possibility of bacterial infection.

Three more sets of experiments were carried out by following the same procedure. These experiments confirmed fully the results described above and gave further information since in one instance virus was recovered from the 24-hour fecal specimen representative of the seventh day after a single feeding of virus.

Discussion. Under the experimental conditions described in the present paper, cockroaches fed a single meal known to contain the virus of spontaneous mouse encephalomyelitis, GD VII strain, excreted daily over a period of as long as 7 days sufficient virus to kill on intracerebral injection the test recipient normal mice. Thus, it is possible that this species of cockroach, and others, in the natural process of feeding on mammalian excreta may acquire virus from the host carrier for later transfer by contamination of food. From the available data it is impossible to say whether these findings have any practical implication in the epidemiology of mouse encephalomyelitis or of other members of the polio-encephalomyelitis group of virus diseases. It is surprising that natural or experimental evidence to suggest a role for cockroaches in the dissemination of virus diseases is limited to the experimental findings of Hurlbut(11) which appeared at the time this manuscript was in preparation. He found that the injection of human poliomyelitis virus, Lansing strain, into the hemocoele of the cockroach, *Periplaneta americana,* made it possible 15 days later to demonstrate virus by the trituration of the whole cockroach and its passage to normal mice. Attempts to demonstrate virus in roach feces and in roach eggs were unsuccessful. However, the possibility that cockroaches can operate to transmit pathogenic microorganisms other than viruses has been established for bacteria under experimental and natural conditions (12-14).

Summary. In experiments in which cockroaches, *Periplaneta americana,* were fed a single meal containing the virus of mouse encephalomyelitis, GD VII strain, proof was obtained that the test cockroaches daily over a period of as many as 7 days excreted sufficient virus to kill test mice. Control experiments showed that the lethal effect was from infection by the virus of mouse encephalomyelitis, GD VII strain, and not from extraneous bacterial or viral infection.

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Influence of Diphenhydramine on Blood Pressure Response to Epinephrine in the Dog under Adrenergic Blockade. (17883)

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A variety of substances have been shown to potentiate the vasopressor effect of epinephrine: *vis.* diphenhydramine·HCl, cocaine, ergotamine, curare, dibutoline, tetraethylammonium chloride (T.E.A.) and a number of ethylene diamine derivatives(1,2,3,4,5,6,7, 8). Two theories have been suggested for

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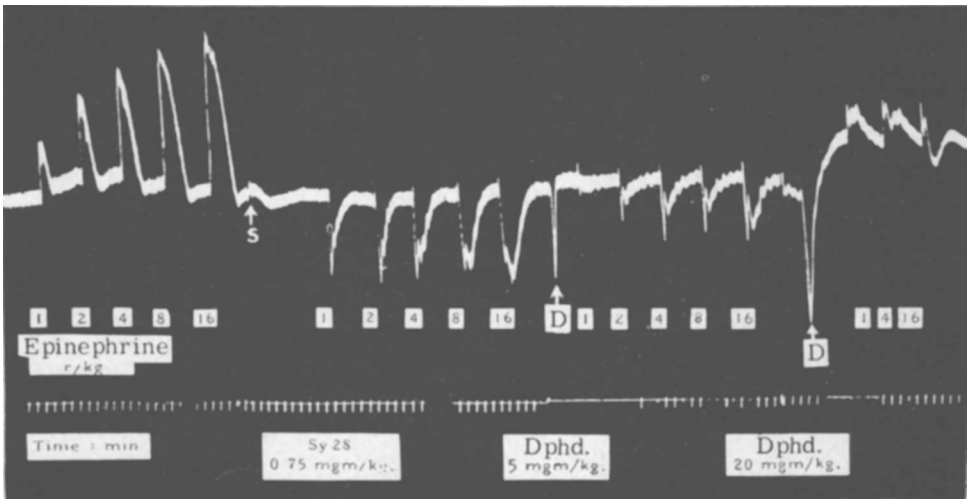

FIG. 1.
Influence of SY-28 and diphenhydramine on the effect of epinephrine on blood pressure in the dog. Pentobarbital anesthesia.

their mode of action: (a) inhibition of the enzymatic destruction of epinephrine, and (b) increase of permeability of sympathetically innervated cells(9,10). However, direct experimental evidence to support these hypotheses is lacking. In the case of T.E.A., the increased vasopressor effect of epinephrine is said to be due to its ganglionic blocking action abolishing the compensatory reflexes (11). In a preliminary report(12), it was mentioned that diphenhydramine can convert the "epinephrine reversal" of blood pressure to a pressor response. In this communication, data are presented to show the influence of diphenhydramine and some other agents on the vascular action of epinephrine and arterenol in dogs under adrenergic blockade. In light of these findings, the action of diphenhydramine in reversing the vasodepressor and in potentiating the vasopressor response to sympathomimetic agents will be elucidated.

Experimental. Dogs under pentobarbital anesthesia were used in our experiments. Blood pressure was measured from the carotid artery; injections were given in the femoral vein.

