permitted very little manipulation.

Two animals have been sacrificed at regular intervals and specimens taken of each region, for gross inspection and histologic examination. No starch material could be visually identified after the 10th day. Absorption of the gelatin sponges was complete by the 30th day. After 50 days, small yellow nodules of fibrin foam were readily identified; their size indicated considerable but not complete absorption during this period of time. All operative regions appeared normal and well healed.

Details as to techniques, and histologic and experimental results on these and other studies of the gelatin sponge, including a series of neurosurgical investigations with 50 monkeys, are being completed.

The authors wish to express their appreciation to Dr. Glenn C. Bond for the immunologic assays, and to Mr. Stuart L. Long for his assistance in the laboratory and with the animals.

14909

Alleviation of Anaphylactic Shock in Guinea Pigs With Synthetic Benzhydryl Alkamine Ethers.

EARL R. LOEW* AND MARGARET E. KAISER.

From the Division of Pharmacological Research, Parke, Davis and Company Research Laboratories, Detroit, Mich.

Recent studies in this laboratory have shown that synthetic benzhydryl alkamine ethers are capable of preventing fatal asthma induced in guinea pigs by administration of histamine either intravenously or by inhalation of atomized aqueous solutions.[1] The experimental data revealed that the potency of several benzhydryl ethers equalled or exceeded that demonstrated for two Fourneau histamine antagonists, 2-isopropyl-5-methyl-phenoxyethlydiethylamine (929F) and N-phenyl-N-ethyl-N'-diethylethylenediamine (1571F). Staub and Bovet[2-4] and others[5-13] have studied the antihistamine and antispasmodic properties of these Fourneau compounds.

Experiments have been conducted to determine whether benzhydryl ethers are effective in alleviating anaphylaxis in guinea pigs. β-Dimethylaminoethyl benzhydryl ether and β-morpholinoethyl benzhydryl ether, both as hydrochlorides, were selected for this study because of their effectiveness in alleviating histamine-induced asthma.[1]

Methods. Guinea pigs of both sexes weighing 250 to 350 g were passively sensitized by intraperitoneal injection of 0.5 cc of rabbit anti-ovalbumin serum. The rabbits had been

* Present address: Department of Pharmacology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Ill.

1 Loew, E. R., Kaiser, Margaret E., and Moore, V., *J. Pharm. and Exp. Therap.* (In press).

2 Bovet, D., and Staub, A. M., *Compt. rend. Soc. de biol.*, 1937, **124**, 547.

3 Staub, A. M., and Bovet, D., *Compt. rend. Soc. de biol.*, 1937, **125**, 818.

4 Staub, A. M., *Ann. Inst. Pasteur*, 1939, **63**, 400 and 485.

5 Ackerman D., and Wasmuth, W., *Z. f. Physiol. Chem.*, 1939, **260**, 155.

6 Rosenthal, S. R., and Brown, Mary Louise, *J. Immunol.*, 1940, **38**, 259.

7 Climenko, D. R., Homburger, E., and Messer, F. H., *J. Lab. and Clin. Med.*, 1941, **27**, 289.

8 Wilcox, H. B., Jr., and Seegal, Beatrice C., *J. Immunol.*, 1942, **44**, 219.

9 Loew, E. R., and Chickering, O., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 65.

10 Bourque, J. E., and Loew, E. R., *Am. J. Physiol.*, 1943, **138**, 341.

11 Burchell, H. D., and Varco, R. L., *J. Pharm. and Exp. Therap.*, 1942, **75**, 1.

12 Hallenbeck, G. A., *Am. J. Physiol.*, 1943, **139**, 329.

13 Hallenbeck, G. A., Code, C. F., and Mann, F. C., *Gastroenterology*, 1943, **1**, 588.

TABLE I.
Efficacy of Benzhydryl Ethers in Decreasing Percentage Mortality in Guinea Pigs Subjected to Anaphylactic Shock.

Treatment	Dose mg/kg I.P.	Mortality Ratio†	%	P‡	LD-50, I.P. in 100-125 g rats mg/kg	Degree of shock§ 0§	*	**	***	****	F.S.
Untreated controls	—	23/45	51			2	13	6	1		23
Theophylline-ethylene-diamine (Aminophylline	50	1/9	11	<0.01	252		1	6		1	1
N-Phenyl-N-ethyl-N'-diethylethylene diamine hydrochloride (1571F)	3	2/13	15	<0.01	142	1	1	7	2		2
β-Dimethylamino-ethyl benzhydryl	3	1/14	7.1	<0.01	82		5	4	3	1	1
ether hydrochloride	12	1/15	6.6	<0.01		2	6	6			1
β-Morpholinoethyl	3	5/14	36	0.3			2	6	1		5
benzhydryl ether	6	6/15	40	0.3		2	3	2	1	1	6
hydrochloride	12	0/12	0	<0.01	185	1	3	7	1		

† Mortality ratio = $\frac{\text{No. died}}{\text{No. used}}$

‡ P values taken from Fisher's table; value less than 0.05 indicates significant difference.

§ 0, no symptoms.

* Teeth chattering, fur ruffled.

