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BRONCHOCONSTRICTOR AND BRONCHODILATOR ACTIONS OF ANTIHISTAMINE DRUGS

BY

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Among the many side actions of antihistamine drugs which have been reported, the only direct action on smooth muscle which is well known is that on the uterus; most antihistamines have some oxytocic activity. It is generally believed that these drugs have no action of their own on the bronchial musculature, but a few exceptions have been reported. Bovet (1934) found that the early precursor thymoxyethyldiethylamine (929F) contracted guinea-pig bronchi, and Staub (1939) observed a similar action with *N*-phenyl-*N*-ethyl-*N'*-diethylethylenediamine (1571F). Castillo and de Beer (1947) show a tracing which illustrates that diphenhydramine (10^{-5}) contracts the guinea-pig tracheal chain, but do not comment thereon. Herxheimer (1953) found that inhalations of aerosols of 3% promethazine or 5% chlorcyclizine caused dyspnoea in guinea-pigs. On the other hand, De Schaepdrijver (1948) found that large doses of antazoline relaxed the bronchi of perfused guinea-pig lungs.

Antihistamines are usually tested against histamine, using only low concentrations of the antagonist. In order to antagonize the anaphylactic contraction of bronchial muscle, much higher concentrations are required. In the course of some work in this field it was observed that all the antihistamines used caused contractions of the guinea-pig tracheal chain in concentrations between 10^{-6} and 10^{-4}, and above these concentrations they caused relaxation. Because these were the very concentrations required to antagonize the anaphylactic contraction of isolated guinea-pig trachea (Hawkins, 1952) or the allergic contraction of isolated human bronchus (Schild, Hawkins, Mongar and Herxheimer, 1951), the bronchoconstrictor action of antihistamine drugs was investigated further. The present work consists of a study of the direct action on the bronchial musculature of a series of twelve well-known antihistamine drugs.

METHODS

Guinea-pig Tracheal Chains.—Tracheal chains (Epstein, 1932; Castillo and de Beer, 1947) were made using 6 to 8 rings, tied tightly with cotton thread, and orientated alternately so that the muscle strips were aligned. Guinea-pigs of all sizes were used, but it was found that chains were easiest to prepare from the tracheas of animals weighing between 500 and 600 g. The preparations were maintained at 37° C. in Krebs-Henseleit solution (NaCl 6.87; KCl 0.43; $CaCl_2$ 0.28; $MgSO_4,7H_2O$ 0.29; $NaH_2PO_4,2H_2O$ 0.18; $NaHCO_3$ 2.10; glucose 1.00 g./l.) aerated with O_2 + 5% CO_2, or in a similar solution containing one-tenth as much $NaHCO_3$ aerated with O_2 alone. The tonus level of the preparations was continuously recorded with a light balsa-wood frontal writing lever giving a magnification of about ×20, tension about 200 mg., writing on a lightly smoked kymograph drum. The preparations were left for 1 to 2 hours before any drugs were given. During this period a marked rise of tonus level invariably occurred, the preparation then relaxing to a steady tonus level. Similar "post-mortem contractures" of isolated bronchial muscle were observed by Macht and Ting (1921).

In general, two or three submaximal doses of histamine, acetylcholine, or adrenaline were given, until regular responses were obtained, before any doses of antihistamine drugs were tested.

Osmotic Change.—In view of the rather high doses of drugs to be used, the effects of osmotic change were investigated. NaCl, added to the bath in concentrations up to 5×10^{-4}, had no distinct effect; a concentration of 10^{-3}, increasing the osmotic pressure by about 10%, produced a small fall in tonus, less than 5% of the maximum response to adrenaline. These results indicated that none of the responses to drugs described in the present work can be ascribed to effects on osmotic equilibria.

p*H Measurements.*—These were made electrometrically.

Human Bronchial Chains.—The methods described by Hawkins and Schild (1951) were used.

Spinal Cats.—The animals were anaesthetized with open ether, and the cord transected at the level of the

second cervical vertebra. The bronchial tone was recorded by the method of Konzett and Rössler (1940), and the common carotid pressure recorded in the usual way. Intravenous injections of drugs were made into the femoral vein and washed in with 2 ml. of saline.

Bronchial Tone in Dogs.—The animals were anaesthetized with ether followed by intravenous chloralose. The method of Konzett and Rössler (1940) was used for recording bronchial tone.

Antihistamine Drugs.—The drugs used were mepyramine acid maleate (Anthisan, May & Baker), promethazine hydrochloride (Phenergan, May & Baker), antergan hydrochloride (May & Baker), tripelennamine hydrochloride (Pyribenzamine, Ciba), antazoline hydrochloride (Antistin, Ciba), diphenhydramine hydrochloride (Benadryl, Parke, Davis), chlorcyclizine monohydrochloride (Di-Paralene, Abbott), phenindamine hydrogen tartrate (Thephorin, Roche), chloropyrilene citrate (Chlorothen, Lederle), methapheniline hydrochloride (Diatrin, William Warner), methapyrilene hydrochloride (Histadyl, Lilly), chlorprophenpyridamine maleate (Chlortrimeton, Schering).

I am grateful to the drug firms mentioned for supplies of the pure crystalline salts. In the present work drug concentrations are expressed in terms of the whole salt. The bath volume was 50 ml.

