Brit. J. Pharmacol. (1949), **4**, 281.

SOME PHARMACOLOGICAL PROPERTIES COMMON TO ANTIHISTAMINE COMPOUNDS

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(Received July 2, 1949)

In recent communications (Dutta, 1948; Burn and Dutta, 1948; Dutta, 1949) it has been shown that β-dimethylaminoethyl benzhydryl ether hydrochloride ("Be adryl," Parke, Davis and Co., Ltd.) possesses some pharmacological properties in common with atropine, pethidine, procaine, and quinidine; it produces a fall of body temperature in mice, abolishes the constrictor action of adrenaline and histamine on the perfused vessels of the rabbit's ear, and relieves histamine-induced bronchoconstriction in the guinea-pig. It was also demonstrated that 2-(N-phenyl-N-benzylaminomethyl)iminazoline hydrochloride ("Antistin," Ciba, Ltd., or "Histostab," Boots' Pure Drug Co., Ltd.) shares some of these properties, for it, too, antagonizes the action of adrenaline on the rabbit ear vessels and is only slightly less effective than benadryl in alleviating bronchial constriction in guinea-pigs after the intravenous injection of histamine. The investigation of these substances has since been continued, and in this paper the actions of β-dimethylaminoethyl benzhydryl ether hydrochloride (which will be called benadryl) and 2-(N-phenyl-N-benzylaminomethyl)iminazoline hydrochloride (which will be called antistin) on cardiac and skeletal muscle and on ganglionic transmission are described. The results of an investigation of benadryl on gastric acidity induced by histamine are also presented.

Local anaesthetic action

The majority of the common antihistamine substances are local anaesthetics. This has been shown to be true for benadryl (Leavitt and Code, 1947) and antistin (Brack, 1946) in man and in frogs (Reuse, 1948). Graham (1947) referred to the local anaesthetic action of these substances on guinea-pigs but did not give any details of his findings. In the present investigation the strength of these substances was determined in relation to procaine by the intracutaneous weal method in guinea-pigs described by Bülbring and Wajda (1945). In guinea-pigs the sensitiveness of the different areas of the skin on the back varies considerably. In order to reduce this to a minimum, Somers and Edge (1947) suggested the use of a statistical design of Latin squares for the arrangements between the doses and the sites at which the substances are to be injected. This was adopted. Three animals were used for each comparison. The back of each guinea-pig was divided into 9 squared areas. Procaine, antistin, and benadryl were injected intradermally in three different concentrations (for each substance) on three consecutive days. All these compounds were given at the same dose level on any one day, and each animal received each substance but at different sites. This is shown in Table I. On the first day of the test guinea-pig 1 received low doses of procaine, antistin, and benadryl in the front, middle, and rear part of the back respectively on the left-hand side. The reaction to 6 pin-pricks was

TABLE I

EXPERIMENTAL DESIGN, SHOWING THE POSITION OF THE INJECTIONS ON THE BACK OF THE GUINEA-PIGS

	Areas	Guinea-pigs 1	2	3
1st day—low dose ...	α	P	B	A
	β	A	P	B
	γ	B	A	P
2nd day—middle dose	α	A	P	B
	β	B	A	P
	γ	P	B	A
3rd day—high dose...	α	B	A	P
	β	P	B	A
	γ	A	P	B

α = front. β = middle. γ = back. P = procaine. A = antistin. B = benadryl.

TABLE II

NUMBER OF PRICKS (OUT OF 36) FAILING TO ELICIT A RESPONSE AFTER INTRACUTANEOUS INJECTION OF PROCAINE, ANTISTIN, AND BENADRYL IN THE GUINEA-PIG

Compounds:	Procaine hydrochloride			Antistin			Benadryl		
Concentration in per cent (w/v):	0.1	0.25	1.0	0.04	0.1	0.25	0.04	0.1	0.25
Pig 1	8	7	30	6	7	29	5	8	31
,, 2	13	20	26	4	20	29	7	26	24
,, 3	4	21	36	8	16	31	12	20	36
,, 4	5	18	22	3	9	5	3	18	15
,, 5	5	16	31	4	15	35	4	20	24
,, 6	10	7	36	11	17	12	7	21	36
Mean:	7.5	15	30	6	14	23.5	6.3	19.0	27.6

determined at each site every five minutes. The total number of times a prick failed to produce a response in the course of half an hour, out of a possible 36, indicated the degree of anaesthesia in that particular spot. Next, guinea-pig 2 was injected with benadryl in the front, procaine in the middle. and antistin in the rear part on the left squared areas as before and so on. On the second day the injections were given in the middle areas and on the third day on the right-hand side squares. Two complete series of experiments were carried out with 6 guinea-pigs.

