the observations in the dog by Plummer *et al.* (6) with chlorisondamine chloride and those of Trapold(7) with chlorisondamine chloride, hexamethonium and pentapyrrolidinium, that peripheral resistance of the mesenteric bed is not greatly decreased after administration of such agents.

That certain sympathetic pathways should not be affected by ganglionic blocking agents is not a novel concept. Freyburger *et al.*(10) and Pardo *et al.*(11) have presented evidence to this effect, and Moe and Freyburger(12) have discussed the subject at length. Cicardo and Dutrey(13) have also presented evidence indicating the ineffectiveness of ganglioplegic agents to block certain ganglionated pressor pathways.

Evidence has been presented by Freyburger *et al.*(14) and Morrison and Farrar(15) that TEA can block the release of epinephrine from the adrenal medulla following splanchnic nerve stimulation. It is not known whether the other blocking agents possess this activity. Apparently, however, epinephrine released from the medulla plays a subsidiary part in the pressor response elicited by faradization of the splanchnic nerve(16).

Summary. The effects of the ganglionic blocking agents, TEA, hexamethonium, pentapyrrolidinium and chlorisondamine chloride on the pressor responses induced by peripheral splanchnic faradization have been determined in 16 cats. These agents did not antagonize the pressor responses when the ipsilateral adrenal gland was present or after it had been ablated. The significance of these findings is discussed.

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Effects of Reserpine on Urinary Bladder Tension. (22436)

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The most prominent actions of reserpine are its "tranquilizing" and blood pressure lowering effects(1-3). Both of these responses are slow in onset, generally commencing from one to several hours after intravenous injection. However, slowness of onset is not characteristic of all the pharmacological responses to this compound. The present communication deals with the response of the urinary bladder to reserpine, an action which begins within 5 minutes after administration.

Methods. Twenty female dogs anesthetized with 30 mg/kg intraperitoneally, plus a continuous intravenous infusion of 0.1 mg/kg/

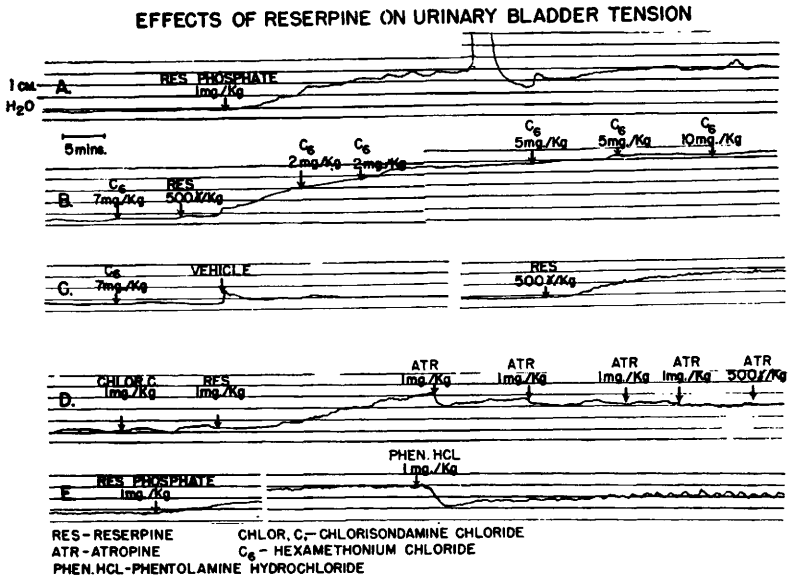

FIG. 1. Reserpine-induced increase in urinary bladder tension and effects of autonomic blocking agents on this response.

minute of pentobarbital were employed in this study. Urinary bladders were exposed through a mid-ventral incision and the ureters ligated and cut. Bladders were then catheterized and connected to a water manometer.

