GANGLIONIC BLOCKING AGENTS[1]

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Because of their structural resemblance to acetylcholine, many quaternary ammonium compounds are pharmacologically active at cholinergic synapses and neuro-effector junctions. Given a new compound of this series, one may expect one or more of the following possible actions: stimulation of cholinergic effector cells, stimulation of ganglion cells (and the adrenal medulla and the carotid chemoceptors), stimulation of striated muscle; inhibition of transmission or blockade at these several sites; inhibition of cholinesterase. Quaternary ammonium salts acting by each of these mechanisms have been described, although such actions are by no means limited to this series of compounds (*e.g.*, atropine, physostigmine, pilocarpine, potassium and magnesium salts, etc.).

After demonstration of the remarkable physiological activity of acetylcholine, interest was centered on compounds possessing similar effects on cholinergic effector cells. Ganglionic blocking action was recognized as a "nicotinic-paralyzing" action, but agents possessing this attribute, other than nicotine itself, were not utilized as tools in physiological or clinical investigation. Soon after the relatively pure ganglionic blocking action of the tetraethylammonium ion (TEA) was described by Acheson and his collaborators (4, 5), this agent was subjected to an intensive investigation, particularly in the study of cardiovascular disorders in human subjects. The present discussion is concerned with the nature of agents reported to produce ganglionic blockade, and with the use of such agents in physiological and clinical investigation.[2] Most of the literature, and consequently the major portion of this review, deals with the actions of tetra-ethylammonium. Insofar as such actions are the result of interruption of ganglionic transmission they may be assumed to apply also to other recently introduced agents.

I. TETRAETHYLAMMONIUM

A. General Pharmacology

1. *Ganglionic site of action:* The "nicotinic paralyzing" action of TEA was recognized by Burn and Dale (44) in 1915 and later confirmed by Hunt (125, 126). Though Hunt and Renshaw (130) suggested that "a compound which would paralyze the ganglion cells of the autonomic nervous system . . . would be

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[2] No attempt has been made to include the literature on nicotine, which can not be regarded primarily as a ganglionic blocking agent, or to cover completely the older literature on TEA and other onium salts, much of which is concerned with the presence or absence of muscarinic and curariform actions. References to such reports may be found in the papers of Cowan and Walter (59), Ing (133), and Acheson and Moe (4), as well as in the book by Bovet and Bovet-Nitti (27).

of considerable physiological interest and possibly of some therapeutic value," they made no attempt to apply TEA as a physiological tool. In the earlier investigations the criterion of a ganglionic paralyzing action was prevention of the pressor action of tetramethylammonium, a criterion not entirely satisfactory since similar antagonism might be expected with "sympatholytic" agents. The ganglionic site of action of TEA was firmly established by Acheson *et al.* (4, 5), who showed that the effects of preganglionic stimulation of the superior cervical and stellate ganglia on the nictitating membrane and heart rate could be prevented by TEA while postganglionic stimulation remained effective. Confirmation has been obtained by other technics: TEA erases the postganglionic action potential aroused by preganglionic stimulation of the stellate in the dog (184), and diminishes or abolishes the response of the nictitating membrane to acetylcholine injected into the perfused superior cervical ganglion (50, 139). The response of the ganglion to potassium is not abolished (5).

Parasympathetic as well as sympathetic ganglia are inhibited, though the proof in some cases must be indirect because of the anatomic distribution of parasympathetic ganglion cells. TEA blocks the cardiac effect of vagal stimulation, but not of acetylcholine (4); the site of the block must be the ganglionic synapse. In the ciliary ganglion, one of the few sites where pre- and postganglionic stimulation are possible, Luco and Marconi (162) demonstrated block of the effects of preganglionic stimulation, but also described a depression of the pupillary response to postganglionic stimulation after large doses. Most of the effects of the drug in man support the concept of widespread inhibition of both sympathetic and parasympathetic ganglia.

In the dog relatively complete blockade of ganglia can be achieved by single intravenous doses of 3 to 5 mgm/kg and maintained by continuous infusion at a rate of 15 to 20 mgm/kg/hour. Safe clinical doses probably do not produce comparably complete effects in the human subject (see section I-C-1, below).

2. *Nature of the blocking action:* The sites of cholinergic mediation have been classified in terms of actions on striated muscle cells, ganglion cells, and smooth muscle or gland cells. This classification is supported by the more or less specific actions of acetylcholine antagonists at the three sites (109). Why curare blocks principally neuromuscular and only to a lesser degree ganglionic transmission, why atropine blocks chiefly "muscarinic" actions, and why TEA blocks chiefly the ganglionic site remain puzzling questions. The differentiation cannot be regarded as absolute; atropine, for example, exerts a potent antagonism to acetylcholine in the perfused superior cervical ganglion of the cat (140). Yet the specificity of the various antagonists is sufficiently striking to suggest some fundamental difference in the reaction of acetylcholine with the several effectors. If one adopts the hypothesis that acetylcholine reacts with three distinct but closely related "receptor substances" at the three sites, and that the antagonists compete with acetylcholine for the receptors, then it may be postulated that TEA makes a good "fit" with the ganglionic receptor but not with the others, and that atropine makes a beter fit with the "muscarinic" receptor.

Specific depression of ganglionic transmission is probably not the result of

impaired energy metabolism for Larrabee *et al.* (148) have shown that cocaine and curare block transmission in concentrations which do not depress the oxygen consumption of ganglia. A similar result would probably be found with TEA and other specific depressants, in contrast to alcohol and the barbiturates which inhibit the synaptic mechanism only in concentrations causing substantial reduction in the rate of oxygen consumption.

TEA occupies an anomalous position in the series of simple quaternaries because of its lack of effect on neuromuscular transmission (133), its ability to cause spontaneous discharge in isolated nerve (59), and its lack of muscarinic and ganglionic stimulating actions (130). At present it is not possible to relate these several attributes to the structure or physicochemical properties of TEA. Ing and Wright (134) found that the curariform activity of the series of tetramethylonium salts diminished when the size of the central atom was increased from nitrogen to phosphorus to arsenic, while curariform activity of the comparable tetraethyl-onium salts was enhanced with increasing weight of the central atom. They concluded that "it is obvious that ethyl groups are not in themselves responsible for the anomalous behavior of tetraethylammonium." Holmes *et al.* (116) believe that the charge density on the central nitrogen atom of quaternary salts must exceed a certain threshold before curariform action can appear, and that the central charge is anomalously low in the tetraethyl ion, but this does not help much in explaining the mechanism of action of TEA itself.

Whether the blocking action is related to the effects of TEA on axones cannot be stated. TEA and various other quaternary salts containing at least three ethyl groups or chains of greater length are capable of restoring some degree of excitability in axones soaked in a sodium-free medium (161), and many of these agents are also capable of inhibiting ganglionic transmission; but no quantitative comparison of these actions has been made, and there is yet no evidence that the phenomena are fundamentally related.

Though TEA does not overcome the ganglionic stimulating effect of potassium (5), it is said to antagonize the negative inotropic action of excess potassium in the frog heart (156), and has been shown to revert temporarily the abnormal electrocardiographic pattern caused by potassium in the dog (240). The interrelationship of these observations is not immediately apparent.

Bronk *et al.* (32) showed that block of transmission in the stellate ganglion resulted from administration of citrate. Block of parasympathetic paths by sodium citrate was also reported by Shafer (230), though comparable inhibition was said not to occur in sympathetic ganglia. The blocking effect of increased pH on the frog's superior cervical ganglion can also be overcome by the addition of calcium ions (227). Calcium has long been known to antagonize the actions of TEA on muscle and on peripheral nerve (59, 174), but no attempt has been made to prevent or overcome the ganglionic blocking action by the addition of calcium.

Whatever the intimate nature of the TEA block of ganglia, it is almost certainly competitive. This would imply that the block cannot be absolute; but since there must be an upper limit to the charge of acetylcholine that can be liberated physiologically by the preganglionic fibers and since there must be a

finite effective concentration of acetylcholine before response of the ganglion cells can occur, the block may be complete for practical purposes. The competitive nature has been demonstrated in the isolated perfused cervical ganglion of the cat (139). Perfusion with a TEA concentration of 1:20,000 may prevent completely the response to a previously just sub-maximal dose of acetylcholine, whereas still higher doses of acetylcholine can again cause stimulation. Competition has also been demonstrated in the atropinized spinal cat, using the pressor response to acetylcholine as a criterion of ganglionic activity (183).

The ganglionic block produced by TEA can be reversed by small doses of neostigmine (215) which has been proposed as an antidote in cases of human overdosage. Neligh *et al.* (191), however, failed to overcome the effects of TEA on intestinal motility with neostigmine, though methacholine restored activity. In view of the competitive nature of the block, antagonism by cholinesterase inhibitors should be expected.

Ganglia sensitized to acetylcholine by denervation are much more resistant to the blocking action of TEA than normal ganglia (139). A similar alteration of sensitivity of denervated structures to acetylcholine-antagonists has been reported by Altamirano *et al.* (9). If the increased sensitivity to acetylcholine is due to absence of cholinesterase in the denervated tissue, the effective dose of acetylcholine reaching the ganglion cell must be the same in both normal and denervated ganglia, and it is therefore difficult to understand why a blocking agent should be less effective in the denervated structure. It would be of interest to learn whether inactivation of cholinesterase by physostigmine would cause a similar decrease in the effectiveness of TEA.