There were 54 individual comparisons at different sites on 6 guinea-pigs. The results are summarized in Table II. Each of the figures in Table II (except at the bottom line) represents the total number of pricks, out of 36, which failed to elicit a response at a given site during the half-hour observation. The mean values for the six experiments are given at the base line. Variation in the sensitiveness of the different areas of the skin is evident if some of the individual figures are examined. For instance, antistin in 0.25 per cent concentration produced less effect than in 0.1 per cent in guinea-pig 4. Similar results were also obtained from guinea-pig 6. The higher concentration of benadryl caused a lower degree of anaesthesia than the lower concentration of the drug on guinea-pig 4. These are the extreme examples.

When the mean figures indicating the degree of anaesthesia for any one of the given substances (shown in Table II) are plotted as ordinates against its logarithmic concentrations as abscissae, a linear relationship is obtained. This is illustrated in Fig. 1. The slopes of the lines for procaine, antistin, and benadryl are approximately parallel within the doses mentioned above. This parallelism did not exist when higher concentrations of antistin or lower doses of benadryl were used. At dose levels where all the three substances prevented 50 per cent of the skin reactions, benadryl was 3.2 times and antistin 2.3 times as potent as procaine.

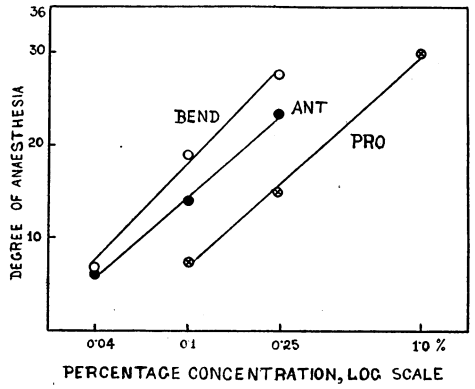
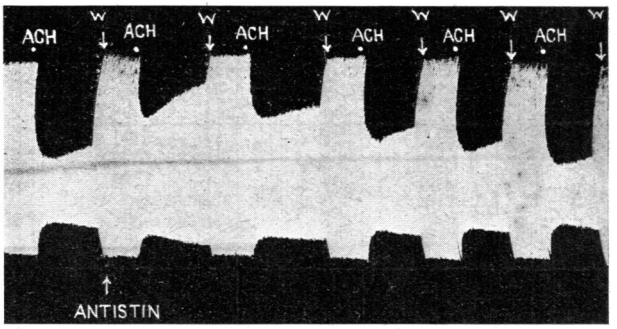


FIG. 1.—Intracutaneous weal in guinea-pigs. The graph shows the relation between the concentration of the local anaesthetic (abscissae) and the number of times there was no response to a prick; total 36 pricks in 30 min. (ordinates). Each point represents the mean of six observations. BEND = benadryl; ANT = antistin; PRO = procaine hydrochloride.

Antagonism to acetylcholine on cardiac muscle

It is known that both antistin and benadryl antagonize certain actions of acetylcholine, and consequently whether they would also antagonize acetylcholine on the isolated rabbit's auricles beating in oxygenated Ringer-Locke's solution at 29° C. was investigated. Both these substances reduced



