THE EFFECT OF HISTAMINE AND ANTIHISTAMINES ON BODY TEMPERATURE

By E. W. Packman, G. V. Rossi and J. W. E. Harrisson

From the Department of Pharmacology, Philadelphia College of Pharmacy and Science

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The body temperature decreasing effect of histamine in dogs and guinea-pigs was first described by Dale and Laidlaw[1]. Similar results with regard to rats were observed by several authors; Gyermek[2] described that this effect increased as the environmental temperature decreased. In contrast, Leschke[3] and Smith[4] reported that histamine had no temperature lowering effect on rabbits. That antihistamines also exert a body temperature decreasing effect was reported by Ambrus, Ambrus, Jacob and Harrisson[5,6,7,8], who described such effect on mice, rats and guinea-pigs. Halpern and Briot[9] compared the temperature decreasing effect of 6 different antihistamines in rats, and stated that a parallelism exists between antihistaminic activity and temperature lowering effect. Ambrus, *et al.*[10], described antagonism between the body temperature lowering effect of certain doses of histamine and antihistamines in mice; above and below this optimal dose range, however, synergism occurred. In guinea-pigs and rats[5,6] small doses of antihistamines (which in themselves did not affect body temperature) prevented the hypothermic action of histamine.

This study was designed to further investigate the above phenomena; specially to examine the effect of histamine and antihistamines on the body temperature of different species and to study the parallelism between antihistamic activity and temperature lowering effect, employing a broader spectrum of antihistamines.

Methods

The animals employed in the test were as follows:—female Swiss albino mice of our colony, female Strong A mice, and female C57 mice, all weighing from 22 to 28 g.; female Sherman albino rats of our colony, weighing from 125 to 250 g.; English smooth-hair guinea-pigs (Rockland Farms), weighing from 300 to 500 g.; New Zealand white rabbits (Rockland Farms), weighing from 3 to 4 kg. Male mice and rats were not used, as preliminary studies revealed greater variations in the normal body temperature of male than in female mice and rats. The mice and rats were maintained on Rockland complete rat pellets; guinea-pigs on Rockland guinea-pig diet, greens and timothy hay; rabbits on Rockland rabbit pellets and timothy hay. All were given water *ad libitum*. The animals were all housed and all experiments (unless otherwise specified) were conducted in air-conditioned quarters maintained at 21° C. Before their use in tests, the mice, rats, and rabbits were deprived of food for 24 hours, but allowed free access to water. The guinea-pigs were deprived of food only 12 hours, since a longer period of fasting was found to weaken them

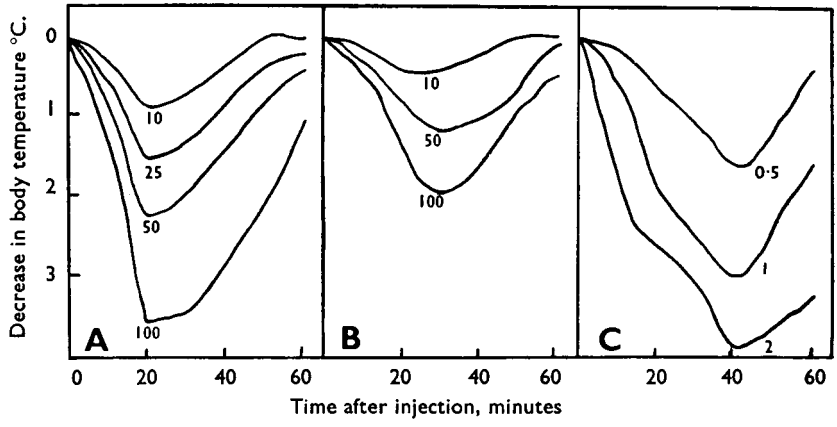
materially and decrease their resistance toward the drugs used. The animals were not used more often than twice weekly, since Fabinyi and Szebehelyi[11] found that mice could be desensitised against the temperature reducing effect of histamine by daily histamine injections over a 12-day period. The dosages of all drugs were based on individual body weight. In the temperature experiments all injections were given subcutaneously. Prior to administration of drugs, the body temperature of each animal was taken 3 times over a 30-minute period. After injection, temperatures were determined at frequent intervals, i.e., every 5 to 10 minutes, until the maximal drop was produced and the temperature began to ascend to normal, after which it was found sufficient to record temperatures at 15- to 30-minute intervals.