3. *Lack of other autonomic actions:* Though various combinations of effects at the sites of cholinergic mediation are common in quaternary salts, the ganglionic blocking action of TEA is relatively pure and uncomplicated by other autonomic effects (4).

TEA does not appear to stimulate ganglia; the pressor action of high doses is probably a direct effect on vascular smooth muscle (4, 174, 250).

An atropine-like action of TEA was described by Külz (143) who found that the "muscarinic" action of tetramethylammonium ion on the frog heart was blocked by TEA. Since tetramethylammonium also has a ganglionic stimulating action, it is probable that Külz observed an effect of both drugs on the vagal ganglion cells rather than on the heart. Hunt (125, 126) noted the lack of an atropine-like action, and Acheson and Moe found no antagonism to the vasodepressor and cardiodecelerator actions of acetylcholine by TEA (4). Heymans and Hoorens (110) found that the actions of acetylcholine and pilocarpine on the iris were not prevented by TEA, but the actions of physostigmine and DFP were diminished, probably because of antagonism at the synapses of the ciliary ganglion.

TEA lacks a muscarinic action (4, 125, 126, 136, 138). The cardiac slowing observed in the frog by Jacobj and Hagenberg (136) was not blocked by atropine and doubtless represented an interruption of accelerator impulses.

Though it is possible that TEA possesses slight central nervous system actions

(see section I-A-4, below), central inhibition does not appear to play a role in its block of autonomic reflexes (108).

4. *Neuromuscular transmission:* While TEA is capable of blocking neuromuscular transmission (6, 24, 39, 133, 234), the necessary concentration exceeds any level that should be attained in clinical practice. Intraarterial injection of moderate doses of TEA causes an increase in the height of the response of the gastrocnemius muscle to nerve stimulation, and induces paralysis only when the dose is greatly increased (6). When administered intravenously to dogs by continuous infusion at a rate which exceeds the excretory capacity, death eventually occurs by central respiratory paralysis (182). At the time of death neuromuscular transmission may be unimpaired. If death be delayed by artificial respiration and the infusion continued, generalized coarse twitching of striated muscle occurs, and only after the administration of perhaps twice the lethal dose does a complete curariform block become demonstrable (183). TEA is said to inhibit the knee jerk and augment the flexor reflex (in the cat?) (225). These effects may represent a central action, as is probably also true of the muscular weakness, dysphagia, dyspnea and ptosis reported in clinical studies. No weakening of the hand is demonstrable when tested with a dynamometer, even though a subjective feeling of weakness may be present (164).

Although TEA itself does not exert a curariform action in clinical doses, it reduces the head-drop dose and lethal dose of both decamethonium chloride ("C-10") and *d*-tubocurarine in the mouse (169). This is probably not a general attribute of ganglionic blocking agents, for pentamethonium ("C-5") increases the LD_{50} of C-10 and does not change the LD_{50} of *d*-tubocurarine.

The stage of muscular twitching represents a peripheral action of the drug on nerve (59), rather than on the neuromuscular junction as described by earlier investigators (136, 174, 252). Local twitching and paresthesias can be produced by subcutaneous or intramuscular administration, and accidental extravascular administration of TEA in the cubital space may cause a flexor spasm of the wrist and hand (166). TEA, like veratrine, is capable of inducing repetitive responses to a single stimulus; and in higher concentration, spontaneous discharge (59). The action on nerve is probably not closely related to its ganglionic blocking action, for pentamethonium salts (C-5) are said not to cause the paresthesias (11). A brief review of the literature on the neuromuscular effects of TEA and its lack of muscarinic and atropine-like actions may be found in the recent book by Bovet and Bovet-Nitti (27, p. 679–685).

B. Cardiac Actions of TEA

1. *Heart rate:* Since tetraethylammonium interrupts transmission in both sympathetic and parasympathetic ganglia, its action upon heart rate depends upon the existing balance between vagal and accelerator influences (4). In the resting human subject in whom vagal tone is relatively high, TEA causes acceleration; in animals under barbiturate anesthesia in whom vagal tone is low, TEA causes deceleration by interrupting sympathetic pathways; in dogs, unanesthetized or under morphine-chloralose anesthesia, vagal tone is high and TEA causes an in-

crease of heart rate (186). In addition to heart rate effects resulting from autonomic blockade, TEA exerts a direct action upon cardiac pacemakers; in large doses it will cause deceleration to a rate lower than that which would be expected to result from denervation, or it will cause acceleration due to the development of ectopic foci (3).

2. *Cardiac output and venous pressure:* TEA exerts a positive inotropic action on hypodynamic heart muscle (3, 156, 157). This does not appear to be a phenomenon in any way related to its ganglionic action, for it can be demonstrated in the embryonic chick heart before nerves reach the cardiac tissue (Barry, 18). Furthermore, of other quaternary salts demonstrated to cause ganglionic block, only a few have been found to exert a positive inotropic action (80).

The action of TEA on cardiac output in the dog has been discussed by Moe *et al.* (186). Under morphine-chloralose anesthesia, cardiac output as measured by means of a cardiac oncometer increases more or less in proportion to the change of heart rate, and indeed the increased cardiac output may mask the diminished peripheral resistance; but in the dog under barbital anesthesia little change of cardiac output occurs. Since a considerable increase of blood flow to the limbs results, it must be supposed that a comparable decrease of blood flow in visceral areas occurs (section I-C, below). Data from a table in the paper of Eckenhoff *et al.* (67) show a decrease of cardiac output apparently caused by TEA. The change, however, is no greater than that observed in a repeated control observation and may be due to time lapse and blood loss due to sampling rather than to the drug itself.

In the normal human subject TEA causes a reduction of right atrial pressure and a slight increase of cardiac output as estimated from ballistocardiographic tracings (122, 241). The increase is probably related to the cardioacceleration which occurs and is comparable in degree to the change produced by atropine. May *et al.* (177) found essentially no change of cardiac output, as measured by the Fick procedure, in either normotensive or hypertensive subjects. Extensive lumbodorsal sympathectomy also fails to cause any significant change of cardiac output, whether or not arterial pressure is lowered, though the chronic result of denervation can not be considered comparable with the acute effects of TEA (Wilkins *et al.*, 256). These observations suggest that venoconstrictor mechanisms are not under a high degree of tonic control in the reclining subject, for if any significant degree of sympathetic venoconstrictor tone exists one should expect that TEA would cause a decrease of cardiac output by increasing the capacity of the venous reservoir and lowering venous pressure. To determine to what extent TEA alters venous return, the heart rate effects should be eliminated by previous administration of atropine.

In patients with congestive heart failure, with or without hypertension, TEA often causes subjective improvement with a marked decline of venous pressure and an increase of vital capacity (Lyons *et al.*, 166; Hayward, 100; Relman and Epstein, 218). The fall of venous pressure could result from improvement in cardiac efficiency, from reduction of the work load of the heart, or from interruption of venoconstrictor impulses. No measurements of the cardiac output

response of the decompensated heart to TEA have been reported; but it is doubtful whether the concentration of TEA attained with clinical doses could exert any significant inotropic action on the heart. Reduction of work load probably contributes, for TEA commonly causes a fall of arterial pressure even in the normotensive cases, attesting to the existence of compensatory vasoconstriction as the cardiac output falls in failure (218). Interruption of venomotor pathways probably is the chief factor in the venous pressure response.

3. *Cardiac arrhythmias:* The production of idioventricular rhythms by epinephrine in hearts sensitized by cyclopropane and other hydrocarbons is said to be inhibited by section of cardiac sympathetic pathways (8). Ganglionic blockade with TEA does not prevent the arrhythmias (185); indeed, it may even increase the duration of ventricular tachycardia produced by epinephrine in dogs under cyclopropane anesthesia, or cause the appearance of idioventricular rhythms after injection of epinephrine in the unanesthetized animal (Stutzman *et al.*, 246). The latter result was obtained after relatively large doses of TEA, which is itself known to cause ventricular tachycardia when given in high concentration (3), and may be the result of summation of direct effects of the two drugs on cardiac automaticity, unrelated to ganglionic blockade. With the procedures used in this laboratory we have never observed enhancement of ventricular arrhythmias induced by epinephrine.

Failure of TEA to prevent cyclopropane-epinephrine arrhythmias suggested the possible existence of cardiac sympathetic pathways invulnerable to TEA. When such pathways were found to exist, as described below (200), an attempt was made to confirm the reputed protective influence of thoracic sympathectomy. It was found that the dose of epinephrine necessary to cause the appearance of ventricular tachycardia was increased after removal of the upper 4 or 5 thoracic ganglia, but in each case arterial pressure was reduced by the operative procedure. Restoration of normal pressure levels by infusion of blood or constriction of the aorta restored the previous level of sensitivity, casting serious doubt on the role of the cardiac sympathetic innervation in the induction of ventricular tachycardia by epinephrine and cyclopropane (201).

