the myotonia occurring spontaneously in man and goat. There is no evidence, however, to establish the identity of the induced and the spontaneous phenomena, similar though they appear. Nevertheless, the demonstrated effect of veratrinic agents on both nerve and muscle suggests that in spontaneous myotonia an as yet undetected repetition may occur in nerve as well as in muscle.

Summary. 1. Both metrazol and DDT evoke a veratrinic response in mammalian nerve and muscle.

2. The characteristics of this response are indistinguishable from those of myotonia occurring spontaneously.

3. The veratrinic effect of repetitive responses to single stimuli is accompanied by a shortening of the relatively refractory period.

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Comparison of Atropine and Tripelennamine in Treatment of Peptone Shock in Dogs.

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Dale and Laidlaw[1] first called attention to the close similarity existing between anaphylactic and peptone shock on the one hand and the type of shock produced by an injection of histamine on the other. Indeed, they postulated that histamine is the substance active in producing the classical signs of anaphylaxis. It was not until 1932, however, that their theory received substantiation, when Dragstedt[2] demonstrated the presence of a substance in blood and lymph in early stages of anaphylactic shock in dogs which resembled histamine chemically and physiologically. It is now generally accepted that histamine plays the major role both in peptone and in anaphylactic shock-like states.

Since the advent of potent anti-histaminic compounds, it has been demonstrated that all drugs which show a marked antagonism to histamine are capable of diminishing the severity of anaphylactic shock.[3] A number of observations, however, would indicate that some factor or factors other than histamine may be involved. For example, Went and Lissak[4] reported that the choline content of the isolated, sensitized heart of the guinea pig decreased following addition of antigen, and, moreover, that acetylation of the perfusion fluid evoked an acetylcholine-like reaction in leech muscle. Furthermore, the isolated, sensitized rodent heart slowed when antigen was added to the perfusing fluid. More recently, Farber and his co-workers[5] found that in 3 of 27 isolated, sensitized hearts (guinea pig) an acetylcholine-like substance was liberated to a perfusate containing physostigmine when the antigen was added. The *normal* heart failed to show the same response. Prior to this, Wenner and Buhrmester[6] reported the acetylcholine concentration in the blood of rabbits in anaphylactic shock to be 1:1,000,000 to 1:10,000,000, whereas measurable amounts were not detected in the blood of normal animals.

The relative importance of acetylcholine in the genesis of peptone and anaphylactic shock

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† Deceased June 28, 1948.

1 Dale, H. H., and Laidlaw, P. P., *J. Physiol.*, 1910, **41**, 318.

2 Dragstedt, C. A., and Gebauer-Fuelnegg, E., *Am. J. Physiol.*, 1932, **102**, 512.

3 Loew, E. R., *Physiol. Rev.*, 1947, **27**, 542.

4 Went, S., and Lissak, K., *Arch. f. Exp. Path.*, 1936, **182**, 509.

5 Farber, S., Pope, A., and Landsteiner, E., Jr., *Arch. Path.*, 1944, **37**, 275.

6 Wenner, W. F., and Buhrmester, C. C., *J. Allergy*, 1937, **9**, 85.

TABLE I.
Pulse Rates Following Administration of Peptone.

Pretreatment	Dose I.V. mg/kg	Exp. No.	Before administ.	During administ.	2-5 min. post-administ.
Atropine • SO_4	2	1	204	180	208
		2	188	168	200
		3	188	176	176
		4	188	152	148
		5	192	180	208
		Avg	192	171	188
Pyribenzamine • HCl	10	1	164	160	180
		2	168	140	180
		3	130	144	140
		4	228	192	268
		5	152	148	160
		Avg	168	157	186
Atropine • SO_4 and Pyribenzamine	2 and 10	1	160	144	150
		2	190	140	208
		3	172	120	184
		4	160	152	188
		5	184	152	192
		Avg	173	142	184
Controls		1	172	160	192
		2	180	180	76
		3	184	144	96
		4	162	140	88
		5	160	140	72
		6	184	160	64
		Avg	174	154	98

has not been assayed, and the present report deals with attempts at a comparison of the beneficial effects of an antiacetylcholine agent and an antihistamine compound in peptone shock.

