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STUDIES ON THE EFFECT OF ANTISTINA, AMIDRYL AND PYRIBENZAMINE ON THE PRAUSNITZ-KÜSTNER REACTION¹

By

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The effect of various antihistamines on urticaria has been described in numerous reports, according to which it may be possible to obtain improvement of the affection in about 50-70 % of the chronic cases and about 80-90 % of the acute cases, the favorable effect applying both to the itch and to the urticarial reaction (1, 3, 7, and 11).

In this connection it will be of interest to elucidate how various antihistamines act upon experimentally produced urticarial hypersensitiveness. This condition was produced by employment of the Prausnitz-Küstner experiment first described in detail by Prausnitz & Küstner (8) in 1921. The technique of this experiment was as follows: A small amount of serum derived from a strongly hypersensitive allergic is injected intracutaneously on a normal person, sensitizing the surrounding skin area. 24 hours later the allergen is injected

¹ The studies here reported were carried out with a view to a prize problem of 1948 at the University of Copenhagen: "Investigation is wanted into the effect of substances presumably antagonistic to histamine on experimentally produced allergic hypersensitiveness of eczematous and urticarial nature."

Antistina (Ciba, Switzerland) = N-benzyl-N-phenyl-aminomethylimidazolin.
Amidryl (Medicinalco, Denmark) = Benadryl (Parke, Davis and Co., U.S.A.)

= β -dimethyl-aminoethylbenzhydrol-ether-hydrochloride.

Pyribenzamine (Ciba, U.S.A.) = N-benzyl-N- α -pyridinaminoethyl-dimethylamine.

into the sensitized skin area. After this, if the test turns out positive, a typical urticarial papule appears at the site of the injection. Thus, the reaction is a local reproduction of the allergic mechanism under experimental conditions as pure as possible.

The literature on the effect of various antihistamines on the Prausnitz-Küstner reaction is only scanty, and the results are divergent. Jadassohn & Diedey (4) have looked into the effect of antistina, antergan and neoantergan upon the reaction when this is produced after ingestion of large therapeutic doses. It proved possible always to obtain a positive reaction, and the authors think that there is no demonstrable inhibition.

Vallery-Radot, Maurice and Halpern (13) gave large doses of antergan and neoantergan prior to the tests in six cases. In 5 of them the reaction turned out absolutely negative, and in one case it was moderately inhibited.

Nexmand & Sylvest (6) gave 0.15 g. amidryl per os, and the test was performed before the ingestion of this substance and then every 15 minutes in the following two hours. The authors were unable to demonstrate any inhibition of the reaction whatever. Arbesman *et al.* (2) examined the effect of pyribenzamine on the Prausnitz-Küstner test, and they found the reaction to decrease when the patients had taken 100 mg. of the remedy by mouth one hour before the test.

EXPERIMENTAL TECHNIQUE

The experiments were carried out in part with serum from a patient suffering from bronchial asthma produced by soy bean meal, and in whom the skin tests with soy meal extract were strongly positive, partly with employment of serum from hay fever patients. Venesection was performed on the soy meal allergic, and 500 cc. blood was evacuated. The serum from this blood was filtered through a bacterium-proof filter. The serum was then transferred to ampules and was now ready for use.

The serum from hay fever patients was employed in the form of dry serum¹. This dry serum had been prepared from 7000 cc. blood from altogether

¹ This dry serum was obligingly placed at my disposal by Dr. Michael Schwartz.

14 hay fever patients with marked hypersensitiveness to pollen. Before its employment, 1 g. of this dry serum was dissolved in 10 g. sterile distilled water.

The experiments were now carried out as follows:

0.1 cc. serum was injected intracutaneously in three different places on the volar aspect of one forearm on altogether 42 non-allergic patients with perfectly normal skin—all confined to bed. After 24 hours, 0.05 cc. of soy bean meal extract or pollen extract was injected intracutaneously—exactly at the site of the sensitizing injection—in three concentrations, namely 0.001 ‰, 0.01 ‰ and 0.1 ‰, the lowest concentration being always injected into the sensitized area situated nearest the wrist joint (pollen extract of 1 ‰ means that 1 g. pollen is extracted with 100 g. extraction fluid and then diluted 1:10).

About 10 min. after the latter injection an urticarial papule appeared always in the area corresponding to the 0.1 ‰ solution, and often corresponding to the 0.01 ‰ solution. The papule was characterized by a plane pale surface with irregular contour and surrounding redness. The reaction kept maximal for about 20 min. and then it subsided during the following half hour. The reaction corresponding to 0.001 ‰ was always negative. The papules were apt to vary considerably from one patient to another, as the cells in different individuals even within corresponding skin areas are not equally easy to sensitize. If the reaction corresponding to 0.01 ‰ was negative, a fourth area was sensitized, and the papule was produced with a 1 ‰ solution, so the arm would always present two positive papules. The papules were depicted on transparent paper 15 min. after their appearance. Furthermore, for the sake of control, 0.05 cc. of the allergen solution was injected intracutaneously into a non-sensitized skin area, and this resulted merely in a small non-urticarial papule which disappeared rapidly.