4. *Coronary circulation:* The action of TEA on the coronary circulation in the dog depends upon the magnitude of the depressor response. Leroy *et al.* (152), using a modified Morawitz cannula for measurement of coronary sinus outflow, reported no change or a slight increase of flow following intravenous or intramuscular injection of doses which caused only a slight decline of blood pressure. Eckenhoff *et al.* (67) reported a passive decline of coronary sinus flow in proportion to the fall of arterial pressure, but found that cardiac work (and therefor oxygen need) was reduced to a greater degree than the coronary flow. Our own observations confirm these results, and indicate that there is little coronary vasoconstrictor tonus in the anesthetized animal (183). When arterial pressure was maintained by means of a stabilizer, TEA caused a moderate increase of flow, but always far short of the effects of small doses of epinephrine or glyceryl trinitrate. Since the pressure stabilizer compensates for decreased peripheral resistance by enforcing an increased cardiac output, the change of coronary per-

fusion induced by TEA may well be the result of increased myocardial metabolic activity rather than interruption of tonic constrictor impulses. TEA was not found to improve the survival chances of dogs subjected to ligation of major coronary branches (112).

The pain of anginal attacks or coronary thrombosis is sometimes relieved for periods as long as several hours even after small doses of TEA which cause little depression of arterial pressure (51, 122, 233). The mechanism of pain relief can in such instances hardly be the result of diminished cardiac work load; neither does it seem likely that small doses could block any presumed vasospasm. This is not the only instance where pain relief by TEA is puzzling (see section I-I, below).

Christy *et al.* (51) reported improvement of the electrocardiographic pattern in coronary thrombosis cases treated with TEA, but the changes are difficult to evaluate in their small series. Hoobler and Lyons have expressed doubt of the safety of TEA in coronary thrombosis, fearing that the tachycardia and sudden pressure fall might be hazardous (122), and Lindgren and Frisk have reported myocardial infarction following the use of the drug in a patient with arteriosclerotic heart disease (154). While a direct causal relationship can probably not be drawn, the possibility of danger should be recognized.

C. Actions on the Peripheral Circulation

1. *Somatic blood flow:* In the experimental animal the depressor response to TEA is clearly due to a decline of total peripheral resistance resulting from interruption of vasoconstrictor pathways (4). Although a direct vasodilator action has been claimed (Boelaert, 25), no supporting evidence for such an action has been obtained in this laboratory. Since cardiac output is not acutely altered during the depressor response, it is obvious that the flow increase recorded in somatic vessels such as the femoral and brachial arteries must be balanced by an equivalent decrease in other areas. This would not, of course, imply actual vasoconstriction in visceral vascular beds, for it should be recognized that a uniform vasodilatation in all vessels would result merely in a fall of arterial pressure with no change in cardiac output. An agent causing vasodilatation varying in degree in different areas will cause an increased flow in the areas in which the action is most intense, and a passive decrease in areas in which the least vasodilatation occurs. Even in the femoral artery the increased flow is not well maintained during continuous infusion of TEA; flow may return to the previous normal level even though arterial pressure remains low (183). This may mean that the relative hyperoxia and hypocapnia induced by the initial hyperemia cause an increase in the "intrinsic" (that is, non-neurogenic) resistance of the vessels. No attempt has been made to check this hypothesis, though perfusion of the innervated leg with a constant output pump should readily yield an answer.

The effect of TEA on blood flow in the extremities of the human subject has been studied in many laboratories (21, 54, 71, 87, 121, 149, 166, 235). Initial reports were concerned with skin temperature changes only, and when TEA was found to produce an increase of digital temperature comparable with that ob-

served after spinal anesthesia or paravertebral block it was assumed that vasoconstrictor tone to the peripheral vessels was completely abolished (21, 54, 166). It has, however, been demonstrated that skin temperature is not an adequate index of peripheral blood flow (86). It is conceivable that a slight shift of flow from deep tissues to the surface could abolish the temperature gradient between thigh and toe, whereas further increases of blood flow would cause no further rise of digital temperature.

Further study of TEA by means of the venous occlusion plethysmograph has shown that the vasodilatation is not complete; although the effect of TEA is greater than that of various other commonly used vasodilator agents (121), it is less than that of paravertebral block or spinal anesthesia (87, 115, 121) and in the hands of some investigators less than the reflex response to heating (71). The reasons for the incomplete action are not entirely clear, but a number of possibilities exist. First, the doses commonly used in the clinic (about 7 mgm/kg) may not produce complete interruption of ganglionic transmission. Hoobler has found in a few subjects that larger than usual doses may cause a still greater dilatation (121), but Ferris *et al.* (73) have maintained that the block of barostatic reflex mechanisms is substantially complete. Secondly, vasodilator pathways may play a more important part in regulation of peripheral blood flow than is commonly supposed. If tonic vasodilator impulses were also interrupted by TEA, the flow response would be less than that induced by specific blockade of constrictor mechanisms. The reflex vasodilatation caused in the forearm by heating of the lower extremities may lead to a three-fold increase in the blood flow of that predominantly muscular area (15), while TEA causes an increase of only 60 to 70% (121). Barcroft *et al.*, however, believe that the response to heating can be explained by withdrawal of vasoconstrictor activity alone. Since TEA causes no change of blood flow in the sympathectomized extremity (121) it must be assumed that whatever vasodilator pathways exist must course along with the sympathetics. Finally, the "borrowing-lending" hypothesis advanced by De Bakey *et al.* must be considered (63).

According to the "borrowing-lending" concept, the vasodilatation produced by TEA or any other general blocking agent must be less than that resulting from surgical denervation or from local nerve block. In a sense this is true. If widespread vasodilatation occurs in response to a drug, the resulting decline of pressure will of course limit the degree of hyperemia in all vascular areas. If, however, the drug interrupts vasoconstrictor pathways without causing a significant pressure fall, as is often true of TEA in normotensive individuals, it is difficult to see how vasodilatation in one limb can reduce the flow response in the neighboring member. In the lower extremities, for example, the blood flow is determined by the pressure at the aortic bifurcation and by the relative resistance of the vascular trees in the two limbs. Blood cannot be "borrowed" from an arteriosclerotic bed on one side as a result of a greater vasodilatation on the other unless a decline of pressure occurs at the bifurcation. In smaller vessels, however, such a mechanism probably operates even in the absence of a change of central arterial pressure. For example, if communicating channels between

arteries to muscle and arteries to skin are subject to intense vasoconstrictor tone which is suddenly released by a blocking agent, the resulting local drop in resistance may reduce the peripheral arterial pressure at the level of the communicating vessels, associated with an increase in the perfusion of the skin, but limiting the blood supply to the muscle (26). This mechanism might be considered responsible for the rather slight effects of TEA on blood flow in the forearm and calf, although the technic of measurement, which requires occlusion of vessels at the wrist or ankle, actually removes from consideration the areas in which the most marked vasodilatation occurs and in which, therefore, the most marked "borrowing" of blood would be expected.

Even granting the importance of the "borrowing-lending" mechanism in smaller peripheral arteries, the hypothesis can hardly explain the difference in effectiveness between TEA and paravertebral block, for anesthesia at the lumbodorsal level should initiate the same peripheral mechanism. We prefer to believe that the effect of TEA is limited because it does not completely abolish vasoconstrictor activity.

2. *Visceral blood flow:* Blood flow in the dog kidney, as measured directly or by clearance methods, usually declines somewhat or does not change as the pressure falls in response to TEA, suggesting that relatively little tonic vasoconstrictor activity exists in this organ (123).

In the human subject the initial response to TEA is a decrease of renal plasma flow, slight in normotensive but more marked in hypertensive individuals in whom the arterial pressure falls. The initial diminution of flow is limited to the first urine collection period of 10 to 15 minutes, after which the flow returns to a level at or near the preceding control value, even though the pressure may remain low for a half hour or more. During the later periods renal resistance is essentially unchanged in the normotensive but moderately reduced in most hypertensive subjects, which suggests that the kidneys partake in a general increase of vasomotor tone in hypertension. A reduction of glomerular filtration rate regularly occurs and is also more marked in hypertensive individuals.

The cause of the initial decrease of plasma flow has not been clearly defined. It cannot be a collection artifact resulting from reduction of urine output, for no "overshoot" of clearance values occurs in subsequent periods. Aas and Blegen (1) ascribe the change to renal vasoconstriction, but in the experience of Hoobler *et al.* (123) no increase of renal resistance occurs. Hoobler suggests that the decrease may be purely passive; that is, that the kidney is not subject to neurogenic vasoconstrictor tone even in hypertension, and that the subsequent return to normal levels represents an autonomous readjustment of the renal circulation (120). It is perhaps possible that the decline results from "sensitization" to circulating epinephrine or sympathin, further production of which would be prevented by the continuing synaptic blockade. Enhancement of the renal vasoconstrictor action of epinephrine by TEA has been reported by Corcoran and Page (58).

On rare occasions, when TEA induces a severe hypotension, all clearance values may be greatly depressed (124). Individuals who react most vigorously and alarmingly to TEA thus may lose the ability to excrete the drug.

When vasoconstriction is induced in the rabbit kidney by splanchnic stimulation or reflexly by crushing trauma of a leg, the resultant early cortical ischemia may be prevented or abolished by TEA (Stock, 245). On the basis of such experiments, Stock has suggested the use of the drug in pre-eclamptic toxemia, reflex anuria and related conditions. The use of TEA in cases of anuria would seem to be a particularly dangerous procedure, and should certainly not be attempted without due respect for the possible hazards.