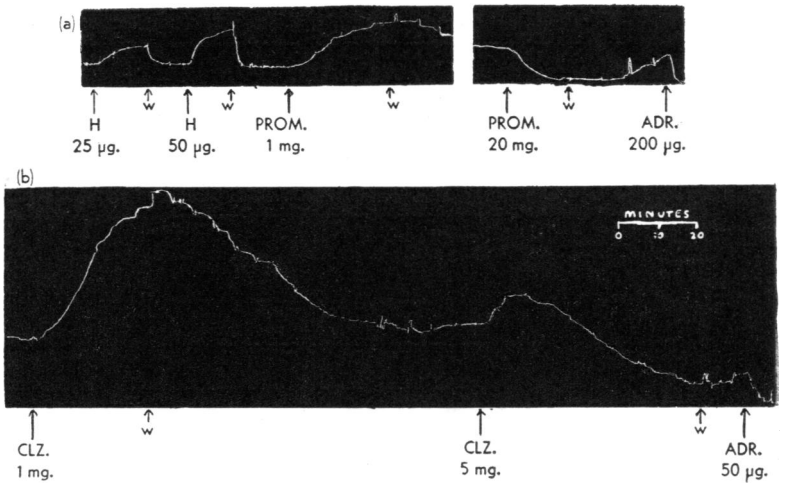

FIG. 2.—Guinea-pig tracheal chains in 50 ml. baths. (*a*) Bronchoconstrictor responses to histamine (H) and to promethazine (PROM): bronchodilator response to a large dose of promethazine. (*b*) Responses to chlorcyclizine (CLZ).] ADR = maximum relaxation given by adrenaline.

RESULTS

Guinea-pig Tracheal Chains

Fig. 1 shows records from a guinea-pig tracheal chain. Following two responses to histamine, contractions produced by diphenhydramine are seen. The contractions in response to diphenhydramine 10^{-5} and 2×10^{-5} are reversible, repeatable and graded. 2×10^{-4} gave a very little larger contraction than did 2×10^{-5}; 8×10^{-4} gave a small contraction and then relaxation.

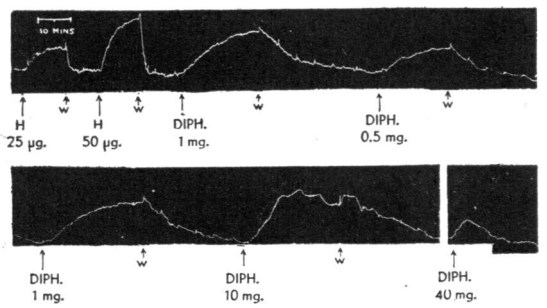

FIG. 1.—Guinea-pig tracheal chain in 50 ml. bath. Bronchoconstrictor responses to histamine (H) and to diphenhydramine (DIPH).

Fig. 2 shows similar effects with promethazine and chlorcyclizine. With promethazine, 2×10^{-5} contracted the trachea, whereas 4×10^{-4} produced a relaxation which was as great as a maximal relaxation caused by adrenaline. On another preparation, chlorcyclizine (2×10^{-5}) gave a big contraction, while chlorcyclizine (10^{-4}) produced a small contraction followed by a nearly maximal relaxation. Similar effects were given by mepyramine, methapyrilene, tripelennamine, phenindamine, chlorprophenpyridamine, antergan, chloropyrilene, methaphenilene, and antazoline.

The actions of these twelve antihistamine compounds, in concentrations from 10^{-7} to 10^{-3}, were studied on some 140 preparations from 64 guinea-pigs. Fig. 3 shows the concentrations at which this series of antihistamines have actions of their own on guinea-pig trachea. Within the range of concentrations 10^{-6} to 10^{-4} they all gave contractions. The compounds in Fig. 3 are arranged in order according to the magnitude of the range over which bronchoconstrictor responses were recorded. The bronchoconstrictor action seems to be a common property of antihistamine drugs and there is little to choose in this respect between mepyramine, diphenhydramine, methapyrilene, promethazine, and tripelennamine, the first five compounds in Fig. 3. Higher doses of all the compounds, within the range of 10^{-4} to 10^{-3}, gave relaxations,

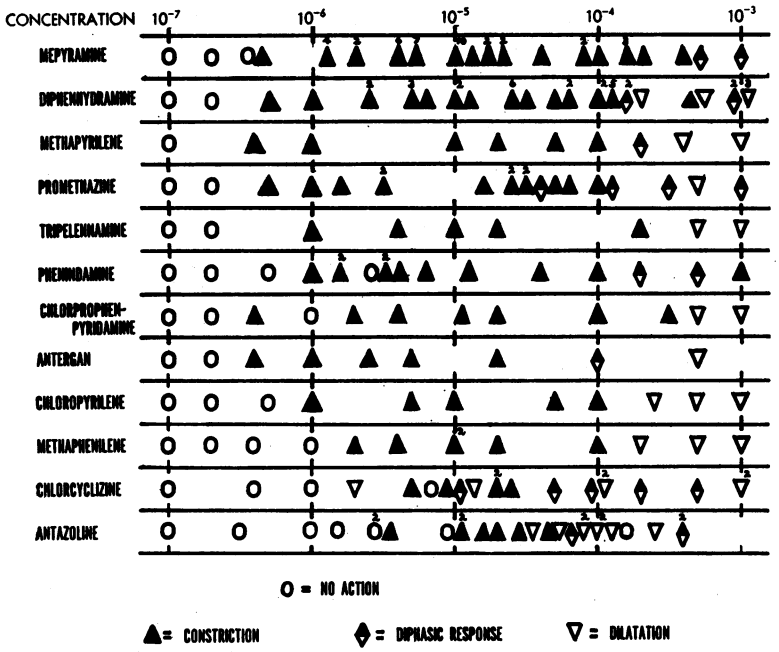

FIG. 3.—Concentrations (logarithmic scale) of antihistamine drugs giving bronchoconstrictor and bronchodilator responses in a series of guinea-pig tracheal preparations. Where more than one response is represented by a single point, the number of responses is indicated.