The patient now was given varying doses of antistina, amidryl, or pyribenzamine by mouth, and the papules were produced on the volar aspect of the other forearm, exactly as before, depicted on transparent paper, and compared with the reactions on the other arm. In this comparison it is to be taken into account that the papules may vary considerably in size, without this being of any significance. The decisive point must be whether the reactions change in character or diminish markedly, possibly fail entirely to appear. In order to assign any definite effect to the remedies, I have insisted that all the papules produced after the intake of antihistamine must be positively diminished in area.

Antistina Experiments.

The results obtained in these experiments are recorded in Table 1. The first four experiments are carried out with employment of serum from the soy meal allergic. Then, as this

TABLE I
Size of papules before and after intake of antistina.

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of antistina	Size of papules after intake of antistina
<i>Soy bean meal.</i>					
1	0.2 g.	1 hour	$1 \frac{0}{00}$	9×11 mm.	12×12 mm.
			$0.1 \frac{0}{00}$	8×10 mm.	10× 7 mm.
			$0.01 \frac{0}{00}$	0	0
2	0.2 g.	1 "	$1 \frac{0}{00}$	17×13 mm.	19×13 mm.
			$0.1 \frac{0}{00}$	9×10 mm.	13×10 mm.
			$0.01 \frac{0}{00}$	0	0
3	0.2 g.	2 hours	$1 \frac{0}{00}$	12×13 mm.	18×11 mm.
			$0.1 \frac{0}{00}$	13×11 mm.	13× 8 mm.
			$0.01 \frac{0}{00}$	0	0
4	0.2 g.	2 "	$1 \frac{0}{00}$	14×14 mm.	12×12 mm.
			$0.1 \frac{0}{00}$	11× 7 mm.	13×13 mm.
			$0.01 \frac{0}{00}$	0	0
<i>Pollen.</i>					
5	0.2 g.	3 "	$1 \frac{0}{00}$	13×11 mm.	8×12 mm.
			$0.1 \frac{0}{00}$	4× 9 mm.	8× 5 mm.
			$0.01 \frac{0}{00}$	0	0
6	0.2+0.2 g.	1 hour	$1 \frac{0}{00}$	17×15 mm.	13×12 mm.
			$0.1 \frac{0}{00}$	17×14 mm.	6× 8 mm.
			$0.01 \frac{0}{00}$	0	0
7	0.2+0.2 g.	1 "	$1 \frac{0}{00}$	18×12 mm.	14×12 mm.
			$0.1 \frac{0}{00}$	12× 8 mm.	13×14 mm.
			$0.01 \frac{0}{00}$	0	0
8	0.2+0.2+0.2 g.	1 "	$1 \frac{0}{00}$	11×12 mm.	22×13 mm.
			$0.1 \frac{0}{00}$	15×13 mm.	13× 8 mm.
			$0.01 \frac{0}{00}$	0	0
9	0.2+0.2 g.	2 hours	$0.1 \frac{0}{00}$	14×12 mm.	13×11 mm.
			$0.01 \frac{0}{00}$	12×11 mm.	11× 9 mm.
			$0.001 \frac{0}{00}$	0	0
10	0.2+0.2+0.2 g.	2 "	$0.1 \frac{0}{00}$	12×12 mm.	9× 9 mm.
			$0.01 \frac{0}{00}$	8× 8 mm.	8× 7 mm.
			$0.001 \frac{0}{00}$	0	0
11	0.2+0.2 g.	2 "	$0.1 \frac{0}{00}$	9×10 mm.	9× 7 mm.
			$0.01 \frac{0}{00}$	6× 9 mm.	6× 6 mm.
			$0.001 \frac{0}{00}$	0	0
12	0.2+0.2 g.	3 "	$0.1 \frac{0}{00}$	15×10 mm.	13×14 mm.
			$0.01 \frac{0}{00}$	8× 9 mm.	13×13 mm.
			$0.001 \frac{0}{00}$	0	0

serum commenced to lose in potency, I went on to use the serum from hay fever patients, and this was employed in the remaining 8 experiments. Antistina was given by mouth in doses of 0.2 g. once, twice or thrice before the reactions were induced in the other arm. When more than one dose is employed, they are given at intervals of three hours.