Preliminary experiments in this laboratory indicate that the mesenteric vessels of the dog may respond like the renal arteries. Hill (112) and Martin (175) and their associates report that TEA causes blanching of the bowel in the dog, fails to prevent the spasm resulting from occlusion of mesenteric arteries or veins, and does not prolong life of animals subjected to ligation of major mesenteric vessels. They explain the failure of TEA to prevent vasospasm in the mesenteric vessels as the result of dissipation of its action on other ganglia, assuming apparently that TEA will not affect a ganglion subject to intense activity. There is no experimental evidence to support such a concept. It may be assumed that a concentration of TEA capable of blocking 90% of the synapses in a ganglion subjected to slight or moderate stimulation will also block 90% of those synapses when under more frequent bombardment. As a matter of fact, the percentage increase of blood flow caused by TEA in an area subject to intense vasoconstrictor stimulation will be much greater than in an area under only slight vasomotor tonus. (Compare, for example, the relative response of femoral and renal blood flow in the dog, or of blood flow in hands and kidneys in the human subject.) Other possible interpretations of the results of Martin and of Hill seem to us more likely. The application of clamp or ligature to the exposed vessel may cause direct stimulation of postganglionic fibers, which effect would not be prevented by TEA; or if the spasm is indeed reflex, the pathways may be invulnerable to TEA, as suggested below. In addition, of course, the fall of arterial pressure which results from ganglionic blockade in the anesthetized animal may cause a passive reduction of blood flow in visceral areas.

Preliminary estimates of hepatic blood flow in the human subject have been carried out, but not yet reported (Hoobler *et al.*, 120). TEA usually causes a reduction of hepatic blood flow (dye clearance) proportional to the blood pressure decrease. Splanchnicectomy, on the other hand, has been reported to result in an early increase of hepatic blood flow (Wilkins *et al.*, 256).

3. *Peripheral vascular disease and causalgic states:* The ability of TEA to increase peripheral blood flow by interrupting vasoconstrictor pathways naturally led to its clinical use as a therapeutic agent and as a tool to evaluate the degree of neurogenic vasospasm in peripheral vascular disorders. Many reports have appeared attesting its value in these conditions (13, 21, 31, 45, 54, 56, 68, 74, 76, 114, 117, 149, 166, 170, 178, 180, 229, 244, 257), but sharp disagreement has been expressed by others (28, 64, 71, 203, 204, 214). The general concensus seems to be that sympathectomy should not be deferred simply because no measurable vasodilatation results from the injection of TEA, though Yeager *et al.* have expressed the opinion that "if TEA does not reveal a substantial degree of vasospasm, surgical sympathectomy will not be of value" (257).

McIntyre *et al.* (178) believe that the subjective response to TEA (pain relief) gives a better prediction of the possible benefit to be derived from sympathectomy than does the degree of increase of skin temperature. Hoobler suggests that when a positive response to TEA occurs, no further proof of the existence of neurogenic vasospasm is necessary; but when TEA fails to produce significant vasodilatation confirmation should be sought by other means (120).

The reasons for the failure of many investigators to obtain reliable responses to ganglionic blocking agents are difficult to discern. TEA is certainly less effective than paravertebral block, as mentioned above; but the qualitative response should be similar. It has been emphasized by the Michigan group that repeated tests are often necessary before a conclusive result can be obtained, for the reason that an apprehensive patient may at the time of injection secrete a charge of epinephrine sufficient to mask the action of the drug (54).

Many investigators have been impressed by the duration of subjective improvement following one or more injections of TEA. The drug is rapidly excreted, and its measurable pharmacodynamic actions on blood pressure, blood flow, heart rate, etc. last for only an hour or so after its intravenous administration. Evaluation of subjective improvement is of course difficult, but it seems possible that in the vicious cycle of vasospasm → pain → vasospasm, even temporary interruption may be expected to bring relief until the next exciting stimulus, emotional or physical, reestablishes the cycle. In spite of such occasional favorable responses, TEA is not generally regarded as a useful therapeutic agent, except perhaps in causalgic states. Since it causes block of *all* ganglia, sympathetic and parasympathetic, the many side-effects preclude its prolonged or frequently repeated administration.

There are a few reports that ganglionic blockade may be effective in relieving vasospasm and in opening collateral channels after traumatic injury or inadvertent ligation of major arteries. Hill, Hammer and Saltztein (111, 112) were able with repeated injections of TEA to save life and function of the posterior extremities of dogs after ligation of the aorta. Cooper *et al.* reported similar protection of dogs after resection of the bifurcation of the aorta and the deep circumflex iliac arteries (57). Hammer has reported a case in which, after a major vessel was severed during a hernia repair, the leg was saved by the repeated administration of TEA (97). Presumably paravertebral block would be more effective, though technically more difficult to achieve.

Successful treatment of frostbite has been reported (13, 31, 117, 257). An experimental evaluation of various therapeutic procedures, including ganglionic block and heparin, has been attempted in mice whose tails were frozen by dry ice. A combination of TEA, heparin and rapid thawing appeared to be significantly more effective in preventing gangrene than other single or combined procedures tested (151).

4. *Pressor action of TEA:* Large or repeated doses of TEA cause a rise of arterial pressure which is probably due to a direct vasoconstrictor action (4, 250). The irregularity of blood pressure responses in dogs reported by Page (195) and by Marzoni *et al.* (176) can probably be explained as the result of doses

approaching the pressor range. The pressor action is believed by Page to be due to liberation of a humoral agent, perhaps norepinephrine, from the liver; for it does not occur, or to a lesser extent, in hepatectomized animals (195, 199). The pressor response is said to be blocked by sympatholytic agents (195); but it is possible that sympatholytic agents may antagonize the direct constrictor action of TEA.

D. Hypertension

1. *Experimental hypertension:* The acute elevation of pressure produced in the dog by carotid occlusion or by section of the buffer nerves is prevented or abolished by TEA (186). Although the rise of pressure caused by carotid clamping is believed by Charlier (48) to result from increased cardiac output rather than from increased peripheral resistance, the reverse was found to be true under the conditions of the experiments in this laboratory, and TEA administered during a period of carotid occlusion caused a fall to the same "floor" as in control observations. The response to TEA is also enhanced in unanesthetized dogs with chronic hypertension induced by denervation of the pressoreceptors (Moss and Wakerlin, 189). Whether in such animals the elevated pressure results from increased cardiac output or increased vasomotor discharge, it must in any event be mediated through autonomic paths vulnerable to the blocking action of TEA.

The acute elevation of pressure induced by epinephrine, angiotonin and other vasoconstrictor agents is not prevented by TEA (4) but is actually potentiated (181, 186, 197). In renal hypertension in the dog, the depressor response to TEA is not significantly different from that in unanesthetized control animals (189), which suggests that the elevation of pressure, presumably on a humoral basis, does not result in a reflex loss of vasomotor tone. Page and Taylor (198) also failed to demonstrate any characteristic difference in the response of normal and hypertensive dogs to TEA and other agents acting upon the circulation. The hypothesis of Reed *et al.* (216) that renal hypertension in the rat is on a humoral basis in early stages but becomes increasingly neurogenic with the passage of time has not been confirmed in the dog. Moss and Wakerlin found no increase in the response to TEA, Dibenamine, and other agents in animals hypertensive for more than 12 months as compared with animals hypertensive for less than 6 months.

2. *Human hypertension:* The effects of TEA in hypertension have been reviewed extensively by Hoobler *et al.* (122), and will be only briefly discussed in this paper. On the basis of animal experiments it seemed obvious that TEA should be a useful tool in the study of human hypertensive disease. The magnitude of the blood pressure fall was expected to give an estimate of the degree to which tonic sympathetic vasoconstrictor discharge contributes to the elevated pressure, and to enable a prediction of the result to be expected from extensive sympathectomy. Early studies showed that most patients with "essential" hypertension respond with a fall of pressure exceeding that observed in the normal subject (149, 166). As a rule, the diastolic pressure at the time of

maximum response to TEA still exceeds normal levels, which suggests that although these patients are under the influence of increased vasomotor discharge, the intrinsic (or humoral) component of vascular resistance is also greater than normal (165). Levinson, Reiser and Ferris (153), observing day to day variations in the response to TEA in hypertensive patients, suggest that the changing "floor" may reflect changes in the relative balance between humoral and neurogenic contributions to the total peripheral resistance. There is no reason to expect that the neurogenic element should remain fixed. Changes in fluid and salt intake have been shown to exert a marked influence on the responsiveness; patients hydrated by excessive ingestion of salt respond poorly, but regain their reactivity after a period of salt deprivation or after administration of a mercurial diuretic (122, 242).

Attempts to correlate the depressor response to TEA with the immediate and late response to splanchnicectomy or lumbodorsal sympathectomy have been disappointing. Although some observers have reported that the result of the TEA test has better prognostic value than other procedures (100, 209, 247), this has not been the general experience. Lyons (165) concludes that patients who repeatedly fail to respond to TEA are unlikely to show a decreased pressure after operation. Since relief of subjective complaints after operation is not well correlated with the depressor response, surgery should not be denied on the basis of such tests. Soloff *et al.* (236) state that neither TEA nor spinal anesthesia is reliable in predicting the results of sympathectomy. Similar conclusions have been reached by the Cleveland Clinic group (22), and by Hinton and Lord (113). Frisk *et al.* (82) have suggested that the qualitative nature of the response to TEA may give some indication of the extent of arteriosclerotic degenerative changes in the vascular tree, and thus may help to eliminate some patients in whom sympathectomy is less likely to be of value. It should be emphasized that a profound fall of pressure resulting from TEA may not mean a high level of vasomotor activity; release of moderately active vasoconstrictor mechanisms in older patients with extensive arteriosclerosis may cause an extreme response because of the rigidity of the arterial reservoir (122).