Results. Effects of reserpine on urinary bladder tension. Reserpine administered intravenously as the water-soluble phosphate or in the commercial vehicle* induces an immediate and prolonged increase in urinary bladder tension (Fig. 1-A). One-half to 1 mg/kg will produce a rise of approximately 2 to 4 cm H_2O which lasts over an indefinite period. Generally the bladder is quiescent, but in an occasional animal, during the sustained increase in bladder tension, it may exhibit a transient total contraction (Fig. 1-A). Since the most prominent effects of reserpine are generally attributed to a central action, it was considered of interest to determine the effects of ganglionic blockade on this response.

Effect of ganglionic blockade on response of bladder to reserpine. Intravenous doses of 1 to 7 mg/kg of hexamethonium chloride and 0.3 mg to 1 mg/kg of chlorisondamine chloride administered prior to reserpine were without effect on the bladder response (Fig. 1-B, C, D). High doses of hexamethonium chloride administered after reserpine were also without effect. Administration of 0.5 to 1 mg/kg of reserpine produced the same effects on the bladder as in the absence of these agents. Reserpine vehicle produced no marked effects on bladder tension (Fig. 1-C). Ganglionic blocking agents in themselves did not affect bladder tension.

Effects of cholinergic and adrenergic blocking agents and LSD on bladder response to reserpine. Atropine in intravenous doses of 1-4 mg/kg produced slight to moderate reduction of the increased bladder tension produced by reserpine (Fig. 1-D). The adrenergic blocking agent, phentolamine, was very effective in reducing the increased bladder tension. Doses of 1 mg/kg consistently lowered the bladder tension to control levels for a period of one-half hour, after which bladder tension returned to its previous level (Fig. 1-E). LSD administered after reserpine in intravenous doses of 20-40 μg/kg did not reduce, but on the contrary, markedly increased bladder tension. LSD also produced a marked increase in bladder tension when given alone.

Effect of reserpine on response of urinary bladder to choline esters. Carbamylcholine and mecholyl in intravenous doses ranging

* Ciba vehicle.

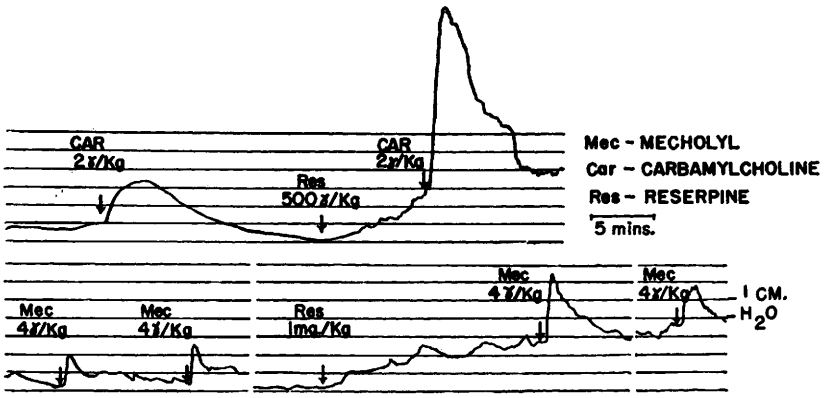

FIG. 2. Effect of reserpine on the response of the urinary bladder to intravenously-administered choline esters.

from 0.1 to 5 μg/kg will produce transient, repeatable contractions of the urinary bladder. After intravenous administration of 0.5 to 2 mg/kg of reserpine, moderate to marked potentiation of the response to these agents could be demonstrated (Fig. 2). In some cases after reserpine administration, these agents produced rapid, transient, total contraction of the bladder.

Discussion. The responses of the central nervous system and blood pressure to reserpine are slow in onset and therefore possibly reflect an action not initiated by the reserpine molecule *per se*, but by some metabolite of it, or to an agent such as serotonin which has been shown to be released from the brain and intestinal tract of rabbits(4,5) by reserpine. Unlike these effects, the onset of the response of the urinary bladder is almost immediate and therefore may be initiated by the unaltered reserpine molecule. That released serotonin may play no important role in this effect is indicated by the fact that the serotonin antagonist LSD does not reduce the increased bladder tension. Unfortunately this evidence is not conclusive, for LSD in itself can produce an increase in bladder tonus which may mask any of its antagonizing effects on this response. However, Shore *et al.* (6) report that in the dog a marked increase in the urinary excretion of 5-hydroxy-indole acetic acid, a major metabolite of serotonin, occurs in the dog following reserpine injection. It is difficult to see how released serotonin, which is rapidly inactivated, could be the cause of the prolonged bladder contraction.