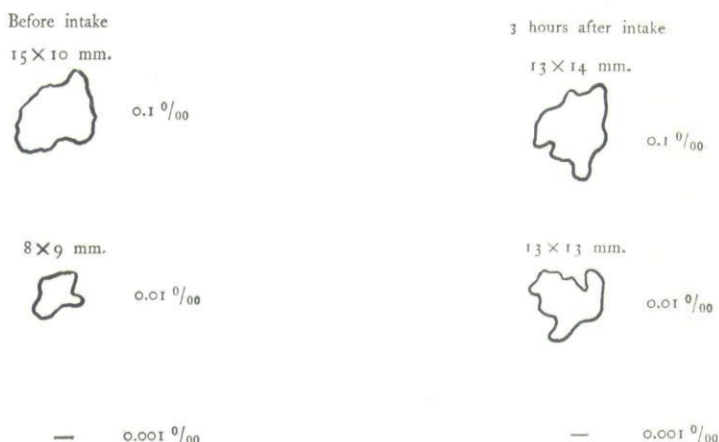


Fig. 1.

Prausnitz-Küstner reactions before and after intake of 0.2+0.2 g. antistina by mouth.

From Table 1 it will be noticed that there was no definite change in the size of the papules after intake of antistina except in Exps. 6 and 11, in which they diminished somewhat. Their character remained perfectly unchanged, however; nor was the threshold affected. Here the term "threshold" means the lowest allergen concentration able to produce a positive, urticate reaction. The reflex erythema was fairly unchanged in all the cases. All the reactions were depicted on transparent paper 15 min. after their appearance. For the sake of space, however, only a single experiment (No. 12) will be reproduced here (Fig. 1). All the measurements recorded for the papules are given in the longest diameter and the greatest diameter perpendicular on this one.

Amidryl Experiments.

The results are given in Table 2.

In the first four experiments serum from the soy bean allergic was employed for the sensitization; in the remaining experiments, serum from the hay fever patients. These experiments proceeded exactly like the antistina experiments, only that in some cases 0.1 g. amidryl was given instead of 0.2 g. antistina.

TABLE 2
Size of papules before and after intake of amidrylin.

Exp. No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of amidrylin	Size of papules after intake of amidrylin
<i>Soy bean meal.</i>					
1	0.1 g.	1 hour	1 $\frac{0}{100}$	13×10 mm.	10×14 mm.
			0.1 $\frac{0}{100}$	9× 9 mm.	9×14 mm.
			0.01 $\frac{0}{100}$	0	0
2	0.1 g.	2 hours	0.1 $\frac{0}{100}$	12×12 mm.	13×13 mm.
			0.01 $\frac{0}{100}$	9×10 mm.	5× 8 mm.
			0.001 $\frac{0}{100}$	0	0
3	0.1 g.	2 „	0.1 $\frac{0}{100}$	10×15 mm.	4× 6 mm.
			0.01 $\frac{0}{100}$	8× 6 mm.	0
			0.001 $\frac{0}{100}$	0	0
4	0.1 g.	3 „	0.1 $\frac{0}{100}$	10× 9 mm.	14× 8 mm.
			0.01 $\frac{0}{100}$	6× 9 mm.	9× 5 mm.
			0.001 $\frac{0}{100}$	0	0
<i>Pollen.</i>					
5	0.1+0.1 g.	1 hour	1 $\frac{0}{100}$	13×16 mm.	12×14 mm.
			0.1 $\frac{0}{100}$	10× 9 mm.	12×14 mm.
			0.01 $\frac{0}{100}$	0	0
6	0.1+0.1 g.	2 hours	1 $\frac{0}{100}$	21×20 mm.	17×13 mm.
			0.1 $\frac{0}{100}$	8×13 mm.	13×11 mm.
			0.01 $\frac{0}{100}$	0	0
7	0.1+0.1 g.	2 hours	1 $\frac{0}{100}$	12×17 mm.	8×10 mm.
			0.1 $\frac{0}{100}$	12×14 mm.	6× 8 mm.
			0.01 $\frac{0}{100}$	0	0

TABLE 2 (cont.)