After complete lumbodorsal ganglionectomy one should expect the response to TEA to be lost; this has been confirmed in preliminary observations by Ray and Console (213). After splanchnicectomy, however, the response to TEA may be equal to the preoperative response (122). After the Smithwick operation in a small group of cases, Brown *et al.* (37) found the depressor response to TEA to be greater than before sympathectomy. Smaller doses postoperatively caused greater and longer-lasting effects than did larger doses preoperatively. The authors postulate that the remaining ganglia may be more completely blocked by TEA after sympathectomy, or that the arterioles are rendered more sensitive to TEA. The first postulate might be acceptable if TEA became fixed in ganglia—an exceedingly unlikely possibility considering its brief duration of action. The second postulate seems unlikely since TEA does not exert any direct vasodilator activity on the arterioles. If, however, there exist in the splanchnic bed vasomotor pathways invulnerable to TEA—a possibility which we have

seriously considered—then surgical section of the visceral sympathetic supply followed by TEA should be expected to cause a greater response than either procedure alone.

Although administration of TEA occasionally results in temporary clinical improvement of patients with essential hypertension, including relief of headache and reduction of venous pressure in hypertensive heart failure, and may, like spinal anesthesia, reverse the EKG pattern of left ventricular strain (224), most investigators are agreed that it cannot be considered a useful therapeutic agent in this disease (30, 122).

In coarctation of the aorta the use of TEA has not aided materially in determining whether the hypertension is on a neurogenic or humoral basis. Hoobler and Lyons (122) found the diastolic pressure response to TEA to range from +10 to −37 mm Hg in 6 cases; Brown and Wood (33) observed an average drop of 8 mm in the radial and 6 mm in the femoral diastolic pressure in 12 cases—responses little greater than those of normal subjects studied by the same authors (34).

TEA will reduce the pressure in toxemia of pregnancy (122) but not to the same extent as in normal pregnant women (40). It does not necessarily follow that the hypertension of toxemia is due to the action of humoral pressor substances, for the presence of increased blood volume and edema may reduce the action of the ganglionic blocking agent, as is true in other hyperhydrated hypertensive states (122). However, preparations of Veratrum viride are said to reduce the pressure in toxemic patients more than in normal women at term (12); since the veratrum alkaloids are believed to exert their depressor action through a reflex inhibition of vasomotor discharge, it is difficult to explain the difference between these agents.

Paroxysmal hypertension occurring in patients with spinal cord injuries can be prevented or relieved by TEA, and is probably reflex in origin and mediated by neurogenic mechanisms (251).

TEA has been reported to cause a sharp rise of pressure in two cases of proved pheochromocytoma (144, 231). La Due postulates that the rise is due to interruption of buffer mechanisms operating to oppose the action of the pressor substance, an interpretation which seems likely in view of the demonstrated potentiation of epinephrine by TEA (181, 197).

E. Vascular Reflexes

The use of TEA in the study of vascular reflexes in the dog has been described by Moe *et al.* (186). By blocking compensatory reflexes, TEA potentiates the pressor and depressor actions of agents acting directly upon vascular smooth muscle (58, 181, 197) and potentiates also the depressor and pressor effects of hemorrhage and plethora (186). A similar mechanism may account for the restoration of the response to renin after tachyphylaxis has developed (196).

Potentiation of the pressor action of epinephrine is more apparent than real. Reflex withdrawal of vasoconstrictor tone occurs when epinephrine is administered to a normal anesthetized animal, but if the dose is great enough the com-

pensatory capacity of the animal will be exhausted and a marked pressor response will occur. At the peak of such a pressor response sympathetic vasomotor tone may be assumed to be greatly depressed or completely abolished, and the pressure level should represent the sum of intrinsic vascular resistance plus the additional constriction produced by the epinephrine plus the increased cardiac output. In the presence of TEA the neurogenic component is already eliminated. Epinephrine now produces a pressor response in small doses which previously caused no change or a fall of pressure; but when large doses are injected, the pressure reaches a level not markedly greater than in the absence of TEA. The absolute rise and the percentage rise of pressure are of course greater, since the starting level is lower in the presence of ganglionic blockade. The magnitude and mechanism of the potentiation are equivalent to that produced by cord destruction and vagotomy. Page has observed further potentiation of epinephrine by TEA after section of the cervical cord, but not after the additional procedure of carotid sinus denervation (195). The explanation is not obscure: one of the compensatory adjustments to epinephrine is a reflex vagal discharge set off by the carotid receptors; TEA should give further potentiation by interrupting the efferent pathway at the vagal ganglia.

In the human subject TEA blocks the vasoconstriction induced by exposure to cold, and thus demonstrates the reflex nature of the response (121, 217). Vasoconstriction induced by pain or by emotional or mental stimuli is also prevented (121). The pressor response to the Valsalva maneuver is blocked, and is therefore presumably the result of increased vasomotor discharge (Sarnoff *et al.*, 226).

TEA was found to reduce the "g-tolerance" of subjects exposed to centrifugal force (35). Since TEA accelerated the rate of increase of pressure in the ankle veins in subjects tilted to the erect position, the decreased tolerance to gravitational or centrifugal force is considered not to be due to failure of venous return and cardiac output, but rather to failure to maintain an adequate peripheral resistance.

Taylor, Underwood and Page (248) reported that TEA prevented the blood pressure and heart response to stimulation of the carotid sinus area in a patient with hyperactive carotid reflexes. The heart rate component, but not the blood pressure fall, was also prevented by atropine. The depressor response to carotid nerve stimulation in the anesthetized dog is also abolished by TEA (186), since both procedures reduce vasoconstrictor discharge. No evidence for an active vasodilator mechanism in response to carotid stimulation was found in these experiments. Further study of patients with the hypersensitive carotid sinus syndrome might reveal the significance of active vasodilator impulses in the regulation of blood pressure in man. If, in the presence of atropine, carotid stimulation provokes a fall of pressure to levels lower than would be caused by injection of TEA, then the protective action of the ganglionic blocking agent must be due to interruption of vasodilator pathways called into action by the carotid reflex. If, on the other hand, the depressor response involves only reduction of tonic vasoconstrictor discharge, TEA should be expected to mimic, rather than prevent, the carotid syncope.

Most autonomic reflexes are blocked by TEA in adequate dosage, but there are some notable exceptions. The failure of TEA to prevent the effects of vagal stimulation on the duodenum is noted below, with some speculation as to the possible reasons for the failure. In addition, studies in this laboratory showed that the asphyxial rise of arterial pressure in the dog cannot be prevented, and indeed is often potentiated, by TEA (Freyburger *et al.*, 79). Because the asphyxial pressure rise was thought to be mediated through sympathetic channels, including liberation of epinephrine, it was expected that TEA should prevent the response in the dog, as it apparently does in the cat and rabbit. A number of possible explanations for this exceptional result have been tested. Firstly, it could be postulated that TEA fails to block cholinergic excitation of the adrenal medulla, perhaps because of the existence of intracellular nerve endings. In a careful study of the adrenals of many species, MacFarland and Davenport (168) failed to find intracellular nerve terminations. Furthermore, TEA prevents the hyperglycemic response to morphine, which has been assumed to be mediated by epinephrine (187) and prevents the liberation of epinephrine following splanchnic nerve stimulation in the cat (Morrison and Farrar, 188). The latter observation has been repeated in the dog in this laboratory: the pressor response to splanchnic nerve stimulation after evisceration is abolished by moderate doses of TEA (183). A second possibility, that hypoxia directly stimulates the medullary cells, as shown by Bülbring and Burn (42), was tested by inducing asphyxia of the head alone. The resultant pressor response in the trunk was not prevented by TEA (183). As a final hypothesis it was assumed to be possible that not all efferent pressor pathways in the dog contain ganglia, or that there might exist two types of ganglia, one vulnerable to TEA and mediating the responses to moderate stress and the other being invulnerable to TEA and mediating the responses to severe stress such as asphyxia. Some evidence for two types of sympathetic ganglia has already appeared (Shaw, 232), though alternative explanations for the data reported seem possible. This final hypothesis was tested on the dog's stellate ganglia. Although the effects of preganglionic stimulation of the accelerator nerves on the normal pacemaker can be readily blocked in both cat (4) and dog (183), it was found that after destruction of the sinus node preganglionic stimulation produced acceleration of the A-V node which could not be prevented by even excessive doses of TEA (200). Further, it was shown in the same preparation that the cardiac acceleration caused by carotid occlusion, but not that caused by cephalic asphyxia, could be blocked by TEA. It is not possible at present to say whether such a pathway is non-ganglionated or possessed of a qualitatively different type of synapse; but the possibility remains, as yet untested, that invulnerable vasoconstrictor paths also exist.

The existence of pathways invulnerable to TEA (and presumably other ganglionic blocking agents) might explain the apparent "incomplete" blockade in the human subject, and it would be important to learn whether a similar mechanism exists in man. As preliminary evidence, it may be observed that in a few cases in whom postural syncope (and cerebral asphyxia) occurred following the injection of TEA, the resumption of the supine position was followed by cardio-

acceleration and elevation of arterial pressure to levels considerably exceeding the previous resting value (Lyons, Hoobler *et al.*, 164).