and intermediate doses often gave diphasic responses, an initial contraction being followed by relaxation to below the resting baseline (Fig. 3).

The only clear difference between the compounds shown in Fig. 3 seems to be with antazoline and chlorcyclizine, where the bronchoconstrictor action was less pronounced, and the relaxing action occurred at lower concentrations. The minimum concentrations of the drugs active in causing bronchoconstriction in guinea-pig tracheal chains were estimated and are shown in Table I. The method of Kärber (Gaddum, 1933) was used to estimate these concentrations. In addition, the lowest concentration which produced bronchodilatation was estimated for each drug, and also the range of concentrations over which the drug exhibited bronchoconstrictor activity. These values are also shown in Table I.

It will be seen from Table I that all the compounds are active bronchoconstrictors, but that chlorcyclizine and antazoline are the least active. Mepyramine, diphenhydramine, and methapyrilene have bronchoconstrictor activity over a thousandfold or greater range of concentrations; the range with chlorcyclizine and antazoline is very limited. Antazoline is the only compound in the series which can cause bronchodilatation in a concentration of less than 10^{-4}.

TABLE I

CONCENTRATIONS OF ANTIHISTAMINE DRUGS HAVING DIRECT ACTIONS ON GUINEA-PIG TRACHEA

Drug	Minimum Active Concn. for Broncho-constriction (μg./ml.)	Minimum Active Concn. for Broncho-dilatation (μg./ml.)	Range of Concentrations Having Broncho-constrictor Activity
Mepyramine ..	0·4	670	1,700
Diphenhydramine	0·3	410	1,300
Methapyrilene ..	0·2	200	1,000
Promethazine ..	0·3	230	730
Tripelennamine ..	0·4	320	710
Phenindamine ..	0·9	440	510
Chlorprophen-pyridamine ..	1·1	400	370
Antergan ..	0·3	100	350
Chloropyrilene ..	0·8	160	200
Methaphenilene	1·4	140	100
Chlorcyclizine ..	4·7	110	22
Antazoline ..	5·3	41	8

The direct actions of antihistamine drugs on bronchial muscle appear to be independent of their antihistamine activities. For example, among the drugs in the series most active in antagonizing histamine are mepyramine, promethazine, and chlorcyclizine; mepyramine and promethazine are active bronchoconstrictors whereas chlorcyclizine is not nearly so powerful in this respect. Of the weaker drugs in antagonizing histamine, diphenhydramine and antergan are active bronchoconstrictors over a wide range of concentrations, whereas antazoline is the weakest of the series as a bronchoconstrictor. The specificity of the antihistamine drug does not appear to influence the bronchoconstrictor activity—for example, both mepyramine and diphenhydramine are active bronchoconstrictors, mepyramine being a highly specific antihistamine, while diphenhydramine has a marked anti-acetylcholine action (Schild, 1947).

In the same way there is no obvious relation between antihistamine activity and bronchodilator activity on the tracheal chain.

Action of Atropine.—The bronchoconstrictor response to mepyramine, 10^{-5}, was not inhibited by atropine, 10^{-5} (Fig. 4a).

As atropine itself has a weak antihistamine action on the tracheal chain, this drug was also tested in high concentrations. Though it had no action in a concentration of 10^{-5}, at 10^{-4} it gave a marked contraction (Fig. 4b).

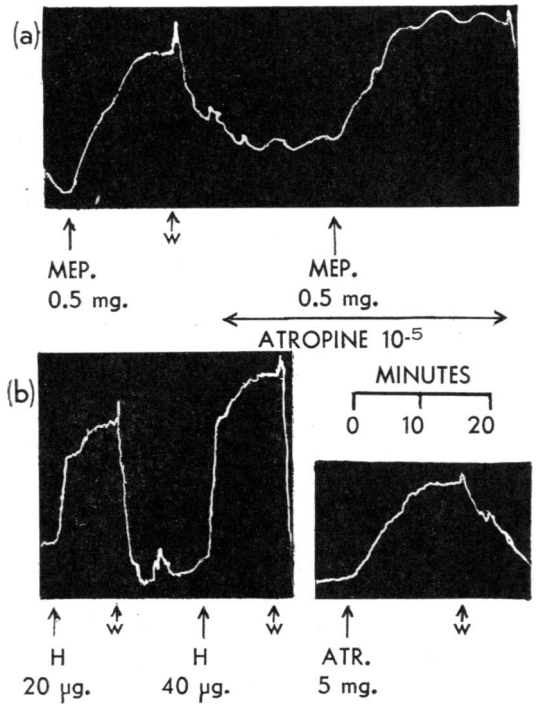

FIG. 4.—Guinea-pig tracheal chains. Bath vol. 50 ml. (*a*) Response to mepyramine (10^{-5}) not reduced by atropine (10^{-5}). (*b*) Bronchoconstrictor responses to histamine (H) and atropine (ATR).

