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The Antihistaminic drugs in the treatment of bronchial asthma

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THE ANTIHISTAMINIC DRUGS IN THE TREATMENT OF BRONCHIAL ASTHMA

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INTRODUCTION

Although it is true that the histamine theory of allergy does not explain all of the allergic manifestations on the basis of histamine activity, evidence has accumulated rapidly, since Dale and Laidlow (20) demonstrated the similarity of the physiologic effects of histamine and of anaphylactic shock, in support of this hypothesis. When Best and Dale (4) demonstrated the presence of histamine in the tissues of the body, there existed a reasonable explanation for the source of histamine in anaphylaxis. Histamine or an histamine-like substance was demonstrated in the blood and thoracic lymph duct of the dog during anaphylaxis in 1932 (24). Next it was found that the amount of histamine in the blood of the inferior vena cava just above the diaphragm in an anaphylactic dog was the same as the amount required to produce the same vascular changes by intravenous injection. With this evidence at hand, it was easy to accept the fact that histamine has an important function in the production of anaphylaxis.

The proof of the role of histamine in allergy is not so conclusive as the proof of histamine's role in anaphylaxis. Indeed, much of the evidence to support

the former rests on the similarity between allergic and anaphylactic responses. The remaining proof is based on the fact that when histamine is administered to man, some of the phenomena of allergy are demonstrated. Experimental evidence began to pile up following the suggestion of Lewis (50) that an acute allergic reaction occurs when histamine or the H-substance is freed by the combination of antigen and antibody. Cerqua, in 1936, made the first studies of blood histamine levels in asthmatics. Parrot, in 1938, confirmed Cerqua's previous results that the blood histamine equivalents were increased three to four times the normal values. Randolph and Rackemann (65) were able to confirm the findings of Haworth and Mac Donald (39) in determining that there is a suggestive increase of the blood histamine above normal during paroxysms of asthma as compared with the time in between attacks. Katz and Cohen (44) showed that the histamine in leukocytes is released from the blood in vitro when a specific allergen is added. They declared that the amounts of histamine released could be large enough to be biologically significant in vivo and assumed that at least at the points of highest concentrations, e. g. tissues of the respiratory or digestive tracts, the histamine released from the blood cells circulating

through these areas should contribute, to a certain extent, to some of the local tissue reactions. More recently, Katz has shown that histamine can be released from the skin when a specific allergen is applied (43).

Weiss et al (84) in 1932 observed no noticeable effect of histamine on the bronchioles of normal persons, but the drug did show a broncho-constricting action in patients with bronchitis, bronchial asthma, emphysema, and cardiac asthma. Curry (19) confirmed the occurrence of broncho-constriction in many asthmatics following the administration of histamine. The sensitivity to histamine varies with each individual and in the same individual with the severity of the attack.

Thus, at present, experimental evidence points to the fact that histamine has an important role in the production of allergic manifestations. Its role is summarized as follows in a composite from the writings of Epstein (29) and Waldbott (80 through 83):

1. The patient becomes sensitized to the antigen
2. Specific antibodies or reagins against the antigen are produced. These settle in some tissue of the body which becomes the so-called "shock organ," and this determines the localization of clinical symptoms.

3. Upon renewed exposure to the antigen, an antigen-antibody reaction occurs at the shock organ and histamine or an histamine-like substance is released
4. This substance dilates the capillaries and induces smooth muscle spasm, especially bronchospasm.

Treatment of allergic manifestations is aimed at breaking in on this chain of events at some point:

1. Eliminate the antigen
2. