurred with TEAC after nephrectomy, adrenalectomy or both and even occurred when the cord was destroyed from C-6 caudad unless the carotid sinus mechanism was inactivated.

Hypertension in dogs with the cord destroyed, carotid sinus mechanism inactivated and the kidneys removed is an interesting phenomenon which we have noticed repeatedly. Examples are dogs No. 942 and 937 in Table 3. Injection of TEAC into such animals gave sharp rises in arterial pressure and the rise following injection of renin persisted sometimes for hours. Hypertension was not attributable to pentobarbital anesthesia, which was not used in these animals because their cords were cut. In most of these animals, TEAC produced little augmentation; further, it did not lower the average arterial pressure, as would be expected if the hypertension were due to autonomic hyperactivity.

Influence of Periods of Severe Hypotension and Shock on Augmentation and Vascular Response.

In normal, hepanectomized or nephrectomized-hepatectomized dogs, periods of severe hypotension (20 to 50 mm. Hg) even of short duration may elicit a period of refractoriness which is little, if at all, relieved by TEAC. An attempt has been made in a number of these hypotensive animals to overcome the refractoriness by elevating and maintaining the pressure at normal levels by intra-arterial transfusion of saline-blood mixtures. Temporarily, the response may be heightened, and after TEAC such easily augmented substances as noradrenaline show some increase in pressor response, but it is seldom maintained, particularly in the hepatectomized animals where the vessels respond similarly to those of animals in terminal shock. Until responsiveness returns, the life of the animal is in danger.

It should, however, be made clear that repeated observation shows no necessary relationship between arterial blood pressure and vascular responsiveness. Rather, responsiveness appears to be related to the length of time hypotension has existed, as well as to the acuteness of its occurrence. We have come to doubt seriously that, within limits, a ceiling exists which prevents even at already elevated pressures further rise on injection of stimulating substances on a floor from which greatly increased responses may be expected. Some highly responsive animals have been those with experimental renal hypertension in which the initial pressure was over 200 mm. Hg and some of the poorest responses have occurred in animals with initial arterial pressure of from 70 to 90 mm. Hg.

The results of our study of the prophylactic and therapeutic effects of TEAC injection in shock have been published. Suffice it here to add further experience we have had in the last three years. It has not been possible without trial to forecast the occurrence of augmentation in an animal with severe hypotension or shock. Sometimes augmentation is remarkable; more often it fails completely. If TEAC elicits augmentation when shock has occurred, both noradrenaline and adrenaline are much easier to augment than renin. While an augmented response to adrenaline is compatible with a low arterial pressure, the chances of its rising are much improved with return of responsiveness and augmentation with TEAC.

Other Means of Altering Vascular Responsiveness.

Procaine and Cocaine Injections.—Five cc. of 2 per cent procaine was injected intra-venously into unanesthetized dogs after the
control test drug injections had been made. The response to nicotine temporarily disappeared but no appreciable augmentation was noted with the other drugs. Then TEAC was injected and augmentation occurred. When large amounts of cocaine (2 doses of 10 mg./Kg. intravenously plus 10 mg./Kg. intramuscularly) were given the adrenaline response was greatly augmented. Barium chloride was slightly augmented but angiotonin and renin were not. If TEAC was then given, little further augmentation occurred. Both angiotonin and barium chloride were slightly augmented. Cocaine given after large doses of TEAC often further increases adrenaline response, but the augmentation is sharply limited by the toxic effects of cocaine. The renin response may be somewhat aided if tachyphylaxis is not induced but does not reach the high levels which usually follow repeated injections of TEAC alone. If tachyphylaxis is elicited, then cocaine alone or followed by TEAC does not overcome it.

**Methylene Blue.**—In 6 experiments, 0.2 grams of methylene blue gave moderate augmentation of the adrenaline response in most cases but none to renin.

**Dibutolin.**—Repeated injection of 20 mg. doses Dibutolin,* in experiments performed several years ago, showed it to cause moderate augmentation especially to adrenaline, confirming the recently published work of Moe. After about 100 mg. of Dibutolin had been given, TEAC caused little further augmentation of adrenaline or barium chloride.

**Dibenamine.**—Doses of 20 mg./Kg. were given intravenously to 10 nephrectomized dogs. As soon as the response to adrenaline was clearly depressor, TEAC was given in repeated doses. No augmentation of the adrenaline response occurred.