Secondary Relaxing Action of Histamine on Guinea-pig Trachea.—In view of the observation of Arunlakshana (1953) that diphenhydramine and antazoline can release relatively large amounts of histamine from guinea-pig and human lung tissue, it was considered of interest to examine the actions of high concentrations of histamine on the tracheal chain, in the absence and presence of antihistamine drugs.

Fig. 5a shows that, following a maximal contraction produced by the action of histamine, 2×10^{-5}, addition of further large doses of histamine to the bath produced relaxation. This secondary relaxing action of high doses of histamine is reminiscent of the secondary depressant action of the drug on the intestine (Olivecrona, 1921).

It was also found that in the presence of sufficient diphenhydramine to abolish completely the contracting action of histamine a high dose of

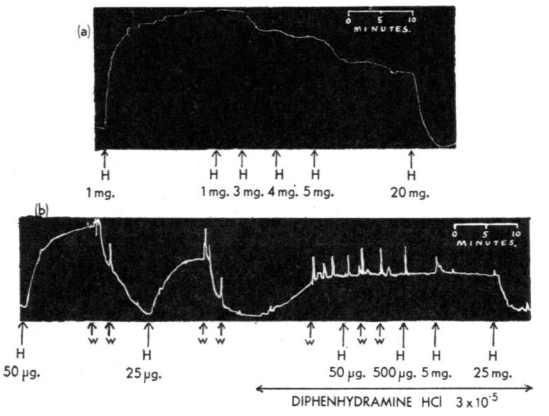

FIG. 5.—Guinea-pig tracheal chains. Bath vol. 50 ml. (*a*) Maximal contraction produced by histamine (H); further large doses of histamine gave relaxation. (*b*) Diphenhydramine (3×10^{-5}) abolished the bronchoconstrictor response to all doses of histamine; in the presence of diphenhydramine, a large dose of histamine (5×10^{-4}) produced relaxation.

histamine (5×10^{-4}) produced relaxation of the trachea (Fig. 5b). Similar results were obtained in the presence of antazoline; the phenomenon has also been observed with human bronchi (Hawkins, 1952). The secondary relaxing action of histamine on bronchial muscle may be related to the relaxing action on the rat's uterus; Gordonoff (1944) has shown that the latter effect of histamine is not antagonized by antergan; Dews and Graham (1946) obtained a similar result with mepyramine.

Guinea-pig Ileum.—Feldberg and Smith (1954) have shown that very small doses of mepyramine can stimulate guinea-pig ileum preparations, particularly after the preparation has been in contact with the histamine releaser 48/80, and have attributed this effect to histamine release by mepyramine. Some support is given to this view by the observation of Mongar and Schild (1952) that previous contact with 48/80 also very much increases the amount of histamine released by guinea-pig ileum in anaphylaxis.

The present observations were confined to high doses of antihistamine drugs. It was found that mepyramine, diphenhydramine, promethazine, phenindamine and antergan, in concentrations of 10^{-4}, all caused slow contractions of guinea-pig ileum preparations. No such action was observed with chlorcyclizine or antazoline in the same concentrations.

pH Measurements.—All the antihistamine salts used produced bronchoconstriction in concentrations which gave no detectable change in the *p*H of the bath fluid. It was considered possible that the highest concentrations tested, which were found

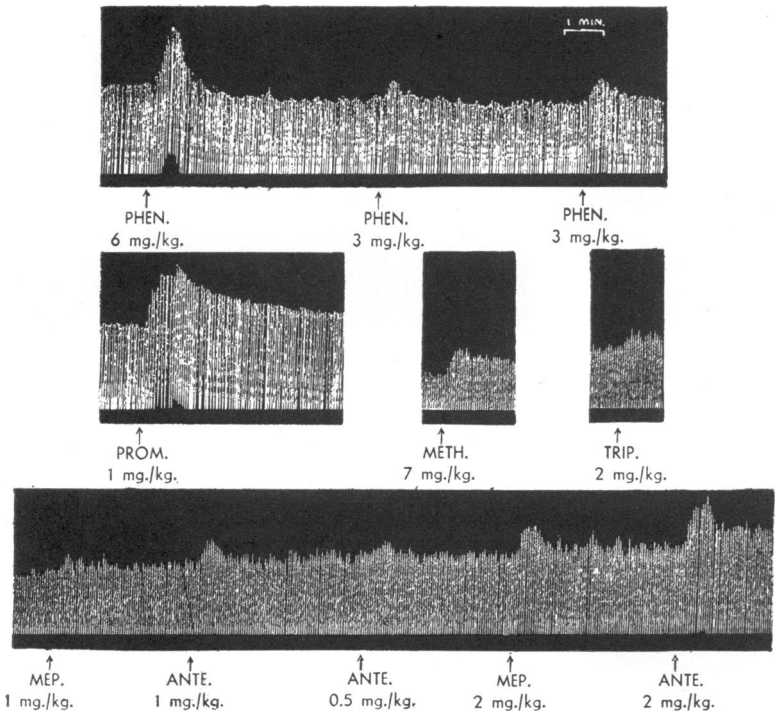

FIG. 6.—Spinal cats, bronchial tone. Bronchoconstrictor responses to phenindamine (PHEN), promethazine (PROM), methapyrilene (METH), tripelennamine (TRIP), mepyramine (MEP), and antergan (ANTE), injected i.v.