The bladder response to reserpine is apparently a reflection of a peripheral action, since it can occur in the presence of large doses of ganglionic blocking agents. Since atropine is partially active in reducing bladder tension, there is a possibility of a cholinergic-like or cholinergic-potentiating action of reserpine upon the bladder muscle. The fact that reserpine has the capacity to potentiate the response of the bladder to mecholyl and carbamylcholine is supportive evidence for this view.

Since the adrenergic blocking agent, phentolamine, can reduce the increased bladder tension, it would appear that some sympathetic humoral substance may also be involved. It is not inconceivable that reserpine could be acting to produce a prolonged release of epinephrine or norepinephrine from some site, possibly the adrenal medullae.

Summary. Reserpine will produce a gradual increase in bladder tension which is initiated within five minutes after intravenous injection. This response is not blocked by ganglionic blocking agents. Atropine has a slight to moderate antagonizing effect on this response. The adrenergic blocking agent, phentolamine, has a marked antagonizing effect on this response. Reserpine can potentiate the response of the bladder to mecholyl and carbamylcholine. The significance of these facts is discussed.

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Antiviral Action of Helenine on Experimental Poliomyelitis.* (22437)

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Recently crude preparations from 2 species of penicillium, *P. stoloniferum* and *P. funiculosum* have been reported to be effective against certain small neurotropic viruses such as Semliki Forest, MM, and Columbia SK (1-3). The crude filtrate of *P. stoloniferum*, known at M5-8450(4), was also found to be effective against poliomyelitis virus inoculated by peripheral routes in mice(5) and monkeys (6). In view of the suspected similarity between M5-8450 and Helenine, the antiviral agent from *P. funiculosum*(4,7), it was of interest to investigate the effect of Helenine on experimental poliomyelitis in mice and monkeys.

Materials and methods. Young male and female cynomolgus monkeys, weighing between 1.1 and 2.8 kg, and young Swiss albino mice, weighing 12 g or less, were used in these studies. Mice were inoculated intraperitoneally with approximately 10 ID_{50} of the MEF_1 strain of type II poliomyelitis virus adapted to suckling hamsters by Powell and Culbertson(5), while monkeys were inoculated subcutaneously with an estimated 100 ID_{50} of the Mahoney strain of type I poliomyelitis virus. All animals were observed daily for the onset of paralysis throughout an observation period of at least 21 days for mice, and at least 30 days for monkeys. Helenine† was obtained as a 10-fold concentrate of the acetone-precipitated material. For purposes of comparison, one experiment included a group of monkeys treated with M5-8450.† Both materials were kept frozen at −70°C until the day of use.

Results. In preliminary tests the maximum daily dose of Helenine tolerated by mice was found to be 0.5 ml of 2-fold concentrate (8). No toxic effects other than a transitory anorexia were observed in monkeys receiving up to 5 ml of 10-fold concentrated Helenine per kg twice daily for 4 days. More extensive toxicity studies were not conducted because of the difficulty of determining whether observed effects were due to the active principle or to impurities in the available preparation.

Data showing the effect of Helenine-treatment in mice infected with poliomyelitis virus are given in Table I. Mice were given Helenine daily for 4 days beginning the day before virus inoculation. The first, third and fourth doses were injected intraperitoneally while the second dose, given the day of virus inoculation, was injected subcutaneously. In only one experiment with mice did Helenine appear to reduce the incidence of paralysis, but this difference is not significant at the 5% level when the data are analyzed accord-

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