**Dihydroergocornine.**—Repeated injection of 0.5 mg. doses had no effect on the response to angiotonin and barium chloride but in some dogs the adrenaline response was reversed. Administration of TEAC now caused no augmentation. The pressor action of noradrenaline seemed a little affected by doses of 2 mg. of dihydroergocornine, which were enough to cause sharp reversal of adrenaline. In other dogs, the response was reduced but not reversed.

We were constantly impressed by the variety of response elicited in different dogs by this drug, both as to its pressor action and blocking effect on adrenaline.

**Tetramethylammonium chloride.**†—This drug, so closely related to TEAC, in repeated doses of 1 mg./Kg. caused nothing but repeated rises of arterial pressure and no augmentation.

**Augmentation in Patients.**

Augmentation of the adrenaline and angiotonin responses has been observed in 3 patients.

**Table 4.—TEAC Augmentation in a Patient with Cord Severed at D-1.**

<table>
<thead>
<tr>
<th>Time</th>
<th>B.P. Change</th>
<th>Average B.P.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:27</td>
<td>0.1 cc. 1/10,000 adrenaline</td>
<td>+30</td>
</tr>
<tr>
<td>2:30</td>
<td>0.5 cc. 1/1000 nicotine</td>
<td>-18</td>
</tr>
<tr>
<td>2:35</td>
<td>2.5 cc. barium chloride 18 mg./cc.</td>
<td>+36</td>
</tr>
<tr>
<td>2:53</td>
<td>2.0 cc. angiotonin 10 u./cc.</td>
<td>+66</td>
</tr>
<tr>
<td>3:01-3:08</td>
<td>500 mg. TEAC</td>
<td>-50</td>
</tr>
<tr>
<td>3:11</td>
<td>0.1 cc. 1/10,000 adrenaline</td>
<td>+56</td>
</tr>
<tr>
<td>3:21</td>
<td>0.1 cc. 1/10,000 adrenaline</td>
<td>+52</td>
</tr>
<tr>
<td>3:27</td>
<td>2.5 cc. barium chloride</td>
<td>+42</td>
</tr>
<tr>
<td>3:33</td>
<td>100 mg. TEAC</td>
<td>-28</td>
</tr>
<tr>
<td>3:38</td>
<td>1.0 cc. angiotonin</td>
<td>+74</td>
</tr>
</tbody>
</table>

after injection of large doses of TEAC, just as in animals. One of these patients had suffered a massive intracerebral hemorrhage, another a cerebral thrombosis, and the third had had resection of 1 cm. of the cord at D-1 for intractable pain resulting from removal of multiple meningiomas from the spinal canal. The results from the latter are shown in Table 4. There is no doubt that the phenomenon is not limited to dogs, cats and rats with or without anesthesia.

† We are indebted to Dr. E. C. Vonder Heide of Parke-Davis and Company for this drug.
AUGMENTATION OF VASOACTIVE SUBSTANCES

DISCUSSION

In examining the data which we present, the following average responses in mm. Hg furnish the control values: adrenaline, +45; nicotine, +44; histamine, −42; barium chloride, +22; renin, +38; angiotonin, +17; TEAC, +10–38 mm. Hg. Since there is wide variation from dog to dog, large numbers of experiments are necessary to assure their significance. We have included in the protocols only examples of the experiments, not so many as to burden the reader unduly and yet, we hope, sufficient to indicate the character of the changes. In most cases, they are great enough to leave no doubt of their validity in the observer's mind.

As the work progressed, it became apparent that so-called “acute” experiments in which the nervous system was roughly handled often lead to contradictory results. For example, pithing in many cases yielded uninterpretable results. In some pithed animals, TEAC seemed to cause augmentation, while in others it did not. Consistency greatly improved when the experiments were conducted as neurosurgical operations and suitable periods of recovery allowed.

A variety of substances show augmentation, but what determines which ones is not clear. We have used test drugs with primary cardiac action as well as those acting more peripherally. Augmentation is not characteristic of one or the other.

We share with Moe the hypothesis that the simplest mechanism accounting for augmentation would be blockade of the compensatory nervous mechanisms which control the homeostasis of the arterial pressure. The proof that this is so is found in the demonstration that after cord destruction from C-6 caudad, plus inactivation of the carotid sinus mechanism, TEAC gives no further augmentation. This was not so easy to prove as might have been expected, because of spontaneous alterations in sensitivity over the period of hours while TEAC was being injected. Whatever the explanation, some dogs, after every reasonable care had been taken to insure adequate surgical denervation, still showed moderate further augmentation, especially when TEAC was repeatedly injected in the course of several hours.