Histamine diphosphate U.S.P., and the following antihistamines were used: *N*-*p*-methoxybenzyl-*N'N'*-dimethyl-*N*-α-pyridylethylenediamine hydrochloride (mepyramine hydrochloride, neoantergan hydrochloride), β-dimethylaminoethyl benzhydryl ether hydrochloride (diphenhydramine hydrochloride, benadryl); *NN*-dimethyl-*N'*-benzyl-*N'*-(α-pyridyl) ethylenediamine hydrochloride (tripelennamine hydrochloride, pyribenzamine hydrochloride); 10-(2-dimethylamino-1-propyl) phenothiazine hydrochloride (promethazine hydrochloride, phenergan); 2-methyl-9-phenyl-2:3:4:9-tetrahydro-1-pyridindene tartrate (phenindamine tartrate, theophorin); 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate (prophenpyridamine maleate, trimeton maleate); *NN*-dimethyl-*N'*-(*p*-methoxybenzyl)-*N'*-(2-pyrimidyl) ethylenediamine hydrochloride, (thonzylamine hydrochloride, neohetramine hydrochloride); 10-[2-(1-pyrrolidyl)ethyl] phenothiazine hydrochloride (parathiazine hydrochloride, pyrrolazote); 2-(*N*-phenyl-*N*-benzylaminomethyl) imidazoline hydrochloride (antazoline hydrochloride, antistine hydrochloride); *NN*-dimethyl-*N'*-(α-pyridyl)-*N'*-(2-methylthienyl) ethylenediamine hydrochloride (thenylpyramine hydrochloride, histadyl hydrochloride); *N*-methyl-*N'*-(4-chlorobenzhydryl) piperazine dihydrochloride (chlorcyclizine hydrochloride, di-paralene), diethylaminocarbethoxybi*cyclo*hexyl hydrochloride (dicylomine hydrochloride, 33536 Merrell); *N*-dimethylaminoethyl-phenothiazine hydrochloride (3015 RP); 2-(10-phenothiazinyl) *iso*propyltrimethyl-ammonium benzonesulphonate (thiazinamium 3554 RP); *NNN'N'*-tetramethyl-*NN'*-bis-β-(10-phenothiazenyl) ether pentamethylene diammonium dibromide (3550 RP).

Body temperatures were taken with copper-constantan thermocouples; readings were made from a potentiometer when the thermo-electric current was counterbalanced as indicated by a galvanometer as described previously[10].

Observations and Discussion

Effect of Histamine on the Body Temperature of Different Species. Histamine causes a definite fall in the body temperature of mice, rats and guinea-pigs; however, it has no effect on the body temperature of rabbits. The effect of varying doses of histamine on the body temperature of these species is shown in Figure 1. There was no significant difference between



A. Mice. Each line is the average of 8 mice.
B. Rats. Each line is the average of 6 rats.
C. Guinea-pigs. Each line is the average of 4 guinea-pigs.

FIG. 1. The effect of histamine on body temperature of different species. The dosage of histamine base in mg./kg. is indicated against each line. Body temperatures were determined every 10 minutes.

the reaction of Swiss, C57, and Strong A mice to either histamine or antihistamines. No effect was evidenced in the body temperature of rabbits even when histamine was given in lethal concentrations (15 mg./kg.). Upon comparing doses on a mg./kg. basis, the order of increasing sensitivity to the body temperature decreasing effect of histamine is: rabbits, rats, mice and guinea-pigs. If a comparison is made between these species by expressing the dose of histamine which will cause a decrease of 1° C. in rectal temperature in terms of a percentage of the lethal dose, the order of sensitivity is: rabbits, guinea-pigs, rats and mice. (Table I.) Since mice

