

A STUDY OF THE EFFECT OF VARIOUS DRUGS ON THE WHEALING REACTION*

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INTRODUCTION

THIS study was initiated in an attempt to explain the failure of antihistaminic drugs to affect favorably many patients with chronic urticaria and/or angioneurotic edema. Our experience does not confirm that of reports published¹⁻⁷ indicating satisfactory responses ranging from 60 to 80 per cent in chronic urticaria. Out of 53 cases seen in one year, 36 failed to resolve regardless of the antihistaminic drug used or the dose prescribed. One especially resistant patient still developed wheals while taking 1600 mg. of Pyribenzamine daily. The experimental literature^{4, 5, 8} emphasizes the inhibitory or "blocking" activity of this category of drugs rather than their effect on already formed wheals. Apparently, once "H" substance, or histamine, has been released and has acted on the skin capillaries, there is little effect on the resultant capillary dilatation and tissue edema by antihistaminics. This fact has not received proper clinical recognition. Accordingly, the following experiments were set up to observe the direct effects of various categories of drugs on both histamine- and antigen-induced wheals to determine the most effective manner of treating chronic urticaria. Many drugs have been recommended as having the property of effective wheal recession, including the sympathicomimetics, salts, aminophyllin, anticholinergics, and vitamins. More recently, a new category of drugs represented by gentisic acid⁹ has been shown to have a favorable effect on the exudative phase of rheumatic fever.

EXPERIMENTAL

Patients with proved clinical sensitivity to ragweed were selected as test subjects. Their response to intradermally introduced ragweed extract and to histamine was observed under set conditions so that the character and course of the wheal response could be recorded. A typical observation is shown in Fig. 1 by wheal tracings.

Thus, in this particular patient, a concentration of ragweed extract containing 0.01 mg. TN/c.c.† was used, and a 1:100,000 dilution of histamine base. Approximately 0.02 c.c. of each was introduced intradermally on the volar aspect of the forearm and observed. The resultant wheals were outlined with India ink and transposed onto transparent tape at various time intervals. In nearly all instances the ragweed wheal reaction reached its maximum size in about 15 minutes; some few at 30 minutes. The histamine wheals reached their maximum size before 15 minutes, and had either diminished or were ill defined by 30 minutes.

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†The symbol TN/c.c. stands for total nitrogen per c.c. of extract.

Preliminary experiments with Benadryl and Pyribenzamine given orally showed a definite capacity to inhibit wheal formation if given 30 minutes prior to the injection of both histamine and ragweed, but failed to show any effect on wheals if given simultaneously or 15 minutes after injection. The primary criticism of this procedure is that there might be faulty absorption from the gastrointestinal tract.

NORMAL COURSE OF WHEALING REACTION

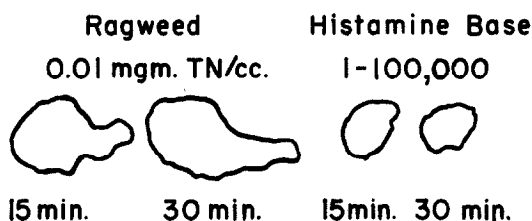


Fig. 1.