F. Miscellaneous Vascular Applications

Ahlquist (7) has used TEA in an attempt to demonstrate that the pressor action of ephedrine is not due to inhibition of epinephrine oxidation. Assuming that TEA blocks transmission in the adrenal medulla as it does in autonomic ganglia, the epinephrine and "sympathin" concentration of the circulating blood should fall after injection of TEA. Ephedrine still produced its characteristic effect on the arterial pressure. With the doses of TEA and the time intervals allowed, however, it could not be assumed that the epinephrine content of blood had been significantly reduced. While ephedrine doubtless does possess a direct action on vessels, the experiment cannot be considered as proof.

Haimovici (95) has described a direct vascular action of nicotine on the vessels of the frog hind-leg preparation. Administration of TEA, *d*-tubocurarine or Dibenamine did not abolish the vasoconstrictor effect, which is therefore presumed not to be the result of stimulation of ganglion cells.

By eliminating reflex compensatory mechanisms, TEA enhances the depressor effect of hemorrhage, but it is said by Glasser and Page (84) to increase the survival of dogs in hemorrhagic shock, presumably because it permits the maintenance of adequate blood flow in spite of the low level of arterial pressure. Similar protection has also been reported with Dibenamine (219, 255).

G. Effects on the Gastrointestinal Tract

1. *Secretion:* Salivary secretion is abolished by tetraethylammonium, and dryness of the mouth is one of the unpleasant side-effects of the drug in the human subject (166, 191). Gastric secretion is also suppressed (38, 46, 72, 191, 258). Neligh *et al.* (191) found that no gastric juice could be recovered from normal subjects for one to two hours after the intravenous injection of 500 mgm, and the secretory volume in peptic ulcer patients was diminished, though usually not to zero. Titratable acidity was reduced to low levels, and the reflex secretory response to insulin was abolished. Zweig, Steigmann and Meyer (258) reported an average of 88% reduction in basal acid secretion in normal human subjects, comparing well with the 95% reduction resulting from complete vagotomy (Stein and Meyer, 243), and also reported a 70% reduction in the secretory response to intravenous infusion of histamine, as compared with 72% reduction following vagotomy. MacDonald and Smith (167) reported reduction but not complete suppression of the response to histamine and the alcohol test meal, and attributed the result to the inhibition of motility.

In the dog, Grossman (91) has reported a lack of effect of TEA on both basal and histamine-induced secretion, a result harmonious with the effect of vagotomy in this species as reported by Hanson, Grossman and Ivy (98). However, Oberhelman and Dragstedt (192) have reported that atropine and vagotomy greatly reduce the histamine-induced secretion of acid in dogs and man. If all effects of TEA on gastric secretion are due to ganglionic inter-

ruption of vagal influence, then histamine must be assumed to act in part at the ganglionic level or above, or perhaps by interaction with acetylcholine liberated by tonic vagal activity.

Prolongation of survival and reduction of the incidence of ulcer by TEA in rats subjected to pyloric ligation is undoubtedly due to reduction of acid secretion and gastric motility (155).

Blockade of sympathetic pathways probably contributes nothing to the actions of TEA on gastric secretion, for sympathetic denervation of the stomach is said not to alter gastric acidity in the human subject (212).

2. *Motility:* In isolated segments of rabbit ileum TEA produces a moderate enhancement of contractions of the longitudinal muscle, and an increase of peristalsis as measured by the Trendelenburg technique (70). The concentrations used (10 mgm % and more) are at least 5 times the concentrations achieved in the human subject. Since the isolated gut strip is already separated from the central nervous system, it is perhaps not surprising that no depression of spontaneous contractions occurs. The role of the intrinsic plexuses, which presumably involve cholinergic synapses, is still not clear. Atropine also often fails to depress the activity of the rabbit ileum. One wonders whether TEA would potentiate the inhibitory actions of epinephrine in this preparation.

Collins (55) has studied the effect of TEA on responses of the isolated guinea pig ileum to angiotonin, histamine, acetylcholine and barium. The normally quiescent segment was stimulated slightly by TEA, and the contractile responses to angiotonin and histamine were enhanced by the drug. Responses to barium and acetylcholine were usually moderately depressed. The action of TEA on angiotonin and histamine responses is difficult to interpret in terms of ganglionic blockade, unless one assumes an autonomous adrenergic inhibitory mechanism involving synapses vulnerable to TEA. Blockade of such synapses should allow an enhanced response to spasmogenic agents. Even this hypothesis could not account for the opposite effect on the responses to acetylcholine and barium. TEA potentiates the action of histamine on ileal Thiry-Vella loops (60), probably by blocking opposing sympathetic inhibitory impulses.

The action of TEA on activity of the small bowel has been studied in anesthetized and unanesthetized dogs. In acute experiments under barbiturate anesthesia the motility of the bowel is usually depressed by the anesthetic agent, and injection of TEA produces no striking further effect. The contractile response of the duodenum to vagal stimulation is not blocked by doses of TEA which interrupt transmission in other autonomic pathways (183, 193). Atropine has long been known to fail similarly, perhaps because of the existence of intracellular vagal endings. Atropine and TEA in combination occasionally, but not uniformly, abolish the duodenal response to vagal stimulation (183). Should there be synapses in the cephalic ganglia of the vagus it is possible that stimulation of the nerve in the neck excites postganglionic fibers which of course, should not be blocked by TEA; but Heinbecker and O'Leary (105), who demonstrated that in the cat the cell-bodies of preganglionic (?) cardiac vagal fibers lie within the vagal centers while those to the bronchi and gut lie in the

nodose ganglia, found no evidence for synapses in the nodose ganglia. If the ganglionic synapse is indeed peripheral, then its sensitivity to TEA is of a very much lower degree than that of the cardiac synapses.

In dogs under morphine-urethane or morphine-chloralose anesthesia, motility of the small bowel is well maintained, probably because of the direct action of morphine. In such animals TEA often causes a pronounced *increase* of tone, due presumably to interruption of sympathetic inhibitory impulses (183). Sympathetic block by whatever means should allow development of the unopposed action of morphine.

Gastric motility and emptying time are not greatly altered by TEA in the normal dog (145), in sharp contrast to the effects of the drug in human subjects.

In unanesthetized dogs prepared with Thiry-Vella fistulae, TEA causes reduction of tone and depression of motility, but not arrest, of the jejunum and ileum (254). Loops of bowel denervated by stripping the mesenteric vessels (that is, section of sympathetic postganglionic and vagal preganglionic fibers) are more sensitive to the depressant action of TEA than loops retaining their nerve supply. Comparable differences in the response to epinephrine and atropine can also be demonstrated. It is difficult to see wherein the denervated Thiry-Vella loop differs from the isolated strip of rabbit ileum, which has also been deprived of its extrinsic nerve supply. Isolated gut segments from puppies, comparable in size to rabbit ileum, should perhaps be studied to determine the role of species differences.

Bozler (29) has found that reflex peristaltic contractions initiated above the site of a mechanical or electrical stimulus can be blocked by local application of TEA. He believes the local response to stimulation is mediated through the intrinsic plexus of the bowel as a myenteric reflex and involves cholinergic synapses which can be blocked by TEA.

Whitrock and Gray (253) have observed brief but marked depression of activity in the colon after intravenous injection of TEA in unanesthetized dogs. Denervation of the colon by section of the sacral and lower sympathetic nerves and supradiaphragmatic vagotomy decreased spontaneous activity, but did not significantly alter the extent or duration of the inhibition produced by TEA. The denervation procedure did not in itself alter the activity of the lower ileum, but the response to TEA was changed from inhibition to stimulation. Only the parasympathetic supply to the ileum was interrupted by the surgical procedures, and it is likely that the increased motility caused by TEA resulted from blockade of the sympathetic paths, exposing the high level of spontaneous activity in the denervated bowel.

The effects of TEA on gastrointestinal motility in the human subject have been noted by Holt (118), Zweig (258), Neligh (191), Chapman (47), Brown (38), Dodds (65), Posey (207), and their respective associates. The drug appears not to affect the esophagus or the cardia (191), but contractions of the stomach as recorded by balloons (258) or by fluoroscopic observation (118, 191) are abolished for at least 30 minutes by the usual intravenous doses. Effects on

the small bowel are equally striking. Balloon recordings show no contractions for 30 minutes or more after 300 to 500 mgm intravenously (47), and on fluoroscopy all three types of activity—segmental motion, peristaltic rushes and mucosal pattern changes—were observed to disappear. Although atropine causes similar inhibition as judged by balloon records, doses up to 1 mgm intravenously failed to produce comparable depression in the fluroscopic picture. Epinephrine, 0.5 mgm subcutaneously, likewise failed to produce complete cessation of activity, although the two agents combined caused inhibition comparable to that resulting from TEA (191).

Since in animals section of both sympathetic and parasympathetic nerves to the gut does not abolish activity, and since the effect of TEA in the isolated gut segment is inconspicuous, the profound inhibition produced by TEA on the human small bowel is surprising. The theory has been proposed that TEA more effectively blocks vagal impulses than sympathetic, but there are several reasons for doubting this possibility (191). There seems to be no satisfactory explanation available; the possibility of an effect not related to the ganglionic blocking action appears unlikely, for similar effects on motility have been observed with other ganglionic blocking agents (159, 194).