Methods. Mongrel dogs from a stock supply were anesthetized with sodium pentobarbital given by vein. The left carotid artery was exposed, cannulated, and connected with a U-tube mercury manometer modified for use with the electrical recording system described by Maison and Haterius.[7] Pulse rates were obtained by palpation. All drugs were administered via the femoral vein. Atropine sulfate, 2.0 mg/kg and Tripelennamine (pyribenzamine),‡ 10.0 mg/kg either alone or in combination were used as prepeptone medication. These were administered as 1.0% solutions. Ten to 15 minutes were allowed after the administration of pyribenzamine before peptone was given. Five cc (1.0 g) per kilo of a 20% solution of Witte's peptone was then injected intravenously as rapidly as possible; the time required for the injection was 1.5 to 3 minutes depending upon the total volume used.

Results. Mortality: Of 6 controls, receiving only peptone, 5 died within 5 to 11 minutes after beginning the injection. Of 6 dogs pretreated with atropine, 5 survived; of 5 receiving pyribenzamine all survived, and of 5 receiving both pyribenzamine and atropine there were no deaths. The statistical significance between control and pretreated dogs is great ($P = < .01$) but none exists between methods of pretreatment.

Pulse rates: During the peptone injection, the heart rate in most of the animals slowed 4 to 52 beats per minute from the initial rate. Within 2-5 minutes after the beginning of injection, the pulse rates of those dogs which were to survive increased to a level greater than that prior to administration of peptone. The controls developing fatal shock did not

[7] Maison, G. L., and Haterius, H. O., *J. Assn. Am. Med. Coll.*, 1947, **22**, 200.

‡ The Pyribenzamine was kindly supplied by Ciba Pharmaceutical Products, Inc.

exhibit this increase, but rather showed a constant decrease in rate until death. The changes in pulse rates are apparent from Table I.

Blood pressure: All of the dogs, regardless of the type of pretreatment, showed an initial

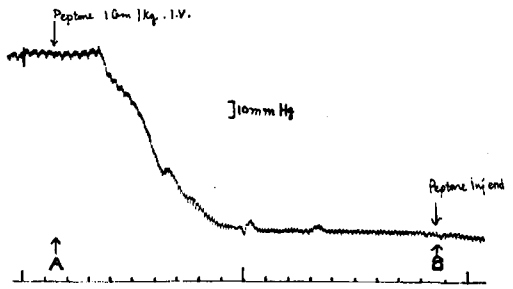

FIG. 1.

A typical example of the effect upon the blood pressure produced by the intravenous injection of peptone, 1.0 g/kg. Injection begun at A, completed at B. Time interval—6 seconds. Pressure at A, 140 mm Hg; pressure at B, 28 mm Hg.

precipitous fall in blood pressure to about 30 mm Hg beginning within 15 to 30 seconds after commencing the peptone injection. Fig. 1 is an example of this initial drop in blood pressure. Continuation of the injection evoked a further fall of only 5 to 10 mm in the treated animals, while the controls showed a progressive decline to zero. In a majority of the surviving animals the blood pressure began to rise in 4 to 10 minutes, reached a peak in 9 to 16 minutes, declined a few millimeters and then began a secondary more gradual rise within 20 to 30 minutes, reaching a plateau in about one hour. (All time intervals given refer to the time elapsed from the beginning of the peptone injection.) This initial rise, as well as the increase in pulse rates to greater than pre-peptone levels, is probably indicative of a generalized sympathetic discharge occurring in response to the profound hypotension. Six animals did not show the initial peak, but exhibited a slow continuous rise to the final plateau. Otherwise they were similar to the remaining animals. A typical example of the blood pressure changes for each of the 3 methods of pre-treatment is given in Fig. 2.

As pyribenzamine potentiates the response to epinephrine,[8] the blood pressure level at 25 minutes post-peptone, (at which time the pressure was at a plateau or just beginning its secondary rise) was used as an indication of the degree of protection afforded by the drugs, since this would minimize the effects of sympathetic discharge which were probably greatest somewhat earlier coincident with marked hypotension. Twenty-five minutes were arbitrarily chosen, because with further recovery the differences between the methods used became less marked. The blood pressure changes are shown in Table II.