EFFECT OF PYRIBENZAMINE ON WHEALING REACTION

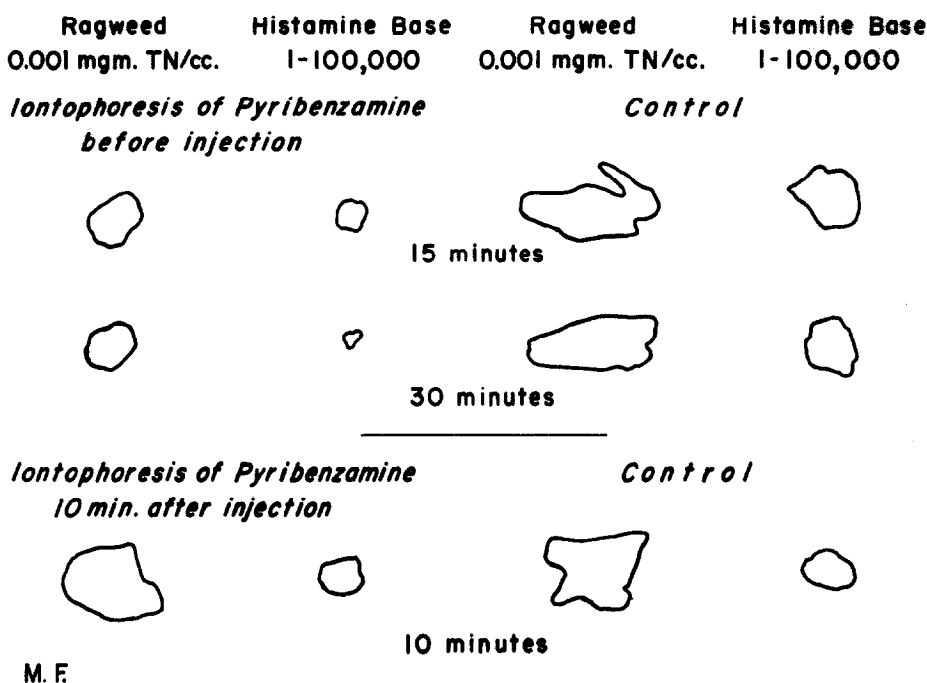


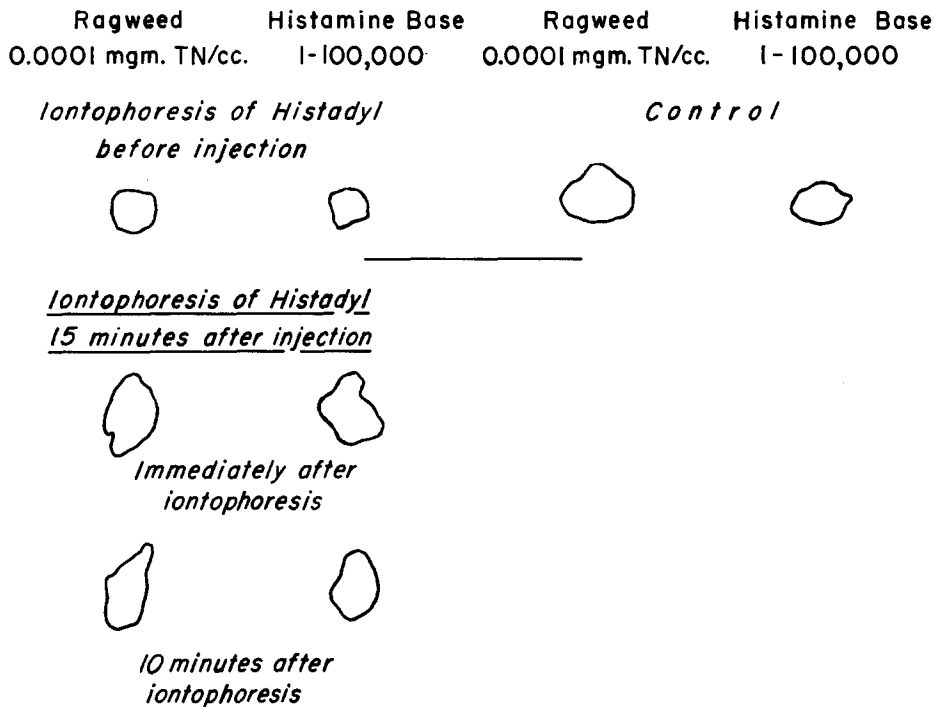
Fig. 2.

Therefore, Benadryl was tried intravenously in 10 and 25 mg. doses given prior to and after the introduction of the wheal-producing histamine and ragweed. Again, similar results were observed, that is, inhibition if administered

before, and no response if given afterward. A possible objection to this technique is that the drug failed to reach the tissue site of reaction in adequate effective concentration. A third method of administering the Benadryl by direct intracutaneous injection of 0.1 c.c. into the selected test site was tried and here again similar results were noted as by the other routes.

Epinephrine hydrochloride 1:1000 given subcutaneously, on the other hand, showed a very definite capacity not only to inhibit histamine- and ragweed-induced wheals if given beforehand, but also to cause a pronounced recession in preformed wheals.

EFFECT OF HISTADYL ON WHEALING REACTION



T. K.

Fig. 3.