to give relaxation of the tracheal chains, might produce effects by altering the *p*H. It was found that the *p*H of the bath fluid could be changed within the range 10.9 to 5.1, by addition of NaOH or HCl, without producing any response of the tracheal chains. With most of the antihistamine salts the highest concentrations used produced only trivial changes of *p*H, within this range, but with phenindamine acid tartrate (10^{-3}) and chloropyrilene citrate (10^{-3}) the *p*H was 4.6. Since these doses produced relaxation, while alterations of the bath *p*H to 1.7 with HCl gave only a small contraction, it is evident that the bronchodilator responses observed with high doses were not a consequence of *p*H change.

The highest concentration of histamine acid phosphate tested was 10^{-3}, which gave a bath *p*H of 5.1. Addition of HCl to the bath to give this *p*H had no action on the preparation, under the experimental conditions.

Spinal Cats and Anaesthetized Dogs

The finding that antihistamines produce bronchoconstriction was confirmed in spinal cats and dogs under chloralose. The bronchial tone was recorded by Konzett's method and drugs were injected intravenously. Fig. 6 shows bronchoconstrictions, indicated by a rise in the record, produced by phenindamine, promethazine, metha-

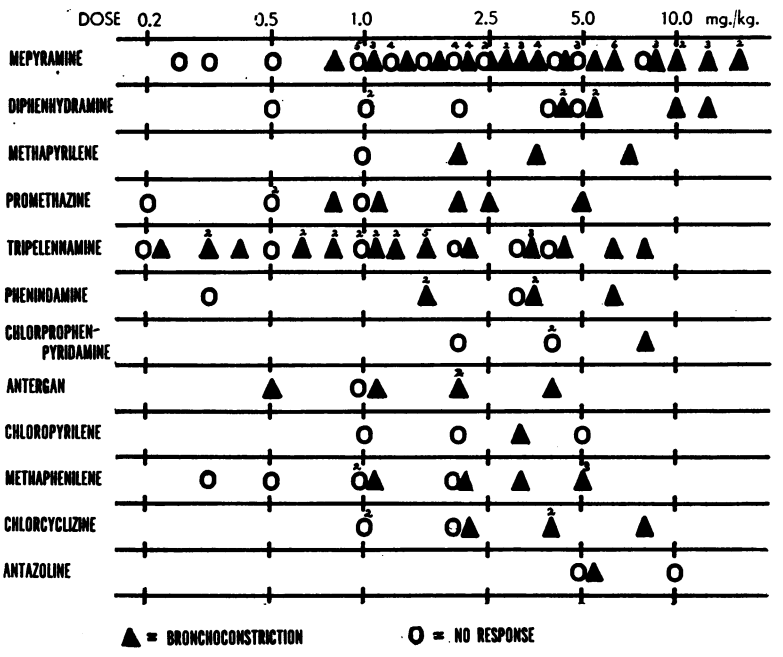

FIG. 7.—Spinal cats; bronchoconstrictor responses to antihistamine drugs injected i.v. Logarithmic scale of doses. Where more than one response is represented by a single point, the number of responses is indicated.

pyrilene, and tripelennamine in spinal cats. A comparison of antergan with mepyramine is also shown, and it will be seen that antergan is a more active bronchoconstrictor than mepyramine in the spinal cat.

The responses from 18 cats are summarized in Fig. 7. All the compounds gave constrictions in doses within the range 1.0 to 10.0 mg./kg. The compounds are arranged in the same order as in Fig. 3. Chlorcyclizine and antazoline have only a feeble bronchoconstrictor action in the spinal cat.

Some responses of the bronchi in dogs under chloralose are shown in Fig. 8. In this experiment, bronchoconstrictor responses to promethazine were compared with similar responses to mepyramine. As in the spinal cats, the bronchoconstrictions were accompanied by depressor responses, and simultaneous recordings of arterial pressure were made. The experiment illustrated in Fig. 8 showed that, although mepyramine and promethazine were approximately equiactive as bronchoconstrictors in the anaesthetized dog, the latter drug was twice as active as the former in lowering the blood pressure. The results of a number of similar experiments, comparing the simultaneously recorded bronchoconstrictor and depressor responses to mepyramine with those to other antihistamine drugs, are given in Table II. It will be seen that there is no correlation between the relative bronchoconstrictor activities and the relative depressor activities determined at the same time. For example, chloropyrilene was as active on the blood pressure as mepyramine, but the former had less than one-fifth of the activity of the latter on the bronchi. Dose levels which were found to be active on the bronchi are included in Table II.