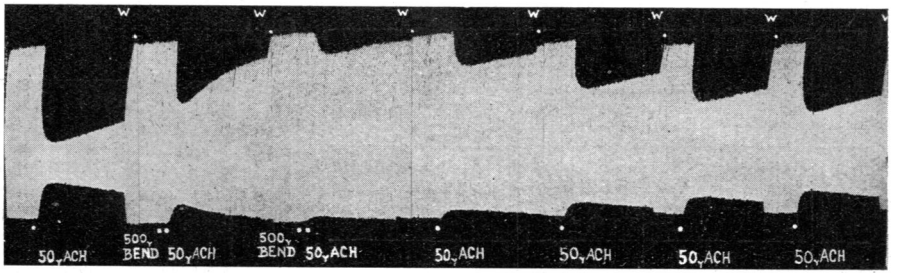


FIG. 2.—Isolated rabbit auricles. Ringer-Locke's solution at 29° C.; 50 ml. bath. *Upper record:* Depression caused by 10 μg. acetylcholine for 2 min. (at the end of which the solution was changed, W) at 6-min. intervals. The second dose of acetylcholine was preceded 1 min. before by 500 μg. antistin. The inhibition due to acetylcholine was reduced. *Lower record:* Depression caused by 50 μg. acetylcholine for 2 min. (at the end of which the solution was changed, W) at 5-min. intervals; 500 μg. benadryl was given 40 sec. before both the second and third doses of acetylcholine. The effect of acetylcholine was greatly diminished in the presence of benadryl.

the depression caused by acetylcholine on the auricular contractions. Repeated washings were required before the inhibition produced by acetylcholine was fully recovered. The experiments are illustrated in Fig. 2.

Effect on the refractory period of the cardiac muscle

Dawes (1946) stated that the quinidine-like action of a substance is associated with its ability to oppose the action of acetylcholine. Benadryl and antistin were, therefore, tested on the isolated rabbit's auricles stimulated electrically in order to determine whether their power to antagonize the action of acetylcholine was associated with a quinidine-like action. The method followed was that of Dawes. The isolated rabbit's auricles were suspended in a 100 ml. bath of oxygenated Ringer-Locke's solution (containing double the usual amount of glucose) at 29° C. The effect of benadryl is illustrated in Fig. 3. Before addition of benadryl to the bath the auricles were able to follow 252 stimuli per min. but not 260 per min. or more. After 100 μg. benadryl had been added to the bath the auricles first followed stimulation at 184 per min. but not at 204 per min. and finally followed 200 per min. Benadryl, therefore, in a concentration 1 in 1,000,000 reduced the maximal rate by 20.6 per cent. The relation between the percentage decrease in the maximal rate at which the auricles could follow electrical stimuli and the logarithm of concentrations is linear. Similar results were obtained with antistin. The results of all the experiments are summarized in Table III. Unlike antistin, the effect of benadryl on the auricles is more persistent; therefore, when its action was compared with that of quinidine, not more than two doses of each of the substances were used on any individual preparation. Benadryl and antistin are about twice as active as quinidine at the level at which the three substances reduce the maximal rate by 15 per cent.

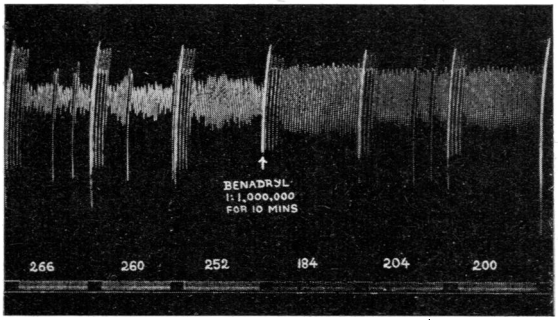


FIG. 3.—Isolated rabbit auricles stimulated by break induction shocks. Ringer-Locke's solution at 29° C., bath 100 ml. The auricles fail to follow up to 260 stimuli per min., but follow 252 per min. After 10 min. exposure to 1: 1,000,000 benadryl at the arrow (the drum was stopped for 9 min.) the auricles follow up to 200 but fail to follow 204 stimuli per min.