To meet the objections to the above methods of administering the test drugs, the technique of iron transfer was used. This is a proved procedure for introducing, with minimal trauma, a depot of a given drug into the skin by utilizing a constant galvanic current and a uniform electrode.^{10, 11}

Preliminary tests were made to determine an effective concentration of each drug to be studied, as well as current and electrode size factors. The nonspecific effect of the ion-transfer stimulation upon wheals was determined by comparing the action of each drug to that of physiologic saline.

Fresh solutions were prepared for each run. A lead electrode 10 sq. cm. was covered with a similar sized piece of asbestos paper which was saturated with the selected drugs dissolved in distilled water. For most trials a current of 3 Ma. for from 1 to 10 minutes was used depending upon the drug introduced. The polarity of the electrodes depended on the chemical nature of the drug. The indifferent electrode consisted of a pad saturated with saline.

EFFECT OF EPHEDRINE SULFATE ON WHEALING REACTION

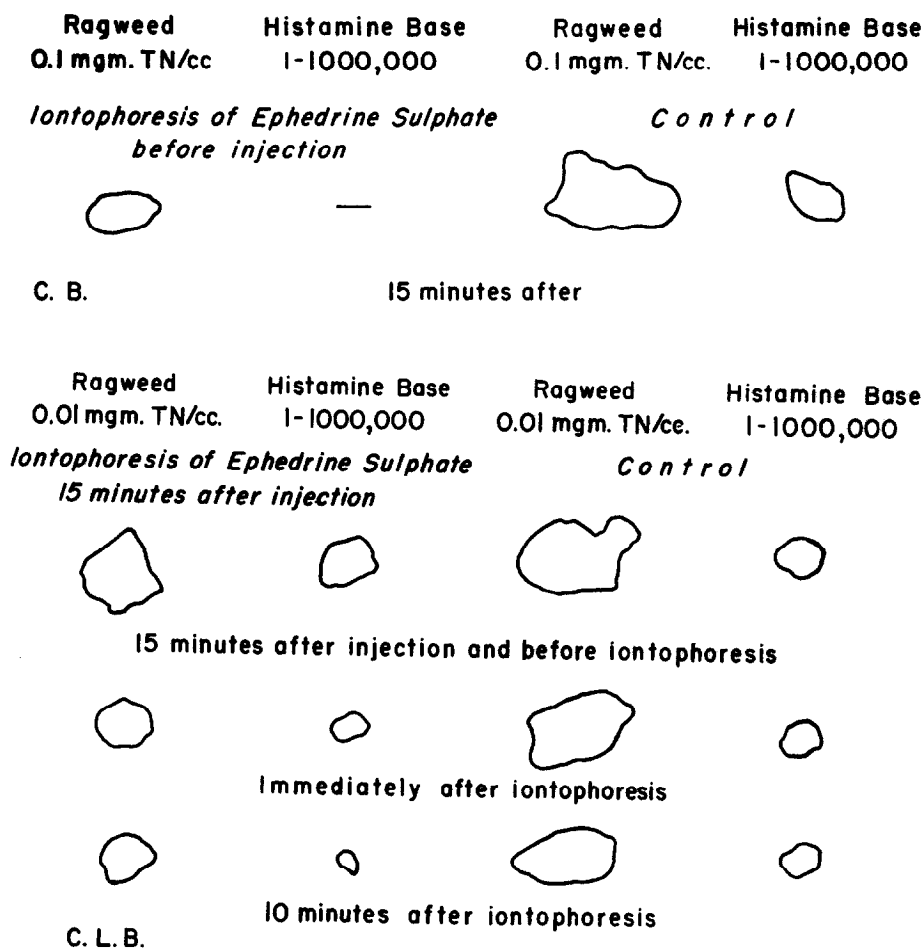


Fig. 4.

With one arm being used for testing and the other as a control, 0.02 c.c. histamine and ragweed solutions of predetermined concentration were given intradermally on the volar surface of the forearms. Wheal tracings outlined with ink were transposed onto transparent tape as a permanent record.

Figs. 1-9 demonstrate typical experimental results for the given conditions and some of the drugs studied.