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of amidrylin	Size of papules after intake of amidrylin
8	0.1+0.1 g.	2 "	1 ⁰ / ₀₀	17×16 mm.	19×10 mm.
			0.1 ⁰ / ₀₀	9× 9 mm.	8×10 mm.
			0.01 ⁰ / ₀₀	0	0
9	0.1+0.1 g.	2 "	1 ⁰ / ₀₀	19×14 mm.	7× 8 mm.
			0.1 ⁰ / ₀₀	8× 6 mm.	3× 6 mm.
			0.01 ⁰ / ₀₀	0	0
10	0.1+0.1 g.	3 "	1 ⁰ / ₀₀	12×10 mm.	12×10 mm.
			0.1 ⁰ / ₀₀	5× 6 mm.	9× 6 mm.
			0.01 ⁰ / ₀₀	0	0
11	0.2+0.2 g.	1 hour	0.1 ⁰ / ₀₀	11× 8 mm.	12×14 mm.
			0.01 ⁰ / ₀₀	6× 9 mm.	7×13 mm.
			0.001 ⁰ / ₀₀	0	0
12	0.2+0.2 g.	2 hours	1 ⁰ / ₀₀	17×17 mm.	13×13 mm.
			0.1 ⁰ / ₀₀	13×13 mm.	13×10 mm.
			0.01 ⁰ / ₀₀	8×13 mm.	8×14 mm.
13	0.2+0.2+0.2 g.	1 hour	0.001 ⁰ / ₀₀	0	0
			0.1 ⁰ / ₀₀	12×12 mm.	14×14 mm.
			0.01 ⁰ / ₀₀	11×11 mm.	8×12 mm.
14	0.2+0.2+0.2 g.	2 hours	0.001 ⁰ / ₀₀	0	0
			0.1 ⁰ / ₀₀	10×10 mm.	15×12 mm.
			0.01 ⁰ / ₀₀	7× 8 mm.	11×10 mm.
			0.001 ⁰ / ₀₀	0	0

From Table 2 it will be noticed that except in Exps. 3, 7 and 9 there was no definite diminution in the size of the papules after intake of amidryl. Further, the threshold was altered only in Exp. 3, in which it changed from 0.01 ⁰/₀₀ to 0.1 ⁰/₀₀. In no instance did the character of the papule undergo any change. Exp. 12 is reproduced in Fig. 2.

Pyribenzamine Experiments.

The results are recorded in Table 3.

Serum from the hay fever patient was used in all the experiments except Nos. 1, 4 and 5 in which the serum from the soy bean allergic was employed.

Pyribenzamine thus appears to have had the same effect in experiments 3, 6, 7, 11, 13, 14, 15 and 16.

It is to be mentioned at once that in no instance did the urticarial character of the papules undergo any decisive change. Here, too, the papules were plane, pale and irregular

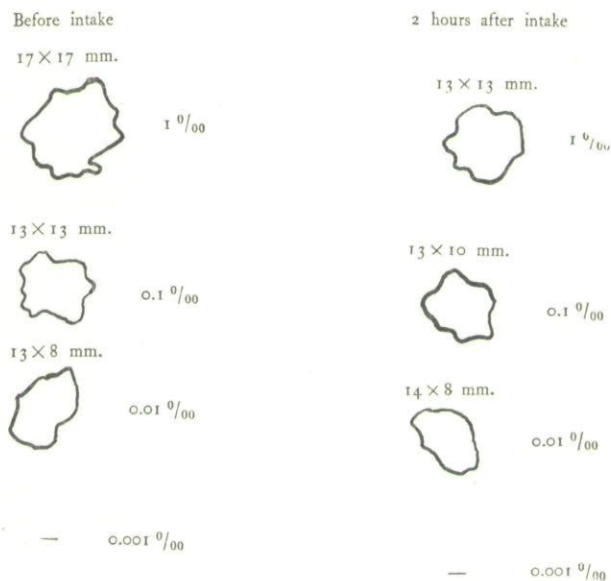


Fig. 2.

Prausnitz-Küstner reactions before and after intake of 0.2+0.2 g. amidryl by mouth.

in outline. In 8 of the 16 experiments the size of the papules diminished, and the reflex erythema was less pronounced. The threshold changed in 6 of the experiments. The reactions were depicted on transparent paper as usual, and Exp. 14 is reproduced in Fig. 3.

In no experiment was the antihistamine given parenterally.

In the literature the antihistamines are often stated to have a mitigating effect on the itch. In the present experiments, however, it is difficult to decide on this point, as the itch associated with the reaction here was only slight.

TABLE 3

Size of papules before and after intake of pyribenzamine.