TABLE I

Species	Histamine LD100 mg./kg., s.c.	Histamine producing 1° C. fall in rectal temperature, mg./kg., s.c.	Percentage of LD100 producing 1° C. fall in rectal temperature
Rabbit ..	12	No fall in temperature with any dose	
Rat	2,000	50	2·5
Mouse ..	2,000	25	1·25
Guinea-pig ..	3	0·5	16·6

and rats are highly resistant to most pharmacological as well as the toxic effects of histamine, this leads us to conclude that they are relatively more sensitive to its temperature lowering effects than the generally more histamine-sensitive guinea-pigs. It appears therefore, that the body temperature decreasing effect of histamine may be used as a convenient test for studies involving histamine in mice and rats. Furthermore, since there are few symptoms of anaphylaxis in mice, we believe that body temperature decrease may be used as an indicator of the degree of anaphylaxis in this species.

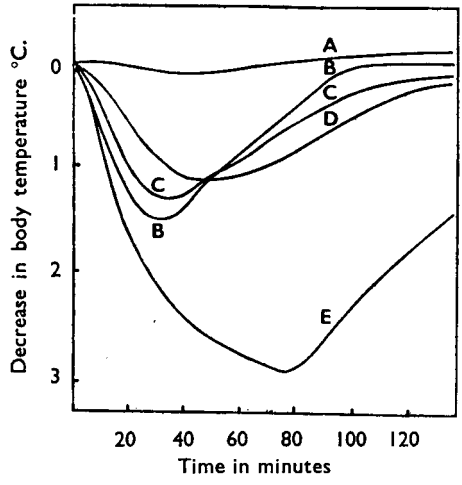


FIG. 2*a*.

A. Dicyclomine.
B. Tripelennamine.
C. Thiazinamium.
D. Prophenpyridamine.
E. Promethazine.

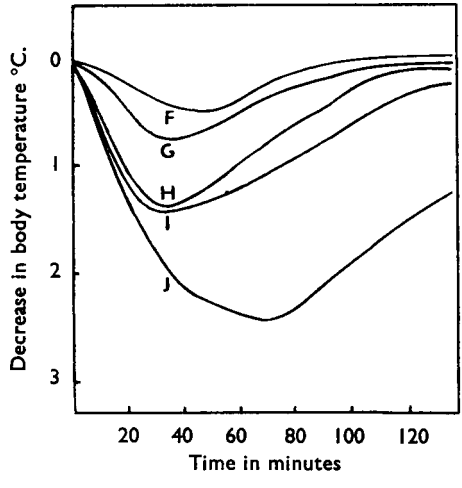


FIG. 2*b*.

F. Phenindamine.
G. Parathiazine.
H. Antazoline.
I. 3550 RP.
J. 3015 RP.

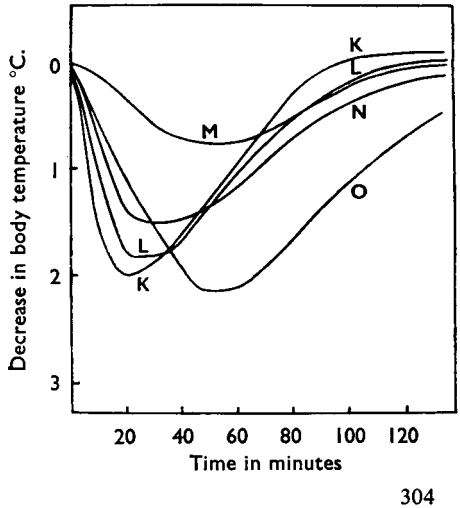


FIG. 2*c*.

K. Thonzylamine.
L. Mepyramine.
M. Chlorcyclizine.
N. Thenylpyramine.
O. Diphenhydramine.

FIGS. 2*a*, 2*b* and 2*c*. Effect of antihistamine bases on the body temperature of mice. All at a dosage of 50 mg./kg. Each line represents the average of 4 mice.