Fig. 2, for example, is a record of wheal tracings on patient M. F. A freshly prepared 5 per cent solution of Pyribenzamine was iontophoresed on the right forearm using a 10 sq. cm. electrode on the positive pole for 5 minutes at 3 Ma. The indifferent electrode saturated with saline was applied to the left forearm. Ragweed extract containing 0.001 mg. TN/c.c. and histamine solution, 1:100,000 were then injected intradermally into the iontophoresed sites on both forearms. Fifteen and 30 minutes after injection the resultant wheals were outlined and recorded. The tracings on the right forearm demonstrated the inhibiting effect of Pyribenzamine as compared with the control reactions on the left forearm.

EFFECT OF EPINEPHRINE HCl ON WHEALING REACTION

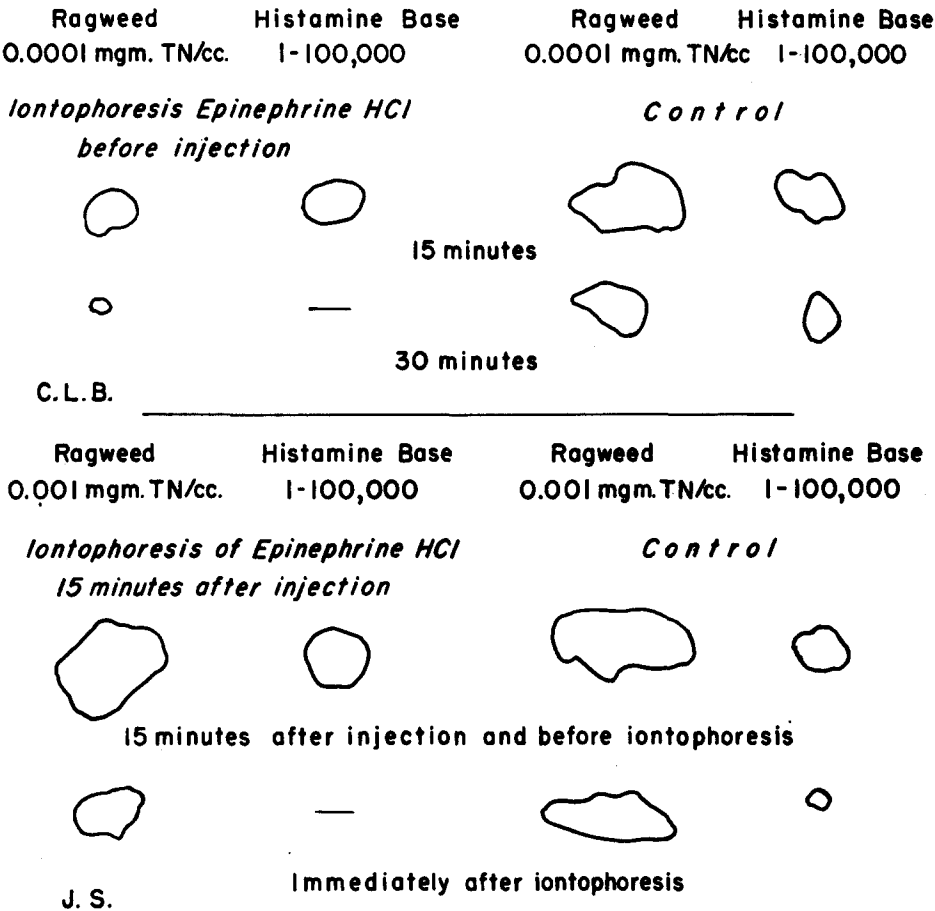


Fig. 5.

The second series of tracings (Fig. 2) were made after the injection of the same strength ragweed and histamine solutions on each forearm. Ten minutes later Pyribenzamine was iontophoresed with the same size electrode for 5 minutes at 3 Ma. over the wheals on the right arm. The left arm was covered with

the negative saline electrode and acted as a control. In this instance no apparent difference was noted between the two arms when tracings were recorded 10 minutes after iontophoresis, that is, the Pyribenzamine failed to affect the already formed wheal.