Exp.No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of pyribenzamine	Size of papules after intake of pyribenzamine
<i>Soy bean meal.</i>					
1	0.1 g.	1 hour	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	16× 7 mm. 8× 5 mm. 0	15× 11 mm. 13× 10 mm. 0
<i>Pollen.</i>					
2	0.1 g.	2 hours	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	9× 10 mm. 5× 6 mm. 0	9× 6 mm. 6× 9 mm. 0
3	0.1 g.	3 "	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	9× 13 mm. 6× 10 mm. 0	8× 5 mm. 0 0
<i>Soy bean meal.</i>					
4	0.2 g.	1 hour	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	12× 10 mm. 6× 10 mm. 0	11× 11 mm. 12× 10 mm. 0
5	0.2 g.	2 hours	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	12× 10 mm. 6× 8 mm. 0	9× 6 mm. 8× 9 mm. 0
<i>Pollen.</i>					
6	0.2 g.	3 "	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	8× 14 mm. 7× 10 mm. 0	6× 8 mm. 0 0
7	0.05+0.05 g.	1 hour	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	14× 14 mm. 10× 12 mm. 0	8× 10 mm. 8× 10 mm. 0
8	0.05+0.05 g.	2 hours	0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀ 0.001 ⁰ / ₀₀	10× 15 mm. 7× 8 mm. 0	16× 11 mm. 6× 7 mm. 0
9	0.1+0.1 g.	1 hour	1 ⁰ / ₀₀ 0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀	11× 14 mm. 7× 12 mm. 0	11× 16 mm. 7× 8 mm. 0
10	0.2+0.2 g.	1 "	1 ⁰ / ₀₀ 0.1 ⁰ / ₀₀ 0.01 ⁰ / ₀₀	19× 15 mm. 12× 10 mm. 0	17× 16 mm. 14× 12 mm. 0

TABLE 3 (cont.)

Exp. No.	Dosage	Interval from last dose to appearance of reaction	Allergen conc.	Size of papules before intake of pyribenzamine	Size of papules after intake of pyribenzamine
11	0.2+0.2 g.	2 hours	0.1 $\frac{0}{100}$	12×15 mm.	5×6 mm.
			0.01 $\frac{0}{100}$	11×10 mm.	0
			0.001 $\frac{0}{100}$	0	0
12	0.2+0.2 g.	2 "	0.1 $\frac{0}{100}$	17×13 mm.	14×14 mm.
			0.01 $\frac{0}{100}$	7×10 mm.	9×13 mm.
			0.001 $\frac{0}{100}$	0	0
13	0.2+0.2 g.	2 "	0.1 $\frac{0}{100}$	16×11 mm.	9×5 mm.
			0.01 $\frac{0}{100}$	13×10 mm.	0
			0.001 $\frac{0}{100}$	0	0
14	0.2+0.2 g.	3 "	1 $\frac{0}{100}$	8×12 mm.	8×4 mm.
			0.1 $\frac{0}{100}$	12×11 mm.	8×5 mm.
			0.01 $\frac{0}{100}$	9×10 mm.	5×6 mm.
			0.001 $\frac{0}{100}$	7×8 mm.	0
			0.0001 $\frac{0}{100}$	0	0
15	0.2+0.2+0.2 g.	1 hour	1 $\frac{0}{100}$	24×16 mm.	13×11 mm.
			0.1 $\frac{0}{100}$	9×9 mm.	5×7 mm.
			0.01 $\frac{0}{100}$	0	0
16	0.2+0.2+0.2 g.	2 hours	0.1 $\frac{0}{100}$	9×14 mm.	8×8 mm.
			0.01 $\frac{0}{100}$	6×10 mm.	0
			0.001 $\frac{0}{100}$	0	0

After this, some experiments were carried out to see how the Prausnitz-Küstner reaction might be influenced when the antihistamine was mixed with the allergen before its injection into the sensitized skin area. Jadassohn & Diedey (4) investigated how antistina, antergan and neoantergan influenced the reaction when one of these substances was mixed with the allergen before the injection. They found a pronounced inhibition in every instance.

The technique employed in my experiments was as follows:

On an experimental subject 6 skin areas—3 on the volar aspect of either forearm—were sensitized with dry serum from the hay fever patient. 24 hours later the reactions were induced by injection of 0.05 cc. of a mixture of equal parts of a 0.1 $\frac{0}{100}$ pollen solution and saline into the sensitized areas nearest

the wrist joints. Into the remaining 4 sensitized areas injections were given of 0.05 cc. of a mixture of equal parts of 0.1 % pollen solution and 1 % solutions of antistina, amidryl, pyribenzamine and metadryl¹, respectively. The injections were given exactly in the same spot as the preceding sensitizing serum. For the sake of control, an injection of the allergen was also given outside the sensitized area. 15 min. later the resulting papules were depicted (Fig. 4). In those experiments where the mixture contained antihistamine, the papules

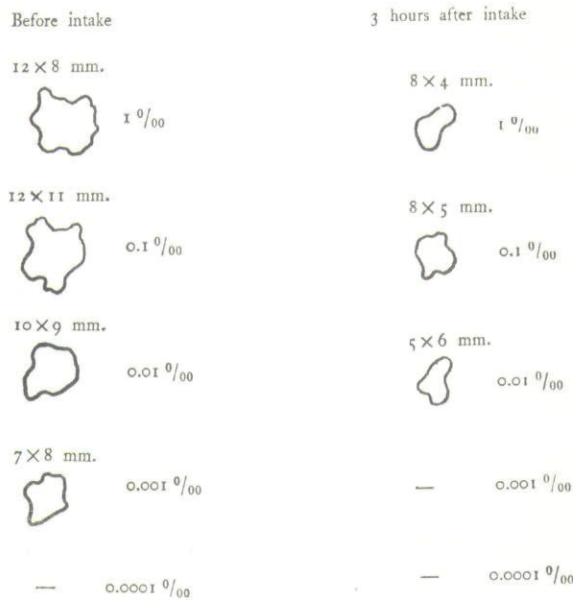


Fig. 3.