Results. The effect of diphenhydramine on the "epinephrine reversal" of blood pressure is shown by the kymographic recordings in Fig. I. The dog was injected at 5 minute intervals with increasing doses of epinephrine, followed by 0.75 mg/kg of N-(2-bromoethyl)-N-ethylnaphthalenemethylamine · HBr (SY-28). Ten minutes later the epinephrine injections were repeated. Being an adrenergic blocking agent, SY-28 reverses the vasopressor effect of epinephrine. Five milligrams per kilo of diphenhydramine was then injected. Subsequently the vasodepressor effect of epinephrine was first decreased, then converted to a pressor effect after a total dose of 20 mg/kg of diphenhydramine · HCl. Similar results were obtained for the vascular action of arterenol under the influence of diphenhydramine and SY-28. The vasopressor response to arterenol can be completely reversed by SY-28 (1 mg/kg); the maximal

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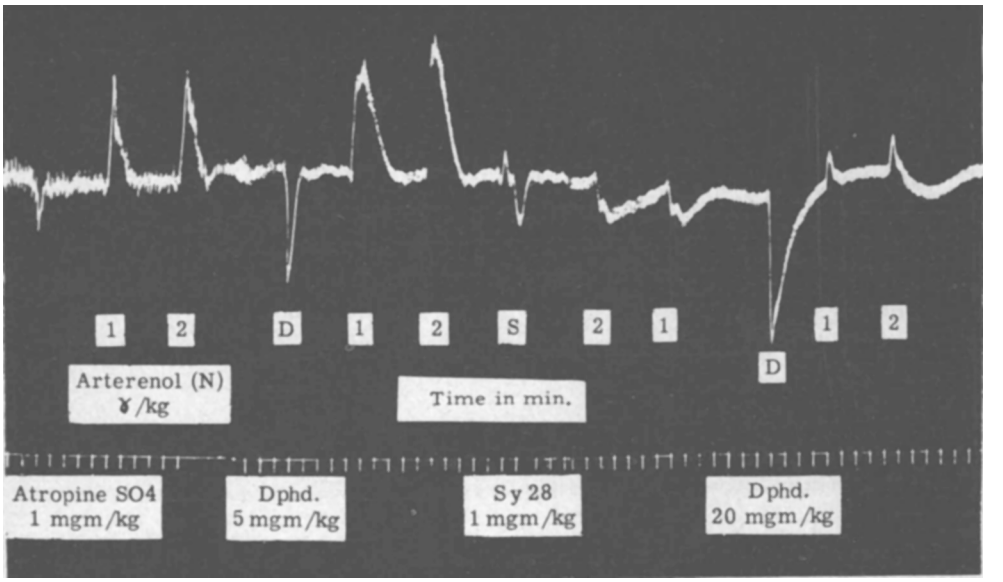

FIG. 2.
Influence of SY-28 and diphenhydramine on the effect of arterenol on blood pressure in the dog. Pentobarbital anesthesia.

vasodepressor effect is, however, only about 1/5 that of epinephrine (Fig. 2).

A number of compounds possessing the pharmacological properties of diphenhydramine were also investigated. The results are given in Table I. One salient feature revealed by the data is that compounds which reverse the vasodepressor response are also capable of potentiating the vasopressor response to epinephrine. Cocaine, diphenhydramine and ergotamine have been shown likewise to produce potentiation of the vasopressor action of arterenol(13,14). In agreement with the observation of others(15,16,17,18) we found ergotamine in pentobarbitalized dogs potentiated, in etherized animals reversed the vasopressor effect of epinephrine. It converts the vasodepressor response following N-isopropyl arterenol to a vasopressor effect in pentobarbitalized dogs. Resembling ergotamine, diphenhydramine (30 mg/kg) reduces the vasodepression produced by 1-2 μg per kilo of N-isopropyl arterenol and in some dogs converts it to a pressor effect.

Discussion. How diphenhydramine reverses the vasodepressor response to epinephrine is not understood. The anticholinergic, antispasmodic and antihistaminic properties of diphenhydramine are not responsible for this action, for atropine, papaverine and 2-n-propoxy-4, 6-diamino-s-triazine are ineffective in reversing the vasodepressor effect of epinephrine. The reversal of the vasodepressor response cannot be due to an increase in elimination of SY-28 in the presence of diphenhydramine or due to competitive inhibition on the same receptors upon which SY-28 acts. If either were the case, there should be expected a graded effect to epinephrine at different dose levels. Instead, as indicated in Fig. 1, after SY-28 and diphenhydramine the vasopressor effects of different doses of epinephrine are the same.