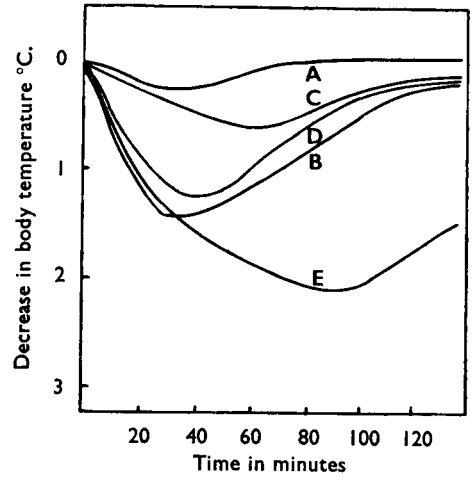


FIG. 3*a*.

A. Dicyclomine.
B. Tripelennamine.
C. Thiazinamium.
D. Prophenpyridamine.
E. Promethazine.

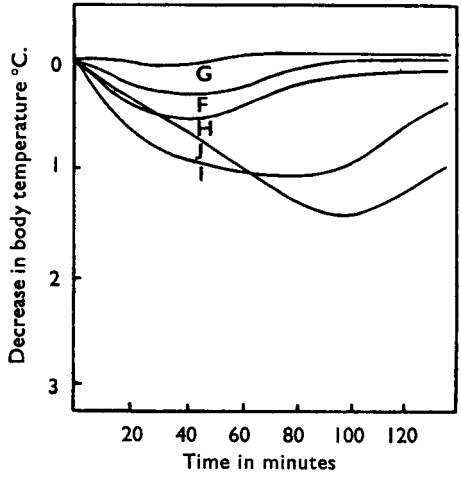


FIG. 3*b*.

F. Phenindamine.
G. Parathiazine.
H. Antazoline.
I. 3550 RP.
J. 3015 RP.

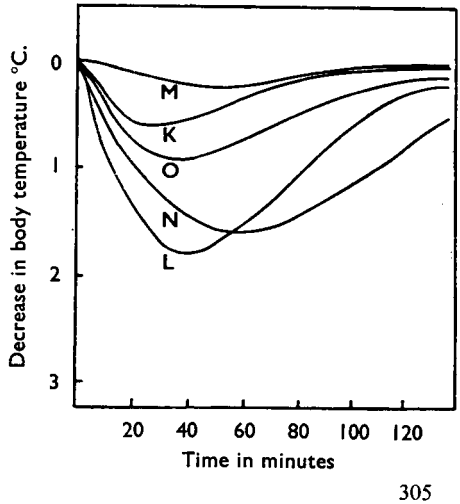


FIG. 3*c*.

K. Thonzylamine.
L. Mepyramine.
M. Chlorcyclizine.
N. Thenylpyramine.
O. Diphenhydramine.

FIGS. 3*a*, 3*b* and 3*c*. Effect of antihistamine bases on the body temperature of mice. All at a dosage of 25 mg./kg. Each line represents the average of 4 mice.

Effect of Antihistamines on the Body Temperature of Different Species. The effect of 15 antihistamines in doses of 10, 25, and 50 mg./kg. was observed in mice; it was found that all cause a fall in body temperature, the degree of fall varies widely among the individual compounds. The results obtained with 25 and 50 mg./kg. are illustrated in Figures 2 and 3, respectively. In general the sequence remains rather constant as the dose is varied; in comparison with the other antihistamines, thenylpyramine hydrochloride shows a proportionately smaller effect with increased dosage. This can be ascribed to the intense cramps produced at higher dosage. In contrast, thonzylamine hydrochloride displays a proportionately greater effect with increased dosage. The reason for this is not clear; it is, however, interesting to note that Feinberg *et al.*[12] demonstrated a greater increase of protective action of thonzylamine hydrochloride against intravenous histamine in guinea-pigs with increasing doses than the increase in protective effect of the other antihistamines under the same conditions.