None of the 3 methods of treatment prevented the initial fall in blood pressure. Both the height of the initial peak and the pressure at 25 minutes were greater in those treated

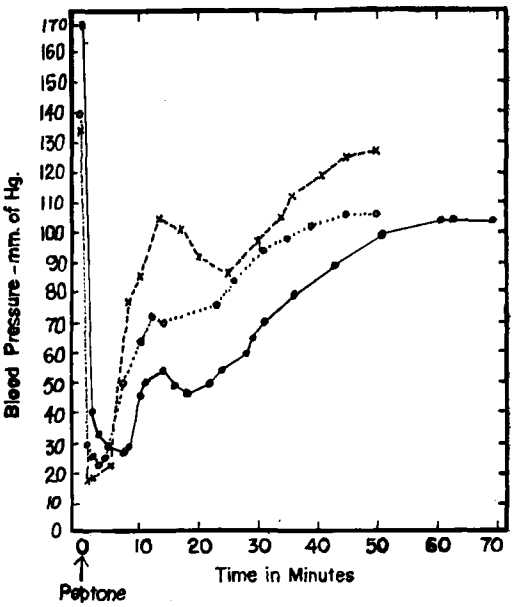

FIG. 2.

Typical blood pressure changes occurring after administration of peptone, 1.0 g/kg body weight. Pretreatment:

●——● Atropine sulfate, 2.0 mg/kg; Exp. No. 2.

x - - - - x Pyribenzamine · HCl, 10.0 mg/kg; Exp. No. 2.

○ · · · · ○ Atropine sulfate, 2 mg/kg, and Pyribenzamine · HCl, 10 mg/kg, Exp. No. 5.

with pyribenzamine alone than in those receiving atropine alone. In the dosages used all 3 methods of treatment protected dogs from death due to peptone. On the basis of blood pressure levels at 25 minutes after the adminis-

[8] Sherrod, T. R., Loew, E. R., and Schloemer, H. F., *J. Pharm. and Exp. Therap.*, 1947, **89**, 247.

TABLE II.
Blood Pressure Following Administration of Peptone.

Pretreatment	Dose I.V. mg/kg	Exp. No.	Blood pressure (mm Hg) Before administ.	2 min. after administ.	25 min. after administ.*
Atropine · SO_4	2	1	138	30	45
		2‡	170	34	56
		3	134	18	44
		4	112	18	10
		5	136	22	96
		Avg	138	24	50
Pyribenzamine · HCl	10	1	126	52	112
		2‡	142	20	88
		3	128	26	104
		4	152	36	76
		5	122	28	88
		Avg	134	32	94
Atropine · SO_4 and Pyribenzamine · HCl	2 and 10	1	80	28	106
		2	68	10	44
		3	144	24	56
		4	136	22	70
		5‡	136	24	80
		Avg	113	22	71
Controls		1	126	10	42†
		2	138	10	—
		3	150	18	—
		4	146	24	—
		5	140	16	—
		6	120	10	—
		Avg	137	15	—

* Statistical evaluation of atropine vs. pyribenzamine (t-test) shows P = .02.
† Only one of 6 controls survived, 5 died in 5 to 11 minutes as blood pressure reached 0 mm Hg.
‡ Data plotted in Fig. 2 as typical examples of each method of treatment.

tration of peptone, pyribenzamine afforded significantly better protection than atropine (P = .02). A combination of the two did not appear to afford better protection than pyribenzamine alone, as the rate of recovery from the hypotensive state was no greater in those receiving both drugs than in those receiving only pyribenzamine.

Discussion. If acetylcholine plays a role in the genesis of anaphylactic and peptone shock, pretreatment with a substance that blocks its action should lessen the severity of reaction. As long ago as 1910 Auer[9] reported atropine to be of value in anaphylactic shock, and obtained a 72% survival in guinea pigs pretreated with atropine before reinjection of the sensitizing serum, as compared with 25% survival in non-atropinized controls. Gross,[10] in finding 0.3 g/kg of Witte's peptone to be the MLD in dogs, reported atropine (0.2 mg/kg) would prevent death in all dogs subjected to 0.5 g/kg of peptone. Atropine in this dosage failed to protect against the lethal effects of 0.6 g/kg. The number of animals used was not stated.