The antihistamine compounds thus have the common property of causing bronchoconstriction in the spinal cat and anaesthetized dog. It seems likely that this is a direct action on the bronchial

TABLE II

BRONCHOCONSTRICTOR AND DEPRESSOR ACTIVITIES OF ANTIHISTAMINE DRUGS IN ANAESTHETIZED DOGS

Drug	Doses having a Broncho-constrictor Action (mg./kg.)	Relative Potencies (Mepyramine = 100)	
		Broncho-constrictor Activity	Depressor Activity
Mepyramine ..	1·0	100	100
Diphenhydramine	2·0	45	20
Methapyrilene ..	2·0	45	125
Promethazine ..	1·0	90	180
Tripelennamine ..	1·0	100	165
Phenindamine ..	1·0	100	125
Antergan ..	1·0	140	200
Chloropyrilene ..	5·0	<20	105
Methaphenilene ..	2·0	—	150

muscle, comparable with that found with guinea-pig trachea. It was seen with all the compounds at dose levels which are comparable in the isolated bronchial muscle and in the whole animal, 10^{-6} to 10^{-4} in the guinea-pig tracheal chain, and 1 to 10 mg./kg. in the spinal cat or anaesthetized dog. Further, though in general direct comparisons of activity were not made in the guinea-pig trachea or spinal cat, the relative bronchoconstrictor activities of antergan and mepyramine were in fact determined on all three preparations. The activity ratios were, as antergan/mepyramine: guinea-pig trachea, 1.4; spinal cat, 1.5; anaesthetized dog, 1.4.

Bronchodilator Action in Spinal Cats and Anaesthetized Dogs.—In the spinal cat, bronchoconstrictor responses were obtained rather irregularly (Fig. 7). It was found that animals which failed to give bronchoconstrictor responses initially often gave them regularly after repeated doses. In addition it was noted that animals which had suffered considerable trauma or delay in the operative procedure gave bronchoconstrictor responses more readily than did animals which showed no evidence of shock after transection of the spinal cord. At the same time it was often observed that the first dose or two of antihistamine gave a long-lasting pressor response

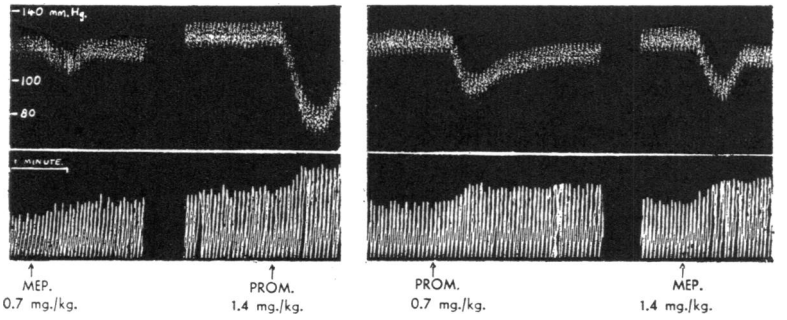

FIG. 8.—Anaesthetized dog. Bronchoconstrictor and depressor responses to mepyramine (MEP) and promethazine (PROM) injected i.v.; 10 min. intervals between doses.

initially which showed tachyphylaxis, becoming depressor after repeated doses.

Fig. 9 shows this effect with mepyramine ; similar results were obtained with the other antihistamines used. The upper tracing in Fig. 9, a record

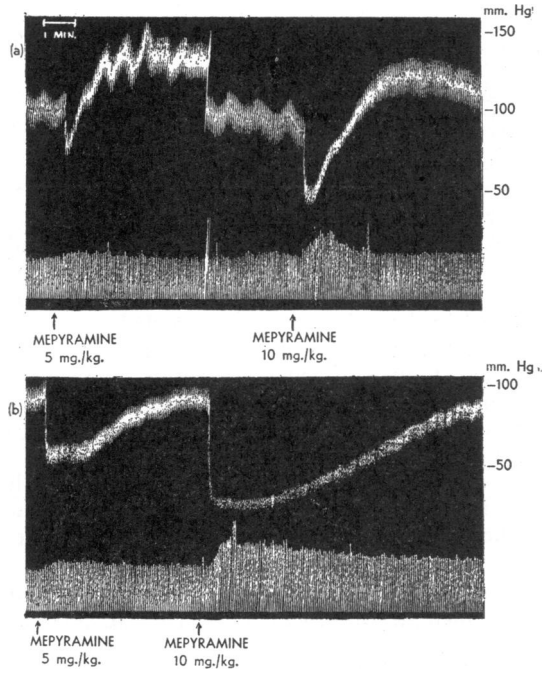

FIG. 9.—Spinal cat; arterial pressure and bronchial tone. Responses to i.v. mepyramine. 45 min. interval between (*a*) and (*b*), with doses of mepyramine at 10 min. intervals.

of the bronchial tone and blood pressure of a spinal cat, shows that initially the response to mepyramine was largely pressor. Three-quarters of an hour later, after repeated doses, the blood-pressure response had become purely depressor, while the bronchial responses were more prolonged.

In one or two animals more extreme changes were obtained, the records showing either diphasic responses consisting of an initial bronchoconstriction followed by prolonged dilatation, or at times a simple long-lasting bronchodilatation, in the early stages of the experiment. These bronchodilatations were tachyphylactic, and after repeated doses pure bronchoconstrictions were obtained. These changes were always paralleled by the blood-pressure responses, bronchodilatations being accompanied by pressor, and bronchoconstrictions by depressor, responses.

Human Bronchi

Isolated Human Bronchial Chains.—Actions of antihistamine drugs, similar to those observed on the guinea-pig tracheal chain, were found with preparations of human bronchi. It has previously been shown (Hawkins and Schild, 1951 ; Schild *et al.*, 1951) that mepyramine will contract human bronchi. In the course of the present work it was found that this drug in concentrations from 4×10^{-6} to 8×10^{-5} caused contraction of human bronchial chains, whereas a concentration of 4×10^{-4} caused relaxation.