In Table II, the antihistamines studied are arranged in groups having a similar degree of action, and these groups are listed in order of decreasing activity. Table II, also gives, on the basis of the literature, data on the same drugs in their order of activity from points of view other than their effect on rectal temperature. It is obvious from this table that there is no relationship between rectal temperature decreasing effect and the other pharmacological effects enumerated.

The effect of mepyramine hydrochloride, diphenhydramine, hydrochloride, phenindamine tartrate, and promethazine hydrochloride, on body temperature was compared on mice, rats and guinea-pigs. As may be observed from the graphical presentation of the results (Figure 4) the sensitivity of these species toward the body temperature decreasing effect of the antihistamines approximates the relative sensitivity to the body temperature decreasing effect of histamine. None of the antihistamines tested had any effect on the body temperature of rabbits, even when given in concentrations which ultimately resulted in death.

The "Antipyretic" Effect of Antihistamines. Friis[13] described promethazine as having an antipyretic effect on guinea-pigs the body temperature of which had been increased by injection of a pyrogenic vaccine. However, it is a question whether this can be attributed to a true antipyretic action or whether it is due to the normal body temperature reducing effect of antihistamines. The procedure of Friis was repeated using rabbits, on which antihistamines have no temperature reducing action. 20 mg./kg. of promethazine hydrochloride does not decrease fever produced by the intravenous injection of 3 ml. of typhoid-paratyphoid vaccine (2000 million organisms/ml.). Within the limitations of this finding it can be concluded that antihistamines have no true antipyretic activity.

The Influence of Environmental Temperature on the Body Temperature Decreasing Effect of Histamine and Antihistamines. The body temperature decreasing action of both histamine and antihistamines was found to be more pronounced at lower environmental temperatures. Figure 5 illustrates the body temperature decreasing effect of 4 antihistamines in mice

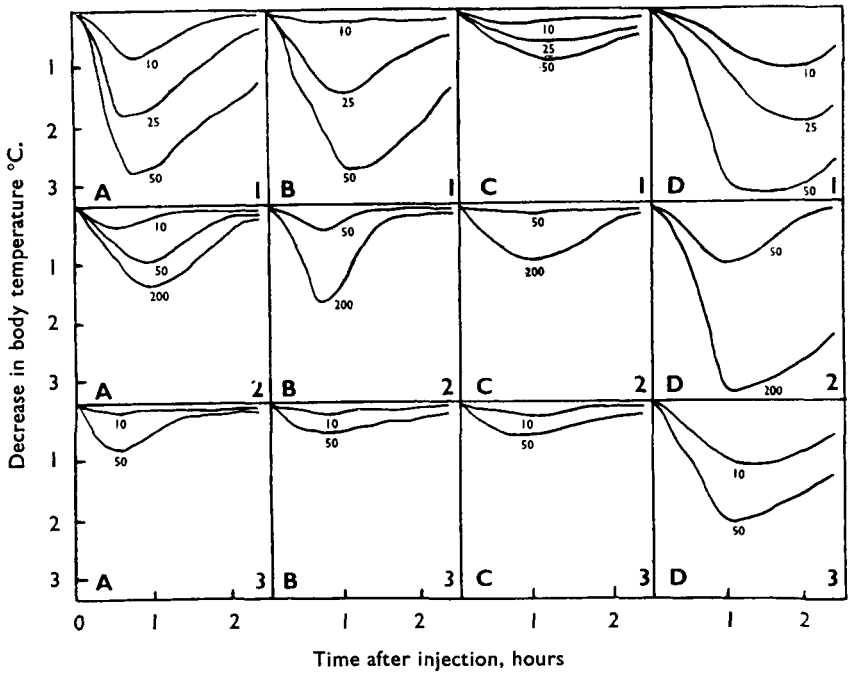
measured at environmental temperatures of 22° C. and at 28 to 31° C. Since vasodilation is probably an important factor in the body temperature decreasing action of these drugs, lower environmental temperatures would tend to increase the rate of heat loss in cases where vessels are dilated by drug action.