Prausnitz-Küstner reactions before and after intake of 0.2 + 0.2 g. pyribenzamine by mouth.

were greatly diminished and had changed in character. They were still plane, but more regular in outline; the color was reddish, and the surrounding redness was limited to an intensely red zone, 4-5 mm. wide, round the papules. There was no definite mutual difference between the antihistamine-treated papules.

The experiment was repeated—this time with employment of 1/2 % solutions of antihistamines. Now 8 skin areas were

¹ Metadryl is an antihistamine produced by the Ferrosan medicinal factory, Copenhagen. It is near-related to benadryl, the only difference being that in the metadryl molecule one more methyl group is linked to the nitrogen atom.

sensitized instead of 6, 2 sensitized areas being injected with a mixture of 2 % procaine and 0.1 $\frac{0}{00}$ pollen solution, besides 2 % pantocaine and 0.1 $\frac{0}{00}$ pollen solution. The various antihistamines here employed have a rather pronounced local-anesthetic effect, which perhaps conceivably might have something to do with the inhibitory effect. Procaine and pantocaine, however, were not able to inhibit the size of the

17 $\times$ 11 mm.



0.1 $\frac{0}{00}$ pollen
+ 0.9 $\frac{0}{0}$ saline, equal parts

17 $\times$ 15 mm.



0.1 $\frac{0}{00}$ pollen
+ 0.9 $\frac{0}{0}$ saline, equal parts

5 $\times$ 6 mm.



0.1 $\frac{0}{00}$ pollen
+ 1 $\frac{0}{0}$ pyribenzamine, equal parts

5 $\times$ 6 mm.



0.1 $\frac{0}{00}$ pollen
+ 1 $\frac{0}{0}$ amidryl, equal parts

5 $\times$ 6 mm.



0.1 $\frac{0}{00}$ pollen
+ 1 $\frac{0}{0}$ metadryl, equal parts

5 $\times$ 6 mm.



0.1 $\frac{0}{00}$ pollen
+ 1 $\frac{0}{0}$ antistina, equal parts

Fig. 4.

Prausnitz-Küstner reactions produced with 0.1 $\frac{0}{00}$ pollen extract
+ antihistamines.

papules. The reactions were depicted as usual (Fig. 5). The antihistamine-treated papules were diminished this time, too, and also their character had changed in the same way as before. There was no definite mutual difference between the antihistamine-treated papules.

Now the question is what inferences may be drawn from these experiments in which antihistamine and allergen are mixed before the injection.

The inhibitory effect might simply be due to destruction or inactivation of the allergen by the antihistamine in the mixture, prior to the injection. Further, it is also conceivable that the inhibition may be due to entirely physical conditions. Intracutaneous injection of antihistamine gives rise to a papule

which does not increase in size, and which is surrounded by a zone of intense redness, presumably signifying a local irritation. The papule disappears rapidly, but the redness persists longer and is gradually replaced by brownish pigmentation, where the skin practically has lost its sensibility.

13 × 15 mm.



0.1 $\frac{0}{100}$ pollen
+ 0.9 $\frac{0}{10}$ saline, equal parts

17 × 15 mm.



0.1 $\frac{0}{100}$ pollen
+ 0.9 $\frac{0}{10}$ saline, equal parts

7 × 6 mm.



0.1 $\frac{0}{100}$ pollen
+ $\frac{1}{2}$ $\frac{0}{10}$ pyribenzamine, equal parts

11 × 8 mm.



0.1 $\frac{0}{100}$ pollen
+ $\frac{1}{2}$ $\frac{0}{10}$ amidryl, equal parts

7 × 7 mm.



0.1 $\frac{0}{100}$ pollen
+ $\frac{1}{2}$ $\frac{0}{10}$ metadryl, equal parts

8 × 12 mm.



0.1 $\frac{0}{100}$ pollen
+ $\frac{1}{2}$ $\frac{0}{10}$ antistina, equal parts

14 × 15 mm.



0.1 $\frac{0}{100}$ pollen
+ 2 $\frac{0}{10}$ procaine, equal parts

15 × 13 mm.