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TABLE III

COMPARISON OF BENADRYL, ANTISTIN, AND QUINIDINE ON THE "DRIVEN" RABBIT AURICLE

Exp. No.	Substances	Conc.	Percentage reduction in the maximal rate at which the auricles followed
4	Benadryl	10^{-6}	10.5
	,,	2×10^{-6}	16.6
	,,	4×10^{-6}	23.0
	,,	8×10^{-6}	27.5
5	Benadryl	10^{-6}	20.6
	,,	2×10^{-6}	39,3
	Quinidine HCl	10^{-6}	8.2
	,, ,,	2×10^{-6}	29.0
6	Benadryl	4×10^{-6}	10.0
	,,	8×10^{-6}	14.1
		1.6×10^{-6}	23.0
7	Benadryl	10^{-6}	13.1
	,,	2×10^{-6}	20.2
	Quinidine HCl	10^{-6}	8.4
	,, ,,	2×10^{-6}	14.0
8	Quinidine HCl	10^{-6}	10.5
	,, ,,	2×10^{-6}	18.2
	Benadryl	2×10^{-6}	22.2
	,,	4×10^{-6}	30.0
9	Antistin HCl	10^{-6}	6.9
	,, ,,	2×10^{-6}	13.6
	,, ,,	4×10^{-6}	29.6
	Quinidine HCl	2×10^{-6}	12.5
	,, ,,	4×10^{-6}	17.0
		8×10^{-6}	27.0
10	Antistin HCl	10^{-6}	3.2
	,, ,,	2×10^{-6}	16.0
	,, ,,	4×10^{-6}	21.5
	Quinidine HCl	2×10^{-6}	10.9
	,, ,,	4×10^{-6}	12.5
	,, ,,	8×10^{-6}	15.3
11	Antistin HCl	10^{-6}	3.6
	,, ,,	2×10^{-6}	6.4
	,, ,,	2×10^{-6}	12.8
	Quinidine HCl	2×10^{-6}	3.9
	,, ,,	4×10^{-6}	7.0
	,, ,,	8×10^{-6}	12.5
12	Antistin HCl	2×10^{-6}	9.5
	,, ,,	4×10^{-6}	13.7
	,, ,,	8×10^{-6}	16.4
	Quinidine HCl	2×10^{-6}	9.0
	,, ,,	4×10^{-6}	12.5
	,, ,,	8×10^{-6}	17.4

Antagonism to acetylcholine on skeletal muscle

These observations were first made on the skeletal muscle of the frog. A strip from the frog's (*Rana temporaria*) rectus abdominis was suspended in the oxygenated frog-Ringer solution in a 5 ml. bath at room temperature. The solution was replaced every three minutes by the frog-Ringer solution containing a known concentration of acetylcholine which was allowed to act for 90 sec. Benadryl (Fig. 4) reduced the stimulant action of acetylcholine on the muscle. Similar results were obtained with antistin. The response to 10^{-5} acetylcholine was considerably diminished after exposure of the muscle to 10^{-4} antistin for 3 min.

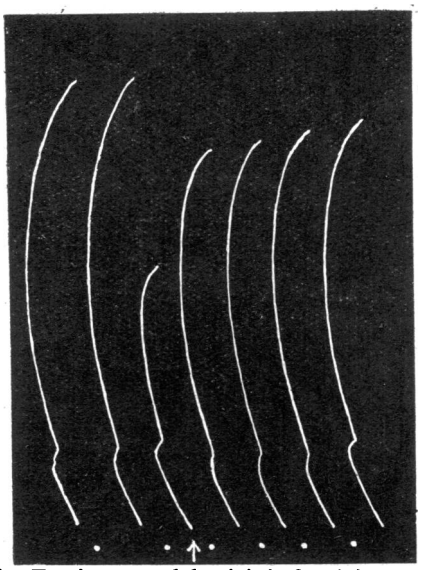

FIG. 4.—Frog's rectus abdominis in frog-Ringer solution at room temperature. The contractions are due to 2×10^{-6} acetylcholine for 90 sec. every 3 min. The contraction at the arrow was preceded by 30 sec. exposure to 2×10^{-5} benadryl.

The effects of these substances were also studied on the isolated phrenic-diaphragm preparation of the rat (Bülbring, 1946). The technique followed was the same as described in the previous paper (Dutta, 1949). The action of antistin is shown in Fig. 5. In a concentration 4×10^{-5}, antistin increased the height of contractions elicited by single, maximal nerve stimulation by about 20 per cent (Fig. 5*a*). After the preparation had been washed out, antistin produced the same effect when direct stimulation was applied (Fig. 5*b*). After the preparation had been washed out again, the addition of 100 μg. of *d*-tubocurarine chloride to the bath

abolished the response of the muscle to nerve stimulation (Fig. 5*c*) but not to direct stimulation (Fig. 5*d*); the addition of the same amount of antistin to the bath was followed by increased muscle twitches as before. Before the wash-out (W), the stimulation of the nerve had no effect. The contractions began to return some time after the Tyrode solution had been changed again (W). This is shown on the right-hand side of the record (Fig. 5*d*). In higher concentrations antistin caused a curare-like depression of the rat diaphragm. The minimum concentration necessary to demonstrate this varied with different preparations. In the experiments illustrated in Fig. 6B, the effect of antistin in a concentration 1.6×10^{-4} was most pronounced. Depression of the muscle was observed with only one quarter of this concentration in other experiments. When the concentration of antistin was high enough to cause marked diminution of the twitch tension of the rat diaphragm, the initial stimulatory stage was seldom missed. However, this was barely evident in the experiment reproduced in Fig. 6B.