High concentrations of promethazine, of the order of 4×10^{-5}, caused relaxation. Antazoline was inactive in a concentration of 10^{-6}, but gave a small relaxation at 8×10^{-4}.

DISCUSSION

It has been shown that 12 well-known antihistamines possess bronchoconstrictor actions when tested on the guinea-pig tracheal chain in concentrations greater than 10^{-6}. The drugs in question have a bronchoconstrictor action when injected intravenously into spinal cats or anaesthetized dogs at dose levels which are comparable to those which are required to contract the guinea-pig trachea. Further, similar results were obtained with isolated human bronchial muscle preparations.

This bronchoconstrictor action seems to be a common property of antihistamine drugs. It is least marked with antazoline and chlorcyclizine, and it is interesting to note the structural feature, not possessed by the other compounds in the series, which these two drugs have in common. The basic structure of an antihistamine of the ethylenediamine series consists of aromatic or heterocyclic rings attached to one of the nitrogen atoms, while the other nitrogen atom is generally substituted by aliphatic groups. The principal modification of this structure possessed in common by antazoline and chlorcyclizine is the inclusion of the " aliphatic *N* " in a heterocyclic ring, the imidazoline ring in antazoline, and the piperazine ring in chlorcyclizine. This cyclization of the aliphatic end of the antihistamine molecule might be responsible for modifying the bronchoconstrictor action and enhancing the direct bronchodilator action seen with higher doses.

Mode of Action.—The bronchoconstrictor action of mepyramine was not inhibited by atropine, and it seems unlikely that this action is parasympathomimetic.

An alternative possibility is that antihistamine drugs possess a " histamine-like " action. Such

actions of antihistamines on smooth muscle as have been described show some parallelism with the actions of histamine. Oxytocic actions on the uterus of the guinea-pig, rabbit, or dog have been demonstrated for antergan, mepyramine, methapyrilene and tripelennamine (Halpern, 1942; Bovet and Walthert, 1944; Lee, Dinwiddie and Chen, 1947; Sherrod, Loew and Schloemer, 1947) and histamine contracts these organs. Scudi, Reinhard, and Dreyer (1948) found that thonzylamine stimulated the isolated rat uterus. Though it is commonly believed that histamine always relaxes this organ, Feldberg (1941) has pointed out that under certain conditions histamine will stimulate it.

On the intestine, Sherrod *et al.* (1947) showed that mepyramine and tripelennamine stimulated the dog's small intestine. Scudi *et al.* (1948) and Dreyer (1950) found that though small doses of thonzylamine caused a transient inhibition of the contractions of the cat's small intestine, *in situ*, high doses frequently caused stimulation. The responses persisted after cutting the splanchnic and vagus nerves. Dreyer (1950) mentions similar results with mepyramine, but found that prophenpyridamine gave stimulation in small doses, larger doses causing depression. Feldberg and Smith (1954) have recently shown that very small doses of mepyramine can not only potentiate the action of histamine on isolated guinea-pig ileum but will, under certain conditions, stimulate this preparation directly. It was found in the present experiments that high concentrations of some antihistamines contracted guinea-pig ileum.

Further actions in which antihistamines resemble histamine are in producing a fall in blood pressure, in causing vasodilatation in the perfused dog's leg (Murray and Huston, 1952), and on the salivary glands in dogs, where antergan causes secretion (Halpern, 1942); in the course of the present experiments on dogs it was noted that the large doses of antihistamines injected caused salivation. In addition it has been reported that diphenhydramine will directly stimulate gastric secretion in man (Doran, 1947; Gilg, 1948), and a number of antihistamines have been found to potentiate histamine-induced gastric secretion (Deutsch, 1947; Emmelin and Frost, 1947; Wood, 1948; Ashford, Heller, and Smart, 1949; Dutta, 1949; Howat and Schofield, 1954).

Whereas histamine in moderate doses causes the guinea-pig tracheal chain to contract, it has been shown that very large doses have a depressant action (Fig. 5). The actions of antihistamines which have been demonstrated on the guinea-pig trachea are therefore similar to those of histamine. In the same way, it may be demonstrated, using the Konzett preparation, that histamine has a bronchoconstrictor action in cats and dogs.

There is thus a considerable degree of parallelism between the independent actions of antihistamines and the actions of histamine itself. It seems likely that the constrictor and dilator actions of moderate and high concentrations, respectively, of antihistamines on bronchial muscle are in fact histamine-like actions.

The possible mechanism of these histamine-like actions of antihistamines may be one of the following: (*a*) A histamine-releasing action, the antihistamine releasing or activating cellular histamine in the tissue concerned. (*b*) An antihistaminase action, resulting in potentiation of the action of small amounts of free histamine in the tissues to such a degree that recognizable effects are produced. (*c*) A truly " mimetic " action, from the structural similarity between the antihistamine drugs and histamine itself being sufficiently marked for high concentrations of antihistamines to stimulate " histamine receptors " in the tissues.