From our experiments the area of cord most concerned with augmentation is from C-6 to D-6, as shown by preganglionic denervation and by cord section. Destruction of the cord distal to the point of section did not affect augmentation significantly. Nor did destruction of the carotid sinuses and aortic depressor nerve mechanisms or decapitation alone greatly reduce the augmentation which TEAC induced. However, in animals with cord destruction plus ablation of the carotid sinus mechanism, with the exception of a few animals in which over a period of several hours some augmentation occurred, TEAC caused no further augmentation. Thus destruction of a part of the nervous mechanism controlling augmentation without removal of the whole of it often leads merely to the taking over by the remainder of the neurogenic control of vascular reactivity. As a corollary, an increase in sensitivity of the residual mechanism often becomes demonstrable.

Further support of this concept was furnished by the behavior of the carotid sinus mechanism when the cord was destroyed from C-6 caudad. It became more active than normal, for, unless the vagus nerves were severed before the carotid sinuses were manipulated during operation, fatal bradycardia and hypotension occurred. Resuscitation often occurred as long as two to three minutes after apparent death when the nerves were severed following sinus irritation. It appeared as though the slowing of the heart was so intense as to cause the death of the animal.

Fitting with the view that an incomplete denervation often influences augmentation little, if at all, is the demonstration that inactivation of the carotid sinus mechanism alone has an insignificant effect. Adding cord destruction to C-6 completes the denervation and elicits maximum augmentation not further enhanced by large doses of TEAC.

The evidence is insufficient to determine the precise mechanism of the action of liver extirpation on TEA augmentation. When hepatectomy alone is performed the animals exhibit increased sensitivity to the depressor
action of TEAC, presumably because one of the compensatory mechanisms—the secretion by the liver of a noradrenaline-like substance—has been removed.\textsuperscript{11} Augmentation in most cases is extremely poor, if it is observed at all. It is somewhat more likely to occur when nephrectomy has just preceded hepatectomy, the presumption being that the removal of the kidneys removes the source of renin which may be secreted during the operation of hepatectomy, making the animal tachyphylactic to its own renin. Further, since nephrectomy itself increases responsiveness, the chances for augmentation to occur are improved. Thus, the fact that TEAC exhibits little augmentating effect after hepatectomy could be due to the facts (1) that the response of the blood vessels is depressed and is not increased by denervation induced by TEAC and (2) that the autonomic nervous system, as a result of hepatectomy, has lost its controlling force on vascular reactivity that its blockade by TEAC no longer results in augmentation.

Nephrectomy, as we have noted, increases response to various substances, but TEAC is still able to augment further their activity. Since the initial doses of TEAC were often pressor in such animals, it suggests the possibility that nephrectomy causes the retention of autonomic blocking substances.

The permanent loss of all of the neurogenic compensatory mechanisms of which we are currently aware, along with the sensitizing effect of nephrectomy, leaves the animal highly vulnerable to pressor stimuli. It is not surprising, therefore, that in animals in good clinical condition chronic hypertension of the order of 160 to 180 mm. Hg may be observed. Injection of renin further increases it, the effects sometimes lasting for hours. That such a mechanism might be in part responsible for the hypertension of simple nephrectomy is evident. Except in severe adrenal insufficiency, we have not observed significant deviations from the normal responsiveness to any of the test drugs in adrenalectomized dogs. Augmentation accompanies regularly the injection of large amounts of TEAC.

An attempt has been made with only slight success further to increase responsiveness by injection of cocaine. When the full response is obtained after large doses of TEAC, cocaine injection further increases the adrenaline response, possibly by protecting it from inactivation. The amount of cocaine required to produce the result is sufficiently large to limit the usefulness of animals so prepared.

The augmenting action of TEAC may also be reduced or blocked by a variety of substances acting on different parts of the neurovascular systems. Thus dihydroergocornine and Dibenamine in some dogs block augmentation of adrenaline or noradrenaline by TEAC. If the predominant sites of blockade by dihydroergocornine and Dibenamine are, respectively, central and peripheral, either site suffices to block the augmenting action of TEAC. It is surprising that so closely related a substance as tetramethylammonium chloride in repeated doses of 1 mg./Kg. produced no augmentation. Its effect was purely pressor, even on the initial dose.

It should be noted that periods of severe hypotension as well as shock elicit a hyporeactive state of the vascular tree\textsuperscript{7, 8} which is not usually overcome by administration of TEAC. Occasionally, however, augmentation is dramatic, responsiveness quickly returns, and arterial pressure usually rises.