Relief of pain due to visceral spasm is often striking, though temporary (38, 191). It cannot be due to interruption of afferent paths, for pain induced by distention of a balloon within the small bowel is not abolished (47). Relief of ulcer pain is believed due to inhibition of motility rather than depression of acid secretion, for it is prompt and occurs in patients with gastric as well as duodenal ulcers (191).

Effects of TEA on the colon appear to be similar to those on the small bowel in man; a reduction in the frequency of bowel movements in ulcerative colitis was noted by Neligh and her collaborators (191). Posey, Brown and Bargen, studying bowel motility by means of the balloon technique in 4 colostomy patients, found that motility of the terminal ileum and colon was depressed longer than that of the stomach (207). The authors believe the rhythmic contractions are neurogenic rather than myogenic in origin.

In spite of the profound effects of TEA on gastric secretion and gastrointestinal motility and the striking relief of pain in ulcer patients, the numerous side-effects produced by widespread autonomic blockade make such agents unsuitable for anything more than acute therapy of gastrointestinal disorders, or as a diagnostic aid in Roentgen examinations of the bowel (94).

H. Ureters and Bladder

TEA abolishes the normal rhythmic contractions of the intact bladder and blocks the effect of preganglionic stimulation of the pelvic nerves in the cat (Root, 222). Nesbit *et al.* (190) have shown that the capacity of the normal human bladder is greatly increased by blocking the ganglia of the parasympathetic motor pathway. TEA had no effect on the ability of the bladder to adjust to increasing volume without change of pressure, and had no effect on the cystometrograms of patients in whom the motor pathway was destroyed (autono-

mouu neurogenic bladder). Inability to void is one of the numerous side-reactions to TEA which interfere with its prolonged clinical use.

Lapides (147) was able to demonstrate an effect of TEA on peristaltic activity of the intact human ureter only when the urine flow was temporarily inhibited or stopped by the drug in subjects who experienced a well-marked reduction of arterial pressure. Even during a period of inactivity resulting from cessation of urine flow, contractions could be started by intraureteral injection of fluid. TEA did not relieve attacks of ureteral colic, or prevent the induction of such attacks by the rapid injection of fluid into the ureter. The lack of any specific action on ureteral motility is considered to be evidence for the autonomous nature of peristalsis in this organ.

I. Action of TEA on Afferent Mechanisms

1. *Chemoreceptors and pressoreceptors:* The pharmacology of the carotid-aortic chemoreceptors is remarkably similar to that of ganglion cells. The analogy extends also to TEA and presumably other ganglionic blocking agents. Recording the respiration as an indicator of carotid body responses, it has been found that TEA prevents the stimulation of the chemoreceptors by acetylcholine, nicotine and lobeline, but not the effect of the cyanide ion or hypoxia. The significance of these observations in terms of the functional organization of chemoreceptor mechanism has been discussed (182). TEA had no demonstrable action on stretch receptors of the lungs and carotid sinuses, or on the special vagal afferents which are stimulated by the veratrum alkaloids, judging again from the respiratory responses.

2. *Sensory perception:* Rapid injection of TEA causes paresthesias of skin and oral mucosa, perhaps the result of repetitive discharges induced by the initial high concentration. When the paresthesias subside there can be detected no impairment of touch, temperature, pressure or position sense, no interference with taste or auditory perception, and no interference with visual or olfactory mechanisms except that resulting from paralysis of accommodation and nasal congestion. In spite of paralysis of the bladder, sensations from within it are not impaired (190).

3. *Pain:* Relief of pain by TEA is often a striking result of its use in the human subject, but unfortunately a phenomenon not easily subject to careful objective analysis. When pain is believed to be due at least in part to smooth muscle spasm, relief induced by a ganglionic blocking agent is not difficult to explain. Presumably the relief afforded in peptic ulcer (38, 46, 47, 118, 191), acute pancreatitis (205) (though not the pain of chronic lithiasis, 122), and peripheral vascular disease is on this basis. Relief of hypertensive headache may be due either to release of vascular spasm or to the reduction of arterial and cerebrospinal fluid pressure. Relief of anginal pain is probably often due to reduction of the cardiac work load. But frequently pain relief, as in causalgia, herpes zoster (54, 75), pulmonary infarction (135), herniated intervertebral disc (69), etc. cannot be clearly related to improvement of blood supply. At present it is impossible to deny an action of TEA on certain pain receptors or central synapses.

While acetylcholine is not known to play a peripheral role in the mediation of pain, it is capable of inducing severe pain when injected intraarterially. An attempt to demonstrate whether TEA could prevent the superficial pain caused by acetylcholine was unsuccessful because of the difficulty of quantitating the pain sensation and because of the paresthesias induced by TEA itself (183). Acetylcholine has been shown to cause discharges of afferent fibers from skin and mesentery in the cat (36), and TEA might be expected to prevent such a "nicotinic" action of the mediator, but this still would not imply a physiological role of acetylcholine in pain mediation. Axone reflex pilomotion and sweating induced by intracutaneous injection of acetylcholine can be prevented by previous local injection of TEA (137), which suggests that efferent sympathetic cholinergic endings might both liberate and be excited by acetylcholine, and that excitation of such endings is a "nicotinic" action of acetylcholine. TEA also inhibits the state of "itchy skin" caused by local injection of histamine (237), which may imply a "nicotinic" action of this agent. Histamine has been implicated as a possible mediator of cutaneous pain (223). If a histaminergic or cholinergic mechanism can be demonstrated in clinical situations, the interpretation of the analgesic action of TEA would be greatly simplified.

Pfeiffer *et al.* have shown that TEA elevates moderately the threshold for superficial pain of the finger pad, although it does not alter tooth pain, and slightly lowers the pain threshold of the nail bed ("sympain") (206, 238). Since the latter mode of pain can be obtunded by stellate block with procaine, it presumably is conducted through pathways which course anatomically through the stellate region, but does not actually involve an efferent sympathetic component. Inhibition of the finger pad pain could represent either a specific action on the receptors or a special thalamic depression (238). It also seems possible that an increase in cutaneous blood flow might cause a relative analgesia by increasing the speed of heat dissipation from the stimulated site, a possibility which could easily be checked by testing the effect of reflex vasodilatation on the pain threshold. An analgesic action has also been reported by Hewer and Keele who found a mild change in the threshold for ischemic pain of the calf muscles (107). The alteration is of questionable significance.

J. Miscellaneous Actions and Applications

On the assumption that vasospasm is an important factor in multiple sclerosis (77), Bell *et al.* (20) and Fisher (74) have used TEA in patients with this disease. Although the time of study has been brief, the authors believe the drug may be of some value in early cases. TEA has also been used in the treatment of psychovisceral manifestations of anxiety, and is suggested as a useful tool in diagnosis and perhaps in therapy (19).

TEA has been used to control pain, vasospasm and sweating in poliomyelitis, and is said to diminish muscle spasm and increase the ease of physical manipulation (146). This is thought to be due to an action on the sympathetic component of striated muscle activity, but may represent another manifestation of unexplained analgesic activity of TEA.

Dyspnea has occasionally been observed as a result of the administration of

TEA (166), and might well result from a direct action of the drug on bronchial smooth muscle after too rapid administration. For this reason asthma has been considered a contraindication to the use of the drug (164). Blomberg and Lindquist observed marked improvement in four of five cases of acute asthma (23), but there must be many better and safer therapeutic agents.

TEA and Dibenamine have been used in attempts to block the secretion of the adrenocorticotrophic hormone. Both failed (249).

K. Absorption, Excretion and Toxicity of TEA

TEA and those of its analogs which have been tested are poorly absorbed from the gut. After oral administration in the human subject, only 5–15% can be recovered in the urine (220); the oral LD_{50} in mice exceeds the intraperitoneal LD_{50} by 15 times (93).

TEA is excreted in the urine rapidly, completely and unchanged. Active tubular secretion has been demonstrated, and in the dog there is some evidence of tubular reabsorption, probably by passive diffusion (220). The rapid excretion is probably fortunate. While attempts have been made to seek a longer-lasting or slowly absorbed preparation of the drug (220), it is certain that the hazards of its use would be multiplied by such procedures.

Death in experimental animals is usually the result of respiratory paralysis (93, 182); chronic administration of maximum tolerated doses causes no pathological evidence of tissue damage (93).

In the human subject certain toxic effects probably not related to ganglionic blockade have been described as mentioned above. While severe reactions may be expected in older subjects with hypertension and impaired renal function, they are infrequent in younger individuals without advanced cardiovascular disease. Exceptionally severe responses have, however, been reported (81). At least two deaths have occurred, one in a patient with advanced hypertensive disease in whom circulatory collapse might have been expected (150) and one in an elderly asthmatic patient who died after the injection of 230 mgm (228). A case of purpura occurring 3 days after the last of a series of injections has been noted, but no causal relationship was established (96).