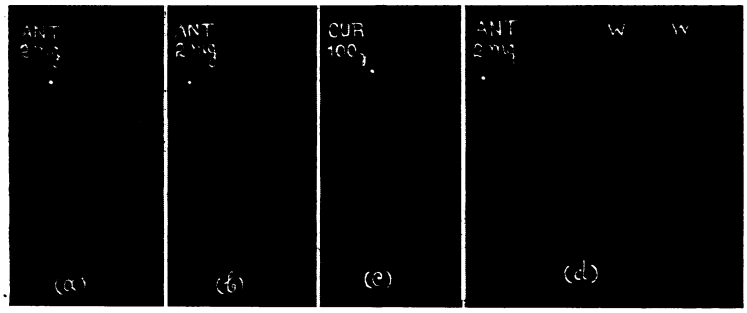

FIG. 5.—Rat diaphragm phrenic nerve preparation in Tyrode solution, 37° C., 50 ml. bath. Single, maximal shock, 7 per min., 0.7 millisecond. Tyrode solution changed between (*a*) and (*b*) and between (*b*) and (*c*). (*a*) Indirect stimulation: 2 mg. antistin increased the muscle contractions. (*b*) Direct stimulation: 2 mg. antistin had the same effect as in (*a*). (*c*) Indirect stimulation: progressive paralysis of the muscle to nerve stimulation after 100 μg. *d*-tubocurarine chloride. (*d*) Direct stimulation: 2 mg. antistin still enhanced the contractions. Before being washed out (W) the muscle gave no response to indirect stimulation, but the contractions began to return after the second washing out, as shown in the right-hand side of the record.

The action of benadryl was very similar to antistin. This substance in a concentration 4×10^{-5} augmented the contractions of the rat diaphragm by 78 per cent on indirect stimulation and by 50 per cent when the muscle was stimulated directly. After the diaphragm had been made insensitive to nerve stimulation by the addition of 100 μg. of *d*-tubocurarine chloride to the bath, the same concentration of benadryl still increased the muscle twitches in response to direct stimulation by 23 per cent. In these experiments the rate of stimulation was 7 per min., the duration of each stimulus being 0.7 millisec. Benadryl in a concentration 4×10^{-5} also caused depression of the contractions in response to nerve stimulation. This decline in the height of muscle twitches was usually preceded by a period of augmentation (Fig. 6D).

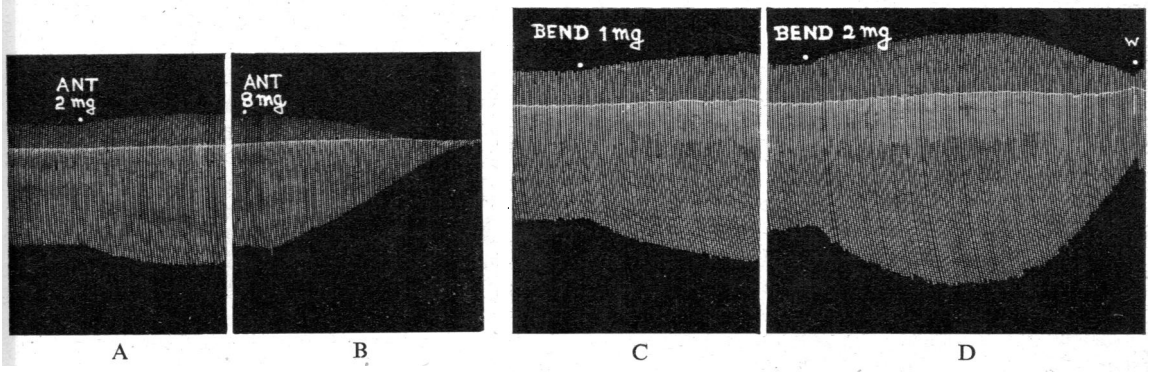

FIG. 6.—Rat diaphragm phrenic nerve preparation in Tyrode solution, 37° C., 50 ml. bath. A and B: single, maximal nerve stimulation, 7 per min., 0.5 millisecond. The solution was changed between A and B; 2 mg. antistin increased the contractions (A) while 8 mg. produced depression of the muscle tension (B) preceded by a very short stage of stimulation. C and D: single, maximal nerve stimulation, 6 per min., 1 millisecond. The solution was changed between C and D; 1 mg. benadryl produced an increase in the amplitude whereas 2 mg. caused an initial increase followed by progressive depression till the bath was washed out (W).