It has in fact been reported that antergan, mepyramine, and the antihistamine compound 2325 R.P. cause marked elevation of the blood histamine when administered orally or intravenously in man (Pellerat and Murat, 1946). Further, Arunlakshana (1953) has shown that diphenhydramine and antazoline release quite large amounts of histamine from guinea-pig or human lung tissue. If it is assumed that the pharmacological action of the intrinsic histamine released is relatively resistant to antagonism by antihistamines, the mode of action of antihistamine drugs on smooth muscle may be interpreted as follows. With the lowest concentrations of antihistamines (less than 10^{-6}), the amounts of histamine released are so small, except in certain special circumstances such as after administration of compound 48/80 (Feldberg and Smith, 1954), as to be inactive. With concentrations of the order 10^{-6} to 10^{-4}, active amounts of intrinsic histamine, relatively resistant to the antihistamine action, are released, resulting in contraction of the muscle. With the highest concentrations of antihistamine (greater than 10^{-4}) sufficient antihistamine activity may be present to prevent any stimulant action of intrinsic histamine, revealing the depressant action of the relatively high concentrations of histamine released locally.

Atropine was also found to have a bronchoconstrictor action in high concentrations; this drug has been shown to release histamine (Burstein and Parrot, 1949; Schacter, 1952).

It is unlikely that the weak antihistaminase action of promethazine and antazoline (Kapeller-Adler, 1949) is related to their bronchoconstrictor actions, since mepyramine, diphenhydramine, and antergan, which possess bronchoconstrictor activity, do not block histaminase. Further, highly active antihistaminase drugs do not contract guinea-pig tracheal chains (Arunlakshana, Mongar, and Schild, 1954).

The available evidence would therefore seem to be compatible with the view that the independent actions of antihistamines are, at least in part, attributable to their histamine-releasing activity. The possibility that the antihistamines may in fact stimulate the same receptors as histamine must also be borne in mind.

Antihistamines and Anaphylaxis in Isolated Bronchial Muscle.—The range of concentrations over which the majority of antihistamines possess bronchoconstrictor activity (10^{-6}–10^{-4}) is in fact the range over which these drugs show some activity in antagonizing the anaphylactic bronchoconstriction in isolated tracheal chains from sensitized guinea-pigs (Hawkins, 1952). Further, as Schild *et al.* (1951) have shown, concentrations of mepyramine sufficient to reduce the allergic bronchoconstriction in isolated bronchi from asthmatic patients, are also sufficient to cause bronchoconstriction.

Concentrations of antihistamines sufficient to produce bronchodilatation (Table I, Fig. 3) could probably not be achieved in the intact animal, owing to the toxicity of the drugs. Hence the bronchoconstrictor activity of the antihistamine drugs tested limits their usefulness in counteracting anaphylactic or allergic bronchospasm.

Relation to the Therapy of Asthma.—Most authorities now hold the view that antihistamine drugs have little value in the relief of bronchospasm in severe asthma, though some authors have found the usual therapeutic doses of the drugs useful in controlling relatively mild attacks of asthma. When efforts have been made to secure higher local concentrations of these drugs, with a view to suppressing severe asthma, bronchoconstriction has been observed. Charlier and Philippot (1949) have shown that antergan or mepyramine, administered as 2% aerosols, can cause bronchoconstriction in man; antazoline, as a 5% aerosol, was inactive. Herxheimer (1952) records that inhalation of aerosols containing antihistamines in concentrations greater than 1 to 3% invariably aggravated the dyspnoea of asthmatic patients.

In addition, a number of authors have reported that ingestion of the usual therapeutic doses of antihistamines by asthmatic and other patients resulted in symptoms suggestive of bronchoconstriction. Levy and Seabury (1947) and Criep and Aaron (1948a and b) found that oral administration of antihistamine drugs caused some reduction of the vital capacity in a proportion of asthmatic patients.

It therefore seems reasonable to conclude that the bronchoconstrictor action of antihistamine drugs may be in part responsible for the failure of the drugs to relieve severe asthma. It would appear to be desirable to develop potent antihistamine compounds which do not possess bronchoconstrictor activity.

Summary

1. A series of 12 well-known antihistamine drugs has been found to possess bronchoconstrictor activity in concentrations within the range 10^{-6} to 10^{-4} when tested on isolated guinea-pig tracheal chains, and in doses within the range 1 to 10 mg./kg. when injected intravenously into spinal cats or anaesthetized dogs.

2. There was no correlation between the relative antihistamine and bronchoconstrictor activities of the antihistamine drugs tested.

3. Three compounds, mepyramine, diphenhydramine, and methapyrilene, caused bronchoconstriction in over a thousandfold range of concentrations; chlorcyclizine and antazoline had only small ranges of bronchoconstrictor activity. Promethazine, tripelennamine, phenindamine, chlorprophenpyridamine, antergan, chloropyrilene, and methaphenilene were intermediate with respect to range of bronchoconstrictor activity.

4. In higher concentrations, $>10^{-4}$, the antihistamine drugs tested caused relaxation of isolated guinea-pig tracheal chains.

5. Similar results with mepyramine, promethazine, and antazoline were obtained using isolated human bronchial chains.

6. Atropine 10^{-5} did not antagonize the bronchoconstrictor effect of mepyramine 10^{-5}; atropine 10^{-4} itself caused contraction of guinea-pig tracheal chains.

7. It is suggested that the direct actions of antihistamine drugs on bronchial muscle are "histamine-like" actions, and may be due, at least in part, to the histamine-releasing properties of the drugs.

8. It is concluded that the bronchoconstrictor action of the antihistamine drugs tested may well be a factor limiting their therapeutic activity in asthma.

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