TABLE II

Action	Order of Decreasing Activity	Subject	Reference
Body temperature . .	Promethazine, Mepyramine, Thenylpyramine, 3015 RP > Tripelennamine, Diphenhydramine, Prophenpyridamine, 3550 RP > Thonzylamine, Antazoline, Thiazinaminum > Phenindamine, Dicylomine, Chlorcyclizine, Parathiazine	Mice. Effect of histamine 25 mg./kg. subcutaneously	This report
Antihistaminic activity	Thenylpyramine > Mepyramine > Phenindamine > Diphenhydramine, Promethazine > Chlorcyclizine, Prophenpyridamine, Parathiazine, Tripelennamine > Antazoline, Thonzylamine	Guinea-pig. Protection against lethal effect of histamine 0·1 mg./kg., intraperitoneally	12
Antihistaminic activity	Tripelennamine > Mepyramine > Promethazine, Thenylpyramine, Chlorcyclizine > Prophenpyridamine > 3015 RP > Diphenhydramine, Thonzylamine, Phenindamine, Parathiazine, Antazoline	Guinea-pig. Inhibition of histamine. Bronchospasm.	12
Antihistaminic activity	Thenylpyramine > Tripelennamine > Mepyramine > Diphenhydramine > Antazoline	Guinea-pig. Relaxed intestine. Strips contracted by histamine, 0·1 μg./ml.	16
Antihistaminic activity	Mepyramine > Tripelennamine > Thenylpyramine > Promethazine > Phenindamine > Diphenhydramine	Guinea-pig. Relaxed intestine. Strips contracted by histamine, 0·1 μg./ml.	17
Antianaphylactic activity	3015 RP, Promethazine, Chlorcyclizine, Thenylpyramine > Parathiazine > Tripelennamine, Diphenhydramine > Phenindamine > Thonzylamine > Mepyramine	Guinea-pig. Protective effect of 3 mg./kg.	12
Atropine-like activity	Diphenhydramine, Phenindamine	Guinea-pig. Isolated intestine	18
Atropine-like activity	Diphenhydramine > Mepyramine	Guinea-pig. Isolated intestine	19
Hypnotic effect	Promethazine > Diphenhydramine > Mepyramine > Tripelennamine	Mice.	20
Toxicity	Tripelennamine > Mepyramine > Diphenhydramine > Promethazine	Mice. Intraperitoneally	21
Toxicity	Tripelennamine > Diphenhydramine > Mepyramine > Antazoline	Mice. Intravenously and subcutaneously	22

Discussion

From the point of view of body temperature decreasing effect, all of the antihistamines studied were divided into 4 distinct groups each group consisting of those drugs with a similar degree of action. Upon comparison of these groups with compilations arranged in the same manner from the standpoint of antihistaminic potency, anti-anaphylactic activity, atropine-like action, hypnotic effect, and acute toxicity, we concluded that the body temperature decreasing effect of antihistamines bears no relationship to any of the other aforementioned actions. These data are arranged in