On the other hand, in a report by Vallery-Radot, Mauric and Holtzer,[11] atropine in doses of 0.004 to 0.5 mg/kg did not prevent anaphylactic shock in rabbits. Of 7 animals, 2 (on a dosage respectively of 0.5 mg and 1.0 mg) did not exhibit shock. Despite this the authors concluded that atropine was ineffective in preventing this type of shock. Danielopolou,[12] however, reported atropine to hinder, and eserine to aid, the development of ana-

9 Auer, J., *Am. J. Physiol.*, 1910, **26**, 439.

10 Gross, E. G., *J. Pharm. and Exp. Therap.*, 1926, **30**, 351.

11 Vallery-Radot, P., Mauric, G., and Holtzer, A., *Compt. rend. Soc. de Biol.*, 1943, **137**, 18.

12 Danielopolou, D., *Acta. Med. Scandinav.*, 1944, **118**, 22.

phylaxis. Dosages were not given.

In the present instance, the failure to prevent the initial fall in blood pressure is consistent with the findings of Yonkman, Hays and Rennick[13] in anaphylactic shock. They reported, however, that the heart rate is apparently not increased during the hypotensive phase in anaphylaxis following pretreatment with pyribenzamine—a circumstance with which our results in the case of peptone shock are not in agreement.

One difficulty to be overcome before accepting the hypothesis that acetylcholine plays a role in the production of peptone shock is that, as yet, no drug is available which exhibits antagonism to acetylcholine without possessing some antihistaminic action. Similarly all antihistaminic drugs show a certain degree of antiacetylcholine activity. Various degrees of specificity are possible however. Thus pyribenzamine is 250 times as potent as atropine against histamine as tested by the aerosol method of producing histamine shock in guinea pigs.[14,15] Atropine is much more effective as an anticholinergic drug than is pyribenzamine. In our experience 10.0 mg/kg of pyribenzamine exerted only moderate vagal blockage, as compared with 0.05 mg/kg of atropine required for vagal blocking in the dog.[16]

To protect 100% of sensitized guinea pigs from lethal anaphylaxis, 0.3 mg/kg of pyribenzamine must be given.[15] The exact dosage required to protect dogs has not been determined, but it seems to be somewhat greater. Thus the protective action of 2.0 mg/kg of atropine in peptone shock can hardly be attributed to its antihistaminic properties. It seems much more likely that the benefit derived is a result of its anticholinergic activity.

Although it is generally accepted that histamine plays an important role in anaphylactic and peptone shock, it is possible that acetylcholine is also involved to some extent. The relative importance of histamine and acetylcholine remains to be determined more precisely. More quantitative comparisons between the antihistaminics and anticholinergic drugs are necessary before the question can be resolved, but the greater degree of protection afforded by pyribenzamine than by atropine, as shown in these experiments by the blood pressure changes, is evidence that while histamine plays the major role in the production of peptone shock, apparently acetylcholine is also concerned.

Conclusions. 1) One gram/kg body weight of Witte's peptone administered intravenously in a 20% solution, proved fatal in dogs anesthetized with sodium pentobarbital.

2) Atropine sulfate, 2.0 mg/kg prevented death from peptone.

3) Pyribenzamine, 10.0 mg/kg, afforded better protection than atropine as determined by rapidity of recovery of blood pressure.

4) The rapidity of recovery of blood pressure was not greater in those animals receiving both pyribenzamine and atropine than in those receiving pyribenzamine alone.

5) These findings support the theory that acetylcholine is concerned in the production of peptone shock, although histamine plays a more important role.

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13 Yonkman, F. F., Hays, H. W., and Rennick, B., *Fed. Proc.*, 1944, **4**, 144.

14 Halpern, B. N., *Arch. Internat. de Pharmacodyn. et de Therap.*, 1942, **68**, 339.

15 Mayer, R. L., *J. Allergy*, **1946, 17, 153.**

16 Sollmann, T. H., and Hanzlik, P. J., *Fundamentals of Experimental Pharmacology*, J. W. Stacey, Inc., San Francisco, 1939.