We have not tried to elicit maximum augmentation in patients because of the very large and variable doses of TEAC required (at least 1800 mg. if figures derived from dogs are valid). In two moribund patients with cerebral injury and one conscious patient with the cord severed at D-1, we have, however, given large doses with striking augmentation. It is likely that the reason Moe\textsuperscript{2} found little augmentation was that insufficient amounts of the drug were given.

There has now accumulated enough clinical experience to validate our warning of several years ago that an unfavorable turn in patients who have had large doses of TEAC should be treated with adrenaline with more than usual caution.\textsuperscript{6} During an emergency, adrenaline is of necessity given by vein and not subcutaneously or by carefully controlled infusion as in the pharmacology laboratory where the outcome is not critical. In one normal young girl.
for instance, during the drug test, arterial pressure became imperceptible. Injection of the usual amounts of adrenaline by vein led to pressure of well over 300 mm. Hg and gross cardiac irregularity. For the first half hour it seemed more likely that she would perish from the adrenaline hyper- rather than the TEAC hypotension.

**Summary**

1. Vasoactive substances such as adrenaline, noradrenaline, angiotonin, histamine and barium chloride exhibit augmented activity after intravenous injection of large doses of tetraethylammonium chloride into dogs, cats, rats and man. Other substances such as pituitrin and Paredrine fail to do so.

2. Cord destruction from C-6 caudad, "total lumbodorsal sympathectomy" and sympathectomy with supradiaphragmatic vagotomy in chronic experiments elicit increase in responsiveness but augmentation with TEAC still occurs.

3. Sympathectomy or cord destruction combined with inactivation of the carotid sinus mechanism successfully reproduces the augmenting effect of TEAC and may be used to supplant it. TEAC does not cause augmentation after these combined operations.

4. The limits of spinal nerve distribution involved in augmentation were determined by preganglionic denervation ("anterior nerve root section") and spinal cord destruction from C-6 to D-8.

5. Two examples are given of local increase in nervous sensitivity as a result of removal of interdependent portions of the nervous system. First, when the cord is destroyed from C-6 caudad, the carotid sinus may become highly sensitive. Second, when a dog is decapitated, the spinal ganglia which in the intact animal show little activity, become sufficiently active that TEAC gives conspicuous augmentation when these ganglia are blocked by it.

6. Hepatectomy reduces or abolishes the augmenting action of TEAC. While augmentation to adrenaline and noradrenaline may occasionally occur in small degree, none has been observed with renin.

7. Nephrectomy after one to two days increases vascular responsiveness which may be augmented by TEAC. Combined cord destruction from C-6 caudad, carotid sinus inactivation and nephrectomy causes greatly heightened vascular responsiveness not further enhanced by TEAC.

8. Adrenalectomy in acute experiments does not alter the power of TEAC to cause augmentation. There is also no change in this respect in animals with cord destruction and/or nephrectomy.

9. Hypertension persisting for many hours may occur in conscious dogs with cords destroyed from C-6 caudad, carotid sinus mechanism inactivated and the kidneys removed. Renin injection causes a further increase in arterial pressure which may persist for hours.

10. Severe hypotension and/or shock induces refractoriness of vascular response which is not usually overcome by TEAC. There is, however, no definite relationship between the height of the blood pressure and vascular responsiveness. Sometimes after periods of severe hypotension, augmentation by TEAC is great.

**Conclusions**

The greatly increased response to many vasoactive drugs elicited by tetraethylammonium chloride (TEAC) in large doses is due to blockade of sympathetic ganglia and the carotid sinus mechanism, so removing their regulatory function. This augmented responsiveness may be reduced or abolished by hepatectomy, periods of severe hypotension and shock. On the other hand, while nephrectomy of itself increases vascular responsiveness, it may be further increased by TEAC.

An exceptionally high degree of vascular responsiveness is induced by the combined operations of cord destruction from C-6 caudad, inactivation of the carotid sinus mechanism surgically or by TEAC, and nephrectomy. Arterial hypertension of necessarily limited duration may follow such operations. Removal of one part of interdependent blood pressure regulatory mechanisms of the nervous system often increases the sensitivity of the remaining complementary parts.
ACKNOWLEDGMENT
We wish to express our gratitude to Dr. Ralph Prince, Dr. Charles Devine, Mr. William West, Mr. Ralph Edmonds and Mr. Robert Parker for their help in some of these experiments.

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Augmentation of Vasoactive Substances by Tetraethylammonium Chloride
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Circulation. 1950;1:1233-1245
doi: 10.1161/01.CIR.1.6.1233

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