** Sneezing, dyspnea, excitation.

*** Urination, defecation, convulsions, gasping, cyanosis.

**** Severe shock, collapse, coma, gasping, cyanosis.

F.S., fatal shock.

immunized with crystalline ovalbumin† by injecting 1.0 cc of a 0.2% solution intravenously 3 times weekly for 3 or 4 weeks, at which time the antibody titer of the blood serum was considered to be sufficiently high as indicated by the fact that precipitins were demonstrated with serum dilutions of 1:100.

Twenty-four hours after passive sensitization of the guinea pigs anaphylactic shock was induced by a shocking dose of 2.0 cc of 0.2% aqueous solution of crystalline ovalbumin. The jugular vein was exposed under local anesthesia produced by subcutaneous infiltration of 1.0 cc of 1.0% procaine. Intrajugular injections of antigen were made into untreated control animals and into those which had received an intraperitoneal injection of a drug 15 min previously.

Results. The data (Table I) reveal that each of the chemical compounds in adequate dosage was effective in significantly reducing the incidence of fatal anaphylactic shock in sensitized guinea pigs. By comparison with the other compounds, the dose of aminophylline used to demonstrate anti-anaphylactic action was large but probably necessary in view of its low potency.[14, 15] β-Dimethylaminoethyl benzhydryl ether and 1571F were effective in reducing mortality when doses of 3.0 mg/kg were administered. Lower doses were not employed so the exact relative potency of these two compounds was not determined. β-Morpholinoethyl benzhydryl ether did not exhibit definite anti-anaphylactic activity with doses of 3.0 and 6.0 mg/kg but activity was demonstrated with a dose of 12.0 mg/kg. It is therefore concluded that β-dimethylaminoethyl benzhydryl ether is more than twice as active as β-morpholinoethyl benzhydryl ether in alleviating anaphylactic shock.

The acute toxicity (Table I) of β-morpholinoethyl benzhydryl ether is approximately one-half that of β-dimethylaminoethyl benzhydryl ether but because of the high potency of the latter compound its therapeutic index is greater.[1]

† Supplied through the kindness of Dr. Gertrude Rodney, Department of Immunochemistry, Parke, Davis and Company, Detroit, Mich.

[14] Young, R. H., and Gilbert, R. R., *J. Allergy*, 1941, **12**, 235.

[15] Emmelin, N., Kahlson, G. S., and Lindstrom, K., *Acta physiol. Scandinav.*, 1941, **3**, 39.

Although the incidence of mortality in guinea pigs subjected to anaphylactic shock was significantly reduced by each of the compounds a complete suppression of symptoms was not observed. In most instances, however, small doses of drugs were purposely employed in order to increase the possibility of obtaining mortality data which would permit more accurate determination of the relative potency of the compounds.

Discussion. The anti-anaphylactic efficacy of aminophylline demonstrated in these experiments corroborates findings reported by Young and Gilbert[14] who employed intravenous doses of 30 to 60 mg/kg to reduce the mortality in guinea pigs subjected to histamine shock or anaphylactic shock. Emmelin *et al.*[15] were cognizant of the fact that the antihistamine or anti-anaphylactic activity exhibited by aminophylline and other xanthines was much inferior to that described for synthetic histamine antagonists such as N-phenyl-N-ethyl-N'-diethylethylenediamine (1571F) and 2-isopropyl-5-methyl-phenoxyethyldiethylamine (929F). Our findings relative to the marked effectiveness of 1571F in alleviating anaphylactic shock are in agreement with published data.[4,8]

Of the two ethers studied, β-dimethylaminoethyl benzhydryl ether proved to be more than twice as active as β-morpholinoethyl benzhydryl ether in reducing mortality in guinea pigs subjected to anaphylactic shock. With the atomized histamine technique approximately the same relative degree of potency was demonstrated.[1] It was also shown that β-dimethylaminoethyl benzhydryl ether, in doses of 3.0 mg/kg intraperitoneally, was capable of protecting against the lethal effect of intravenous injections of histamine. It is evident, therefore, that benzhydryl ethers, in small doses, are capable of reducing mortality of guinea pigs either following administration of histamine intravenously and by inhalation as an atomized aqueous solution or following liberation of histamine from tissues during the antigen-antibody reaction such as occurs in anaphylaxis.[16]

We have reported (1) that β-dimethylaminoethyl benzhydryl ether is twice as effective as 1571F in alleviating bronchoconstriction induced in guinea pigs by inhalation of atomized histamine. The data regarding anti-anaphylactic activity of these two compounds do not permit a precise determination of relative potency, but it is apparent that they are probably the most potent compounds studied thus far.

In view of the fact that these synthetic benzhydryl ethers are effective in alleviating both histamine shock and anaphylactic shock the data constitute additional indirect evidence that the chief symptoms of anaphylaxis are referable to histamine.

Summary. The hydrochlorides of β-dimethylaminoethyl- and β-morpholinoethyl benzhydryl ether proved to be markedly effective in alleviating anaphylactic shock in guinea pigs. The potency of the former compound may equal or exceed that of 1571F, the most effective Fourneau histamine antagonist. These antispasmodic benzhydryl ethers should prove useful in studies dealing with the role of histamine in various physiological mechanisms and pathological conditions.

[16] Dragstedt, C. A., *Physiol. Rev.*, 1941, **21**, 563.