Action on the perfused superior cervical ganglion

From the results of the previous experiments a suggestion arose that the curare-like action of these substances on the skeletal muscle might be exerted by blocking the neuromuscular transmission. This led to an examination of the effect of benadryl and antistin on the perfused superior cervical ganglion of the cat. The procedure was the same as described in the earlier paper (Dutta, 1949). The ganglion was perfused with Locke's solution at 35° C. In Fig. 7 (upper record) the depressant action of benadryl is illustrated. The record shows the contractions of the nictitating membrane in response to preganglionic stimulation (16 per sec., every 3 min.). The third stimulation was preceded by a dose of 250 μg. benadryl and the response to the next stimulation was abolished. The ganglion recovered gradually. The effect of antistin is shown in Fig. 7 (lower record) and the results of all the experiments are summarized in Table IV.

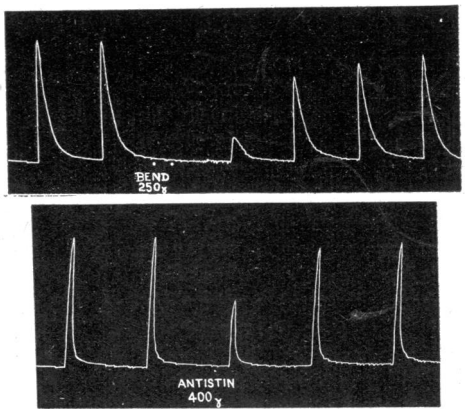

FIG. 7.—Superior cervical ganglion of the cat, perfused with Ringer-Locke's solution. Contractions of the nictitating membrane in response to preganglionic stimuli, 16 per sec. for 10 sec. every 3 min. *Upper record:* response to stimulation was abolished after 250 μg. benadryl. The ganglion recovered shortly. *Lower record:* response to stimulation was diminished after 400 μg. antistin.

TABLE IV

ACTION ON SUPERIOR CERVICAL GANGLION OF THE CAT

Exp. No.	Drug	Amount injected in μg.	Height of contraction of the nictitating membrane in mm.		Percentage inhibition
			Before addition of drug	After addition of drug	
2	Benadryl	100	18	3	83
3	,,	200	65	0	100
4	,,	400	51	37	27
5	,,	400	36	21	42
6	,,	300	30	25	17
7	,,	400	42	34	19
7	,,	600	40	0	100
8	,,	250	47	0	100
4	Antistin	500	40	29	28
5	,,	200	52	48	8
5	,,	400	52	26	50
6	,,	600	28	18	36
8	,,	200	53	39	26

Effect on histamine-induced gastric secretion

There has been some difference of opinion about the effect of benadryl on the gastric secretion evoked by histamine. Experiments were therefore carried out on cats by the method described by Howat and Schofield (1948). A cat, which had been kept without food overnight, was anaesthetized with chloralose and a rubber tube was inserted in the pyloric end of the stomach for withdrawal of the gastric juice. The stomach was washed out with warm water through an opening made in the oesophagus which was reached by an incision in the neck of the animal. This was later closed. The cat was warmed so as to maintain a constant rectal temperature. Atropine sulphate (1 mg./kg.) was injected intravenously to reduce the effect of vagal impulses. After an hour the stomach was washed with N/200 HCl and 25 ml. left in. Every 15 min. the stomach was emptied and refilled with 25 ml. of fresh dilute solution of the acid. The amounts of free and total acid present in each sample were estimated by titration with N/20 NaOH, thymol blue being used as indicator. The samples drawn out immediately before each histamine infusion were taken as the initial level for each secretory curve. Histamine acid phosphate (0.0045 mg./kg./min.) in normal saline was infused intravenously for 45 min. by a slow infusion pump. The total amount of acid secreted during this period constituted the first response. After the secretion had returned to the basal level a second infusion of histamine was given and the total amount of acid secreted formed the second response. Benadryl was injected intravenously before the beginning of the second histamine administration.