A. Mepyramine.
B. Diphenhydramine.
C. Phenindamine.
D. Promethazine.

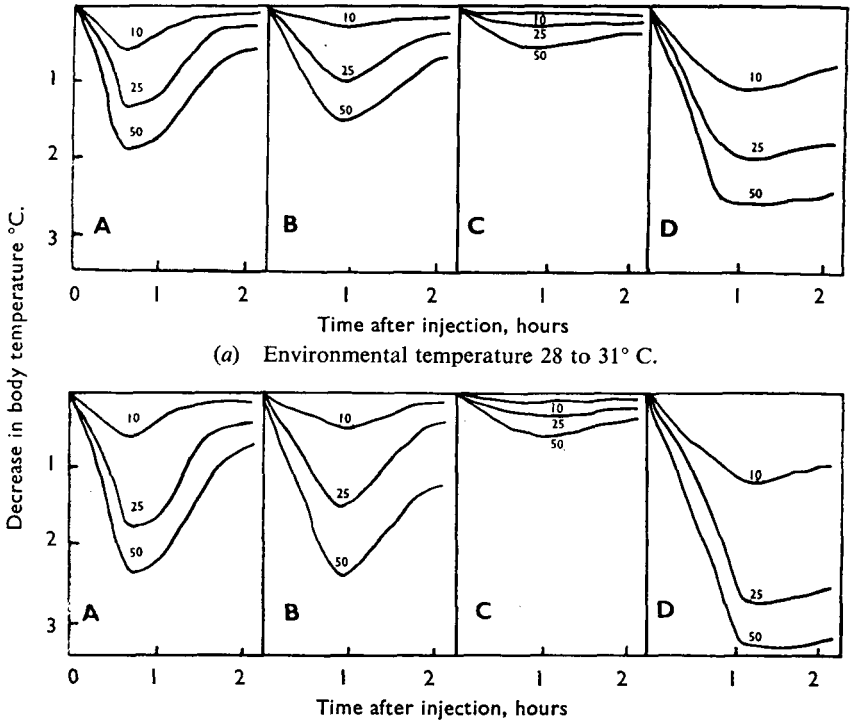
1. Mice. Each line is the average of 4 mice.
2. Rats. Each line is the average of 2 rats.
3. Guinea-pigs. Each line is the average of 2 guinea-pigs.

FIG. 4. Effect of antihistamines on the body temperature of different species. The dosage of antihistamine base in mg./kg. is indicated against each line.

Table II. This conclusion is in contrast with the hypothesis advanced by Halpern *et al.*, concerning the parallelism of body temperature reducing action and antihistaminic potency, based on the results obtained with 6 antihistamines.

The mode of action of the body temperature decreasing effect of histamine and antihistamines remains uncertain. Wood[14], studying the effect of promethazine hydrochloride and mepyramine hydrochloride, simultaneously on body temperature and oxygen consumption concluded that these drugs may act by decreasing heat production. Issekutz *et al.*[15], concluded as the result of calorimetric studies that small doses of histamine may decrease body temperature partly by increasing heat loss as a result of the dilation of the vessels of the skin and mucous membranes, and partly by decreasing heat production.

From our results a number of observations suggest that the mode of action of histamine and antihistamines may be similar, from the point of view of body temperature decreasing action, notably (*a*) both histamine and all of the antihistamines examined produced a fall in the body temperature of mice, rats, and guinea-pigs; (*b*) neither of these agents has any



(*a*) Environmental temperature 28 to 31° C.

(*b*) Environmental temperature 22° C.

A. Mepyramine.
B. Diphenhydramine.
C. Phenindamine.
D. Promethazine.

FIGS. 5*a* and 5*b*. Influence of environmental temperature on the effect of antihistamines on the body temperature of mice. The dosage of antihistamine base in mg./kg. is indicated against each line. Body temperatures were determined every 15 minutes.

effect on the body temperature, of rabbits; (*c*) a decrease in the environmental temperature increases the body temperature lowering action of both agents, and (*d*) the order of relative sensitivity of the different species towards the body temperature decreasing effect of histamine is similar to that of antihistamines. Furthermore, (*e*) Wood[14] showed that adrenalectomy increased the body temperature reducing effect of histamine as well as of antihistamines in rats.

SUMMARY

(1) Both histamine and antihistamines cause a decrease in the body temperature of mice, rats, and guinea-pigs. Neither of these agents has any effect on the body temperature of rabbits.

(2) Antihistamines reduce the body temperature of normal animals as well as of those with artificially induced fever, therefore this affect cannot be attributed to a true antipyretic activity.

(3) The body temperature decreasing action of histamine as well as of antihistamines is greater at lower environmental temperatures.

(4) There is no parallelism between the body temperature decreasing effect of the 15 antihistamines tested and their antihistaminic potency, antianaphylactic activity, atropine-like effect, hypnotic action, and acute toxicity.

(5) The possible mode of action of histamine and antihistamines on body temperature has been discussed.

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