Fig. 3 records the effect of Histadyl on the wheal reactions of ragweed 0.0001 mg. TN/c.c. and histamine 1:100,000 on patient T. K. using the same technique as described above. Histadyl 5 per cent was iontophoresed for 5 minutes with 2 Ma. on the right forearm, with the left arm acting as the control. Definite inhibition may be observed on the 15 minute wheals. Iontophoresis of Histadyl 15 minutes after the injection of ragweed and histamine failed to diminish the size of the wheals when recorded immediately and 10 minutes after iontophoresis.

EFFECT OF ISUPREL ON WHEALING REACTION

Ragweed	Histamine Base	Ragweed	Histamine Base
0.01 mgm. TN/cc.	1-100,000	0.01 mgm. TN/cc.	1-100,000

Iontophoresis of Isuprel

before injection

Control



H. D.

15 minutes

Ragweed	Histamine Base	Ragweed	Histamine Base
0.01 mgm. TN/cc.	1-100,000	0.01 mgm. TN/cc.	1-100,000

Iontophoresis of Isuprel

15 minutes after injection

Control



15 minutes after injection and before iontophoresis



Immediately after iontophoresis



D. H.

10 minutes after iontophoresis

Fig. 6.

Fig. 4 is a study using a 1 per cent solution of ephedrine sulfate iontophoresed for 4 minutes at 3 Ma. With this drug there is a marked inhibition

Figs. 5 and 6, showing the effects of epinephrine and Isuprel upon the whealing reaction, reveal similar results as with ephedrine. With both of these drugs, however, there was evidence of systemic absorption affecting the control sites to some degree.

EFFECT OF AMINOPHYLLIN ON WHEALING REACTION

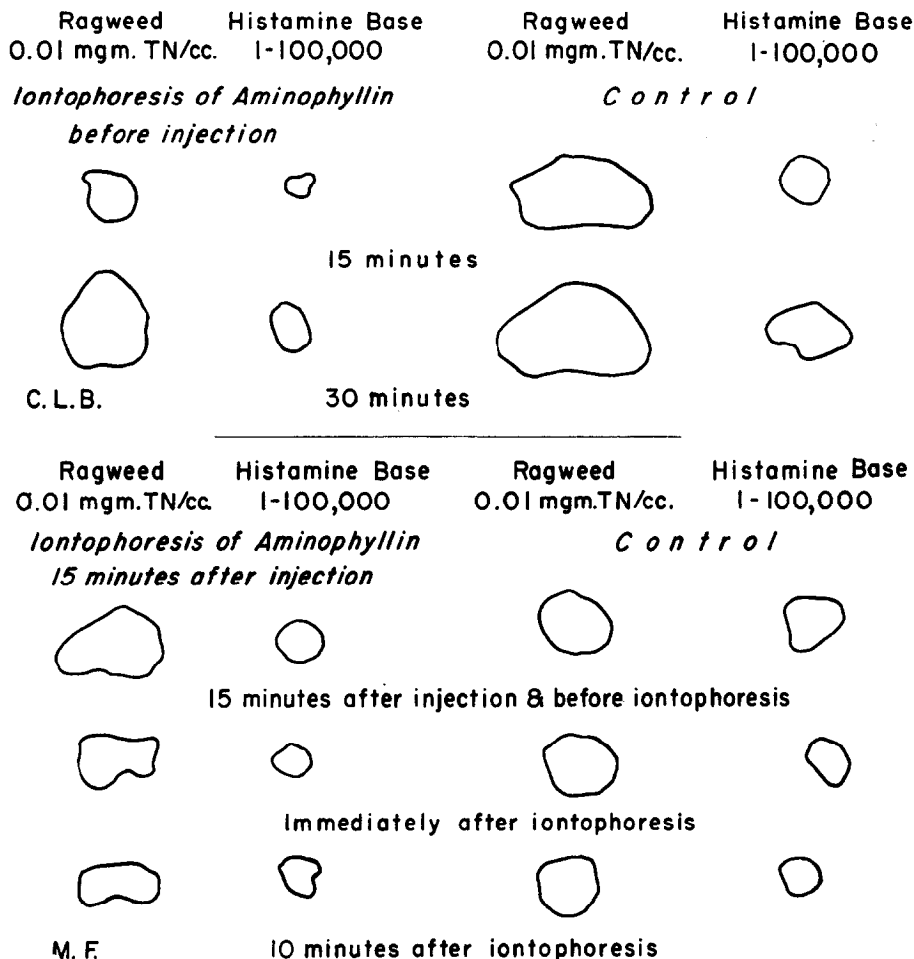


Fig. 7.