The secretion of free hydrochloric acid rose steadily during the infusion of histamine and declined progressively as soon as the infusion ended. It returned to the basal level within an hour. The figures for total and free acid were very close to one another. The amount of acid secreted during each response is expressed throughout as millilitres of

TABLE V

DOUBLE HISTAMINE TEST ON GASTRIC SECRETION IN CATS (AFTER ATROPINE)

1st and 2nd responses = total acid secreted during 1st and 2nd infusions of histamine respectively

Controls				Benadryl 3 mg./kg. between 1st and 2nd responses			
Exp.	Wgt. kg.	1st response N/20 HCl ml.	2nd response N/20 HCl ml.	Exp.	Wgt. kg.	1st response N/20 HCl ml.	2nd response N/20 HCl ml.
1	3.2	10.2	21.1	1	3.2	8.2	13.9
2	3.2	3.3	9.3	2	5.5	18.2	18.1
3	3.3	17.7	11.7	3	3.3	12.0	13.8
4	3.3	10.4	11.4	4	2.8	7.5	31.8
5	2.5	6.5	9.3	5	3.0	7.9	16.0
6	2.5	9.6	22.8	6	3.2	4.8	11.9
7	4.9	21.6	14.1	7	2.8	6.8	18.4
8	4.5	10.3	9.8	8	3.0	8.1	14.1
9	3.4	20.4	18.9	9	2.8	6.1	12.0
10	3.0	12.2	10.0	10	3.0	17.9	10.3
Mean		12.22	13.84	Mean		9.75	16.03
Mean difference 1.6 ± 2.2, t = 0.73, ± Std. error p = 0.5, not significant.				Mean difference 6.28 ± 2.66, t = 2.36, ± Std. error p is less than 0.05, significant.			

N/20 HCl. When these figures are compared (Table V) the variation between the responses of individual cats becomes obvious. In four of the ten control experiments (Table V), in which no drug was administered between the two injections of histamine, the output of acid during the second response was greater than the first; in another four cats the first response was greater than the second, and in the remaining two no appreciable difference between the two responses was noticed. The mean total amount of acid secreted during the first response (Table V) was 12.2 ml. and during the second response it was 13.8 ml.; the mean difference, which was 1.6 ml., was not statistically significant. Fig. 8 shows graphically the mean results of ten control experiments. In the experiments with benadryl, the mean titratable acidity of the second response was greater than the first by 63.3 per cent (Table V). Since t = 2.36, the value of p was less than 0.05, i.e., the second response differed from the first significantly. Thus after benadryl the gastric cells secreted a greater amount of acid in response to histamine than before the administration of the antihistamine substance.

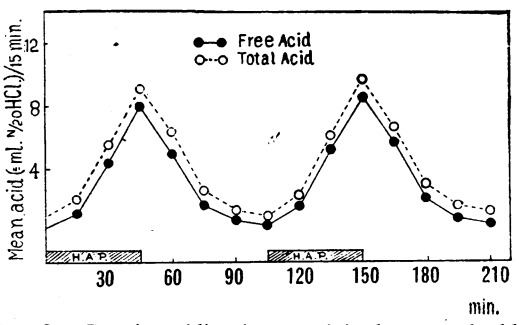

FIG. 8.—Gastric acidity in atropinized cats; double histamine test. Mean of ten control experiments in which no drug was administered between the two histamine responses. Histamine acid phosphate (0.0045 mg./kg./min.) was perfused intravenously for 45 min. each time. The mean second response showed an increase by 13.0 per cent over the first. This was not statistically significant.

DISCUSSION

Benadryl is reputed to possess an atropine-like action, for it reduces the depressor response of acetylcholine in the dog (Loew, MacMillan, and Kaiser, 1946), antagonizes the stimulant effect of acetylcholine on the gut (Loew, MacMillan, and Kaiser, 1946), causes mydriasis, and alters accommodation (Harris, McGavack, and Elias, 1946). Antistin also prevents the contractions of the isolated intestine induced by acetylcholine (Meier and Bucher, 1946). The effect of benadryl and antistin in inhibiting the action of acetylcholine on the isolated rabbit auricles is additional evidence in this direction.

Dawes (1946) reported that the substances which prolong the refractory period of cardiac muscle are antagonists of acetylcholine. This is also true for benadryl and antistin, for both of them reduced the

maximal rate of the electrically stimulated rabbit auricles. This effect is not due to the generalized depression of the auricular tissue. If doses of benadryl and antistin which are sufficient to reduce the maximal rate of contractions of electrically driven auricles are added to a bath in which isolated rabbit auricles are beating freely, the amplitude of contractions is increased. It is necessary to raise the concentration several times before any reduction of the height of contractions or slowing of the organ is noticeable.