0.1 $\frac{0}{100}$ pollen
+ 2 $\frac{0}{10}$ pantocaine, equal parts

Fig. 5.

Prausnitz-Küstner reactions produced with 0.1 $\frac{0}{100}$ pollen extract
+ antihistamines.

The pigmentation and anesthesia may persist unchanged for several weeks. The hyperemic zone may possibly prevent the urticarial reaction from developing fully. Thus Török & Rajka (12) have reported that hyperemia—for instance, produced by heat applied to the skin—inhibits the development of histamine papules in the hyperemic area. In order to elucidate this question, the following iontophoretic experiments were carried out.

Iontophoretic Experiments.

These experiments were carried out with 5 % solutions of antistina, amidryl and pyribenzamine as hydrochloric salts. In these solutions the substances dissociate into antihistamine ions, with positive charge, and chloride ions, with negative charge. The electrode, consisting of a thin disc of lead, 2.5 cm. in diameter, was connected with the positive pole of the iontophoresis apparatus, and a circular piece of filter paper, moistened with the antihistamine solution, was placed on the electrode. Iontophoresis was carried on for 5 min. with a current of 2 milliamp. This gave rise to moderate redness and some miliary papules at the place of iontophoresis. Both the redness and the papules disappeared within 1-2 hours.

Altogether six experiments were carried out with the following technique.

In three places on the volar aspect of either forearm the skin was sensitized with dry serum from the hay fever patient as described before—at suitable intervals. 24 hours later the three antihistamines—pantocaine, procaine, atropine sulphate—distilled water and tap water were introduced by iontophoresis, each to its sensitized skin area. Iontophoresis was carried out with all these substances in order to make sure that a possible antihistamine effect really would be due to antihistamine activity, not to the local-anesthetic effect of these substances or to atrophine effect (9), let alone the local irritation produced by the current. 1-2 hours later when the local effect of the current had subsided, the reactions were induced with the 0.1 $\frac{0}{\infty}$ pollen extract solution, and the results were depicted 15 min. later. The experiments are recorded in Table 4.

In Exp. 1 iontophoresis was performed on the left arm with saline and a 2 % atropine solution. In both cases the positive electrode was employed so that sodium and atropine ions entered the tissue. Over the third sensitized area no iontophoresis was performed. On the right arm iontophoresis was performed with antistina, amidryl and pyribenzamine. The actual introduction of these three substances by iontophoresis was ensured by iontophoresis with histamine over a part of the area into which the antihistamine had been introduced. Corresponding to this area, some redness appeared, while corresponding to the rest of this area, over which histamine had been introduced by iontophoresis, vesiculation due to the histamine effect appeared about half a minute later. Then, one hour later, the allergen was injected into the six sensitized skin areas, and the reactions were depicted (Fig. 6).

From Fig. 6 it will be noticed that all the three antihistamine-treated

TABLE 4
Prausnitz-Küstner reactions in skin areas exposed to iontophoresis with antihistamines.

	Iontophoresis with	Size of reaction	Iontophoresis with	Size of reaction	Iontophoresis with	Size of reaction
Exp. 1	saline	14 × 12 mm.	—	16 × 15 mm.	2% atropine	12 × 12 mm.
	5% antistina	13 × 7 mm.	5% amidryl	16 × 8 mm.	5% pyribenz.	12 × 10 mm.
Exp. 2	2% pantocaine	10 × 12 mm.	—	10 × 12 mm.	saline	9 × 10 mm.
	5% pyribenz.	10 × 12 mm.	5% amidryl	10 × 12 mm.	5% antistina	10 × 16 mm.
Exp. 3	tap water	15 × 15 mm.	—	17 × 18 mm.	2% atropine	14 × 17 mm.
	5% pyribenz.	6 × 9 mm.	5% amidryl	10 × 12 mm.	5% antistina	12 × 14 mm.
Exp. 4	saline	15 × 19 mm.	tap water	12 × 16 mm.	—	16 × 12 mm.
	5% antistina	11 × 15 mm.	5% amidryl	12 × 12 mm.	5% pyribenz.	12 × 9 mm.
Exp. 5	tap water	19 × 19 mm.	2% procaine	13 × 13 mm.	—	15 × 17 mm.
	5% pyribenz.	11 × 7 mm.	5% amidryl	9 × 8 mm.	5% antistina	13 × 7 mm.
Exp. 6	saline	10 × 12 mm.	tap water	11 × 11 mm.	tap water	13 × 14 mm.
	5% pyribenz.	8 × 9 mm.	5% antistina	8 × 5 mm.	5% amidryl	8 × 13 mm.

papules were a little smaller than the other three reactions. The urticarial character of the papules and the time it took them to develop, however, were quite unchanged. The papules submitted to iontophoresis with atropine and with saline were not smaller than the papule which had not been exposed to iontophoresis.