Aminophyllin likewise showed marked inhibitory properties on whealing (Fig. 7). The iontophoresis of aminophyllin on wheals induced 15 minutes before showed a definite diminishing effect on these wheals immediately and 10

minutes after iontophoresis. The experiment with atropine was somewhat complicated since this drug has some whealing and vesiculating properties of its own (Fig. 8). However a 1 per cent solution of atropine sulfate iontophoresed for 2 minutes at 3 Ma., using the same technique, failed to inhibit ragweed and histamine wheal formation, and the iontophoresis of atropine onto 15 minute ragweed and histamine wheals did not cause them to resolve.

Five per cent sodium gentisate iontophoresed for 5 minutes at 3 Ma. likewise showed no inhibitory or resolving properties (Fig. 9).

EFFECT OF ATROPINE SULFATE ON WHEALING REACTION

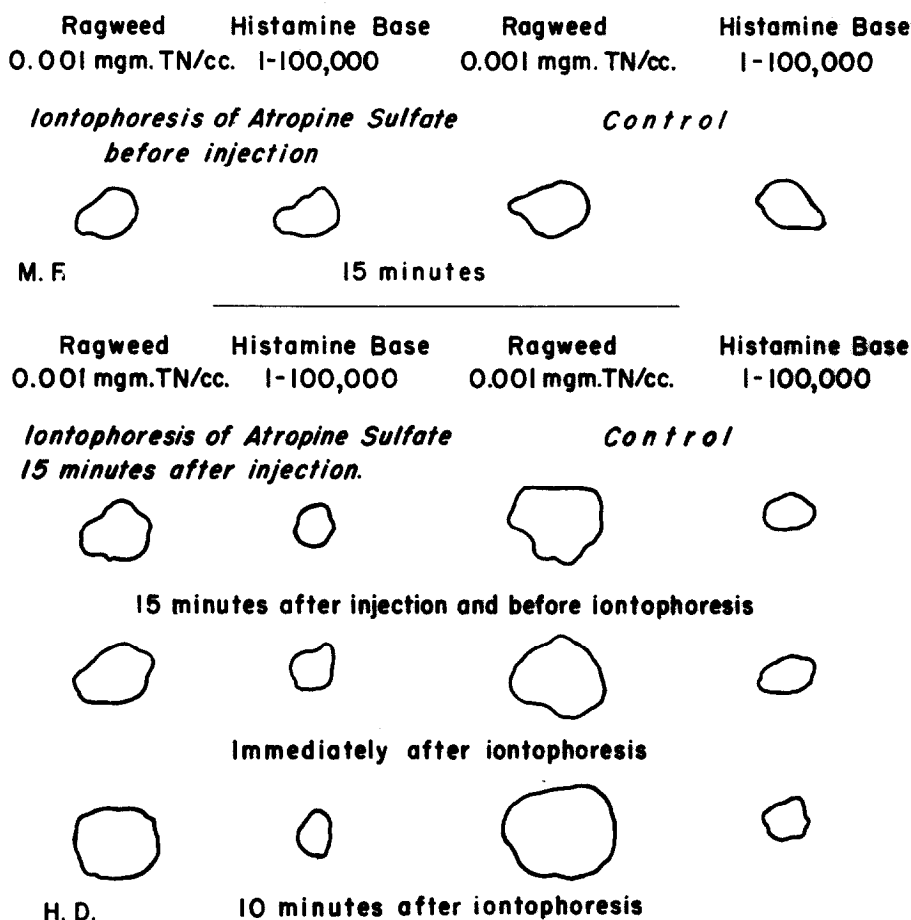


Fig. 8.

In two known tuberculin skin test positive patients Pyribenzamine was iontophoresed into a site on the right forearm using a 75 sq. cm. electrode. A depot of Pyribenzamine was obtained which inhibited whealing from histamine for 72 hours. Vollmer tuberculin patch tests were applied to both forearms of each patient and after 48 and 72 hours typically positive eczematous reactions developed both in the treated and control sites.