Acetylcholine increases the maximal rate of contraction of the driven auricles (Dawes, 1946; Elío, 1947); this effect is increased by eserine or physostigmine and abolished by atropine (Elío, 1947). Elío has further suggested that " the transmission of the impulse in cardiac muscle may be effected by a mechanism in which acetylcholine is a key substance." Recently, Bülbring and Burn (1949) showed that the isolated rabbit's auricle is capable of synthesizing acetylcholine, and that the contractions of an auricle, which has been allowed to beat continuously until it has stopped, can be started again by the addition of acetylcholine to the bath. If, therefore, one assumes that acetylcholine takes part in transmission of cardiac impulses, it is not difficult to explain the action of benadryl and antistin in reducing the maximal rate of the rabbit's auricle; for both of them share the property of opposing the action of acetylcholine at various sites.

On the skeletal muscle of the rat diaphragm these substances produced a dual effect. In small concentrations they increased the response to a single maximal electrical shock, but in higher doses the opposite effect is produced. The evidence is strong that both benadryl and antistin act on the muscle directly, since the augmentation of the muscular twitches caused by indirect stimulation was also seen in response to direct stimulation and was not affected by *d*-tubocurarine chloride. Both benadryl and antistin prevented the contractions of the nictitating membrane in response to preganglionic sympathetic stimulation in the perfused ganglion. It may be that the diminution of the twitch tension of the rat diaphragm in response to nerve stimulation when under the influence of these substances is at least in part due to some blocking of the neuromuscular transmission.

In three of their four dogs with vagal denervated gastric pouches, Loew, MacMillan, and Kaiser (1946) noticed a significant decrease of the acid secretion in response to histamine after benadryl. Using about three times the dose employed by the previous workers, Friesen, Baronofsky, and Wangensteen (1946) failed to observe any such effect. Sangster, Grossman, and Ivy (1947) also did not notice any evidence which justified the conclusion that benadryl diminished the response of the gastric glands to histamine in dogs. Studies on man (Moersch, Rivers, and Morlock, 1946; McElin and Horton, 1946) did not provide any definite evidence that benadryl antagonized the action of histamine on the gastric secretory response. On the contrary, in some subjects the output of acid was actually stimulated (Gilg, 1948; Ashford, Heller, and Smart, 1949). The results of the present investigation clearly show that after benadryl the secretion of titratable acid from the stomachs of atropinized cats is usually increased in response to histamine. Recently Bain, Broadbent, and Warin (1949) have shown that the early effect of the antihistamine substance phenergan is to potentiate the reaction to an intradermal injection of histamine.

SUMMARY

1. Both antistin and benadryl

(i) when tested by the intracutaneous weal method in the guinea-pig, show a linear relationship between the logarithmic concentration of the substances and their local anaesthetic effect. Both are more potent than procaine;

(ii) reduce the depressant action of acetylcholine on the isolated rabbit's auricle;

(iii) decrease the maximal rate at which the isolated rabbit's auricle will respond to electrical stimulation. The relation between the percentage decrease in the maximal rate and the logarithm of the concentration is linear for both these substances. Both of them are more active than quinidine;

(iv) reduce the contractions produced by acetylcholine on the isolated frog's rectus;

(v) in small concentrations increase the twitch tension of the rat's diaphragm elicited by single, maximal nerve volleys. These enhanced muscular contractions are also seen in response to direct stimulation in the curarized preparation. When concentrations of these substances are raised, a decline in the muscle's response to indirect stimulation follows;

(vi) depress the contraction of the nictitating membrane in response to preganglionic stimulation when injected into the fluid perfusing the superior cervical ganglion.

2. In cats after atropine, benadryl significantly increased the rate of hydrochloric acid secretion from the stomach during intravenous perfusion of histamine.

express my grateful thanks to Professor J. H. Burn for his advice, encouragement, and help. I wish to thank Dr. J. W. Trevan, Director of the Wellcome Physiological Research Laboratories, for treating the results on gastric secretion statistically and to Dr. D. Hutcheon for his help.

The work was carried out during the tenure of a fellowship from the Government of India.

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