In Exp. 2 iontophoresis was carried out with saline and a 2 % pantocaine solution, besides the three antihistamines. Here, too, the electrode was made

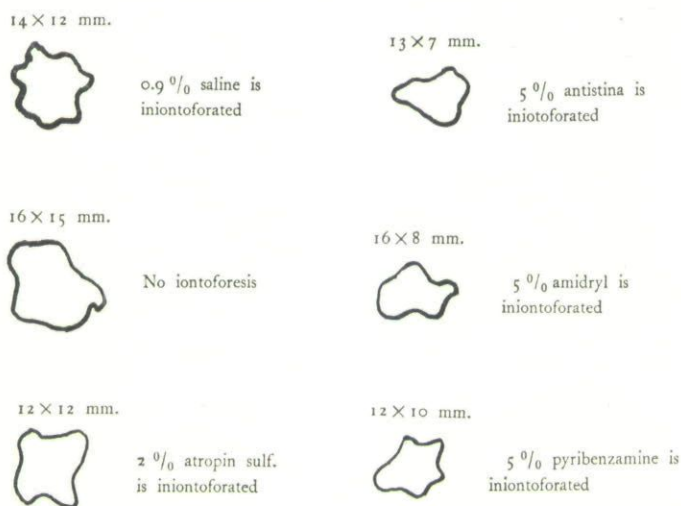


Fig. 6.

Prausnitz-Küstner reactions in skin areas with iontophoresis of antihistamines.

positive, so that the pantocaine ions might enter the tissue. There was no guaranty, however, that this actually did take place. Thus, no local anesthesia appeared, corresponding to the antihistamine areas. There is no reason to think, however, that some pantocaine ions would enter into the tissue. The reactions were induced as usual, but in this experiment there seemed not to be any definite difference in the size of the papules. Possibly this may be due to the circumstance that here the allergen was injected as early as 20 min. after the iontophoresis, *i.e.*, before the local irritation had subsided completely. Thus the remaining hyperemia corresponding to the sites of iontophoresis may have had a disturbing effect.

Table 4 gives also the results of Exps. 3, 4, 5, and 6. The antihistamine-treated papules, on the whole, were smaller than the papules which had not been exposed to iontophoresis or had been submitted to the influence of tap water, saline, atrophine sulphate, procaine or pantocaine.

The results obtained in Exp. 3 are reproduced in Fig. 7. In this experiment pyribenzamine appears to have been superior to amidryl and antistina in this respect. In the remaining 5 experiments there appears to have been no definite mutual difference between the three antihistamines.

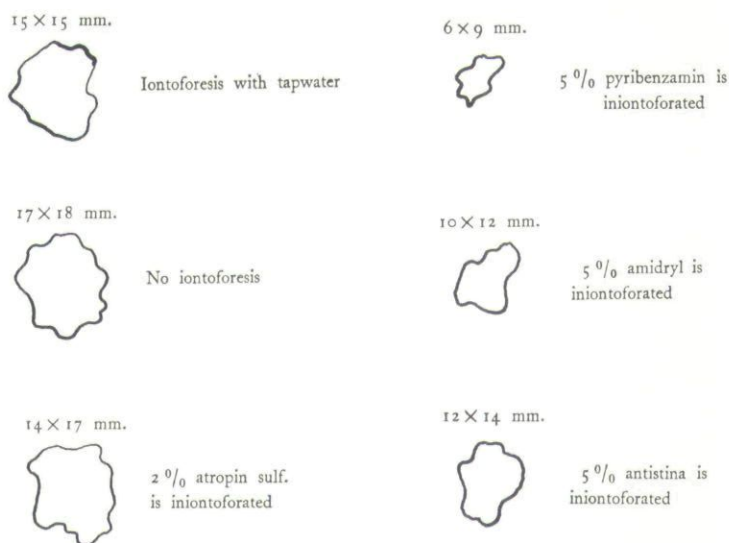


Fig. 7.

Prausnitz-Küstner reactions in skin areas with iontophoresis of antihistamines.

SUMMARY

Studies are reported on the effect of three antihistamines—antistina, amidryl and pyribenzamine—on the Prausnitz-Küstner reaction when these substances are 1) given per os in varying doses, 2) mixed with the allergen prior to its injection, and 3) introduced into the skin by iontophoresis, before the reactions are produced. On peroral administration, only pyribenzamine appears to have any effect. When they are mixed with the allergen prior to the injection, all three antihistamines inhibit the size of the papules. On employment of iontophoresis the three substances likewise appear to have some inhibitory effect.

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