DISCUSSION

Under the conditions of these experiments Pyribenzamine and Histadyl demonstrate the property of inhibiting the formation of histamine and ragweed wheals. Ephedrine, epinephrine, Isuprel and aminophyllin likewise showed definite inhibitory effects. Only ephedrine, epinephrine, Isuprel and aminophyllin showed the property of diminishing the size of a preformed wheal. Atropine, methylglucamine ascorbate, CaCl, KCl, and sodium gentisate had no apparent effect, either of inhibition or diminution.

EFFECT OF SODIUM GENTISATE ON WHEALING REACTION

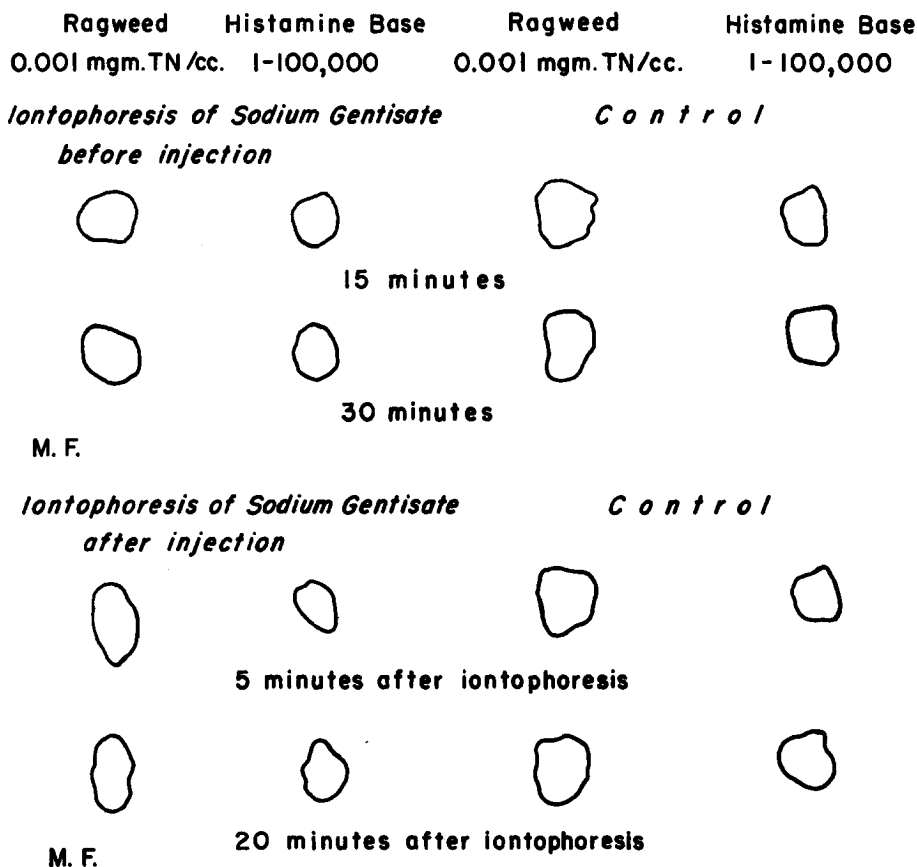


Fig. 9.

From these results it would seem that the ideal treatment for urticaria would be a combination of sympathicomimetic and antihistamine drugs. However, the fact that this form of therapy is not always effective in chronic urticaria suggests that some mechanism other than histamine release may be involved.

SUMMARY

1. Antihistaminic drugs exhibit the property of inhibiting histamine- or antigen-induced wheals, but do not affect preformed wheals.

2. Sympathicomimetic drugs and aminophyllin both inhibit and cause resolution of histamine- or antigen-induced wheals.

3. Some mechanism other than "H" substance or histamine plays a role in many cases of chronic urticaria.

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Materials were obtained as follows:

Pyribenzamine—Ciba Pharmaceutical Products Incorporated.

Histadyl—Eli Lilly & Company.

Benadryl—Parke, Davis & Co.

Sodium gentisate—Hoffmann-La Roche, Inc.

Isuprel—Winthrop-Stearns, Inc.

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