II. OTHER COMPOUNDS

A. Quaternary Ammonium Compounds

1. *Miscellaneous quaternaries:* Of the hundreds of quaternary salts that have been studied in the past eighty years, a large number have been shown to possess "nicotinic-paralyzing" activity, either to the exclusion of other properties, or in addition to muscarinic, curariform or other actions. In the papers of Hunt and his associates (125–131), the criterion of activity was a fall of blood pressure not blocked by atropine, or prevention of the pressor actions of ganglionic stimulating compounds (tetramethylammonium). Since it is probable that acetylcholine and tetramethylammonium act similarly on the same receptor (52), the latter criterion may be assumed to indicate ganglionic blocking activity. On this basis, at least 30 of Hunt's compounds have been shown to be active; since most

have received little further study and have not actually been tested on ganglionic transmission, they are not listed here. It is not possible to rank these agents according to potency from the available data. In general, it will be found that the majority of the compounds contain at least three ethyl radicals or longer chains. Comparable steric forms of phosphonium bases, and probably of sulfonium, arsonium, and stibonium salts, also have activity (126, 127).

A series of more than a hundred compounds have been studied by Freyburger and Moe (80), but no agents significantly better than TEA with respect to potency, safety, duration of action, or absorption from the intestine were found. Though few generalizations about structure-activity relationships could be made, it was found that activity was in general reduced by introduction of oxygen as a terminal hydroxyl radical or as a bridge between ethyl groups to form a morpholine ring. For example, the molar activity of N,N-diethylmorpholinium was estimated to be one half, and of beta-hydroxyethyltriethylammonium one third that of TEA. Addition of cyclic groups to form an ether linkage again increases activity, as in the benzyl, benzhydryl and alpha-naphthylmethyl ethers of beta-hydroxyethyltriethylammonium, the comparative activities of which are approximately 1.5, 1.8 and 2.5 times that of TEA. While in general the presence of two or more methyl groups reduces ganglionic blocking activity. the benzhydryl ether of choline was found to be as active as TEA on a molar basis. The ethyl analog of choline and of its esters have been shown to possess a predominantly "nicotinic-paralyzing" action (119, 127).

Acheson (2), using a screening procedure similar to that of Freyburger and Moe, has studied an additional series of 65 quaternary salts. The most active agents in his series were a group of substituted phenyl ethers of beta-hydroxyethyltriethylammonium, one of which was found to be 10 times as potent as TEA on a molar basis. Intravenous toxicity in the mouse was also high, and none of the group possessed a greater margin of safety than TEA.

Ganglionic paralyzing activity alone or in combination with other actions has also been reported in a miscellaneous group of quaternary salts: the methiodide of hexamethylenetetramine (83), quaternary derivatives of procaine (221), lauryldimethyl-beta-hydroxyethylammonium (106), derivatives of choline (61), Dibutoline (92), phenoxyethyltriethylammonium and the analogous ethers of resorcinol and pyrogallol (43).

2. *2,6-dimethyl diethyl piperidinium:* This agent, studied in detail by Longino, Chittum and Grimson (88, 158, 159, 160), produces effects in animals and man comparable to those of TEA, but is three to five times as potent.

3. *Polymethylene bis-quaternary ammonium salts:* Ganglionic blocking activity of bis-triethylammonium salts was demonstrated by Chou and de Elio (50). Activity is low in the ethylene, trimethylene and pentamethylene compounds, but double the activity of TEA in the decamethylene compound. In the series of polymethylene bis-trimethylammonium salts prepared by Barlow and Ing (16), however, ganglionic blocking activity reaches a maximum with the hexamethylene chain, and is almost wholly replaced by curariform activity with the decamethylene chain (202). The pentamethylene derivative (C-5, pentametho-

nium) has been extensively studied (10, 11, 85, 89, 90, 194). It is about 10 to 20 times as potent as TEA and produces effects lasting considerably longer (90, 194). Whether the greater duration is due to slower excretion or to fixation is not yet known. C-5 has little curariform activity (16, 85), and antagonizes the curariform action of C-10 (169, 194), although a case has been reported in which C-5 administered after C-10 resulted in respiratory arrest (17).

The actions of C-5 are in general similar to those of TEA but certain differences have been noted. It has a slight anticholinesterase activity (85), and may have a direct dilator action on peripheral vessels (10). Arnold, Goetz, and Rosenheim (10) reported that C-5 increased the digital pulse volume in 3 of 4 patients who had been subjected to sympathectomy. TEA, which lacks direct vasodilator activity, has not been observed to affect peripheral blood flow in the sympathectomized extremity (121). Arnold and Rosenheim (11) believe that disturbances of accommodation and of bowel and bladder function are less marked than with TEA; the difference may be a function of dosage, for generalized blockade of ganglia should cause effects on these parasympathetically innervated structures.

B. Tertiary Amines

It has been established by Harvey (99) that procaine inhibits ganglionic transmission, and similar activity has been noted for diethylaminoethanol itself by Mercier and Mercier (179), Clark and Helpern (53) and Freis *et al.* (78). Recently a number of derivatives of diethylaminoethanol (Hazard *et al.*, 102) have been shown to exhibit some degree of ganglionic blocking activity.

Among other amines said to possess this property are 933F and a series of related compounds studied by Bacq (14), sparteine (101, 103, 179), and dibenzylmethyl-beta-dimethyl amino propionate (49).

Koppanyi and Vivino (142) have shown inhibition of ganglionic transmission by 2,3- and 2,4-dimethyl piperidines. In this laboratory, the effect of these agents on blood pressure is more complex than would be expected on the basis of ganglionic paralysis alone. A brief depressor phase is followed by a pressor effect which may be due to a direct peripheral vasoconstrictor action (80).

Thiophanium derivatives have been shown to block ganglia (210, 211). Of these, d-3, 4- (1′,3′-dibenzyl-2′-keto-imidazolido) -1,2-trimethylene thiophanium-d-camphor sulfonate (Nu-2222) is said to be thirty times as potent and to have two to three times the duration of action of TEA. It is, however, considerably more toxic than TEA in dogs. The fall in blood pressure produced by this agent is considerably greater than would be expected from ganglionic blockade alone. It thus seems apparent that the compound has a peripheral action in addition to ganglionic blocking activity.

The ganglionic depressant action of atropine has been emphasized by Marrazzi (171) who recorded postganglionic action potentials during preganglionic stimulation, by Dutta (66) and by Konzett and Rothlin (140) who recorded the response of the nictitating membrane to acetylcholine injected into the perfused superior cervical ganglion. Konzett and Rothlin were able to produce almost complete temporary suppression of the response to nearly maximal doses of

acetylcholine by as little as 0.1 microgram of atropine sulfate. Although atropine has a high order of potency, the doses used in ordinary pharmacological investigation (0.1 to 1.0 mgm/kg) or in clinical practice (0.5 to 2.0 mgm total dose) produce little or no evidence of ganglionic blockade. A fall of blood pressure, so characteristic of the action of TEA in the dog or cat under barbiturate anesthesia, does not follow the injection of atropine except in very high doses. Cardiovascular sympathetic reflexes are not appreciably inhibited by ordinary doses of atropine.

Epinephrine, nor-epinephrine and various other sympathomimetic amines were also shown to inhibit ganglionic transmission (163, 172, 173, 208). The blocking action of these drugs is certainly not complete in the ordinary clinical or pharmacological dosage. The action of the sympathomimetic amines on ganglionic transmission is said to be bi-phasic, a phase of inhibition being followed by a phase of facilitation (173). Bülbring (41), however, noted facilitation of transmission with low concentrations, and inhibition only with higher dose levels.

Dutta (66) and Hebb and Konzett (104) have demonstrated that high concentrations of meperidine, methadon and quinidine depress ganglionic transmission in the superior cervical ganglion of the cat, whereas morphine exhibits no such activity. Koppanyi and Karczmar (141) have stated that very high doses of anticholinesterase agents depress ganglia, presumably because of the blocking action of accumulated acetylcholine.

C. Inorganic Ions

Magnesium ion has been reported by Stanbury (239) to prevent the stimulant action of both acetylcholine and potassium on the superior cervical ganglion. Antagonism of the pressor action of nicotine by potassium thiocyanate may also represent a ganglionic blocking action (62).

SUMMARY

In the past few years ganglionic blocking agents have been extensively used in clinical and physiological investigation of the cardiovascular system and to a lesser extent of the gastrointestinal tract and other systems. The use of tetraethylammonium as a physiological tool is subject to two limitations: it inhibits transmission in both sympathetic and parasympathetic pathways, and in the human subject it does not, in safe clinical doses, cause complete interruption of autonomic discharges. For many purposes an agent which specifically and completely blocks vasoconstrictor pathways would be preferable. The action of TEA on cardiac output, for example, is complicated by effects on heart rate, and probably also by interruption of sympathetic inotropic effects.

The action of TEA in the experimental animal is relatively pure and uncomplicated by actions other than ganglionic depression; in the human subject there is evidence in addition for a limited analgesic activity. When the mechanisms of pain perception are eventually understood, the analgesic action of TEA may be interpretable in terms of ganglionic blocking activity.

TEA has effects on axones and on cardiac muscle which do not appear to be general or necessary attributes of ganglionic blocking activity. The intimate mechanism of acetylcholine antagonism at the ganglionic synapse has not been worked out. Elucidation of the mechanism should contribute to our understanding of the action of acetylcholine itself.

Not all autonomic mechanisms in the dog can be interrupted by TEA. The failure to prevent the effects of vagal stimulation on the duodenum, and the effects of cardiac sympathetic stimulation on the ventricles suggest the existence either of non-ganglionated pathways or of invulnerable ganglia.

Ganglionic blocking agents may have a limited field of usefulness in the study, diagnosis and therapy of vasospastic disorders in the human subject; but it may well develop that their chief value lies not in answering questions, but rather in posing them.

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