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TABLE I.
Reversal of Vasodepressor Effect of Epinephrine on Dog's Blood Pressure.
*SY-28 (Sympatholytic) = 0.75 mg/kg
Epinephrine = 1 γ/kg

	Compound	mg/kg I.V. (total dose)	Effect reversal
1.	Diphenhydramine†	10	Partial
		30	Complete
2.	P-methyl substituted derivative of diphenhydramine†	10	Partial
		30	Complete
3.	Cocaine†	20	Partial
		50	Complete
4.	Tripelennamine†	10	Partial
		45	Complete
5.	Pyranisamine maleate†	15	,,
6.	d-Tubocurarine†	0.25	,,
7.	Dibutoline • SO_4†	10.0	,,
8.	Ergotamine†	0.2	,,
9.	T.E.A.†	5	No
		20	Partial
10.	Atropine	35	No
11.	Papaverine	5	,,
12.	2-N-propoxy-4,6-diamino-s-triazine	105	,,

* N-(2-Bromoethyl)-N-ethyl-naphthalenemethylamine • HBr.
† Compounds which also potentiate the vasopressor effect of epinephrine.

This same rise of blood pressure may be due to the effect of epinephrine on the heart(19).

The action of diphenhydramine on the vasodepressor response to epinephrine can neither be explained by the increase of permeability of sympathetically innervated cells nor by an inhibition of the enzymatic destruction of epinephrine, for if so, a greater depressor response to epinephrine should be expected. The increase of the vasopressor effect of epinephrine by diphenhydramine may be through its antagonistic action on the vasodepressor mechanism in response to epinephrine. Since the blood pressure changes by epinephrine represent a composite picture of both the pressor and the depressor response(20), the results in Fig. 1 and 2 may be interpreted as follows: SY-28 blocks the vasopressor receptors while diphenhydramine antagonizes the response of the vasodepressor effectors. With sufficient quantities of the two, the action of epinephrine (or arterenol) on the sympathetic neuro-effectors (both vasoconstrictor and vasodilator) may be completely inhibited; the blood pressure response then is principally due to its chronotropic and inotropic action on the heart, as indicated by the last portion of the graph.

With the information now available it is not possible to state the site of action of diphenhydramine on the vasodepressor mechanism whether the peripheral vasodilator receptors or the central nervous pathway. The various agents which reverse the vasodepressor effects of epinephrine and arterenol may do so by acting on the different sites of the neurovascular system. The fact that they also potentiate the pressor effect of epinephrine and arterenol suggests that potentiation of the vasopressor response may be due to an inhibition on the vasodepressor effectors by these substances.

Conclusion. Diphenhydramine was found to convert the vasodepressor effect of epinephrine and arterenol in the dog under adrenergic blockade with SY-28 to a vasopressor effect. The para-methyl substituted derivative of diphenhydramine as well as cocaine, tripelennamine, pyranisamine maleate, d-tubocurarine, dibutoline and ergotamine can produce the same effect. Atropine (anticholinergic), papaverine (antispasmodic) and 2-N-propoxy-4,6-diamino-s-triazine (antihistaminic) are ineffective. An inhibition of

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the vasodepressor mechanism is suggested as a possible mode of action of these compounds on the reversal of the vasodepressor response and the potentiation of the vasopressor response to epinephrine and arterenol.

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Response of Circulating Eosinophils to Nor-Epinephrine, Epinephrine and Emotional Stress in Humans. (17884)

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The diminution of the number of circulating eosinophils after subcutaneous injection of epinephrine is believed to be due to an increased secretion of adreno-cortical glucocorticoids, elicited by a discharge into the blood of adrenocorticotrophic hormone(1,2) which, in turn, constitutes a typical reaction to injected or secreted epinephrine(3,4). On the other hand, it is becoming increasingly apparent that l-nor-epinephrine plays a prominent role in the manifestations of sympathetic stimulation as the specific chemical neuro-transmitter of the sympathetic system (5) and as a secretory by-product of the adrenal medulla(6,7). It seemed of interest therefore to investigate the following questions: (a) Does nor-epinephrine exert an analogous effect upon the pituitary-adrenocortical system as its methylated homologue epinephrine? (b) Are the neurovegetative phenomena of emotional stress attributable mainly to discharges of epinephrine from the adrenal medulla or to neuro-secretory discharges of nor-epinephrine?

Methods. Twelve patients with various disorders but not acutely ill, were tested to compare the response of the circulating eosinophils to equal amounts (by weight) of subcutaneously injected natural l-epinephrine* and synthetic l-nor-epinephrine† (0.25 mg of each). Blood samples from the finger tip were taken early in the morning for the initial eosinophil counts and the injections were administered immediately thereafter. Four hours later the eosinophil counts were repeated. No nourishment was taken preceding and during the tests. In 24 healthy medical students in the fasting state, finger tip blood samples for eosinophil counts were taken in the morning, 5 to 20 minutes before the students were to begin their mid-year examinations. Blood pressure and pulse rate were also recorded (after only a few minutes rest in sitting position). Several weeks later when no examinations were in sight the same students were again tested in the same manner. In all instances the direct eosinophil counts were carried out according to the method employed by Forsham *et al.*(2). However, the staining method of Randolph(9), as modified by Henneman *et al.*(10), was used in-

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* Adrenaline hydrochloride Parke & Davis was used, which contains besides l-epinephrine an estimated 10-19% admixture of l-nor-epinephrine(8).

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† We are indebted to Dr. M. L. Tainter of Sterling-Winthrop Research Laboratories for l-arterenol bitartrate (l-nor-epinephrine).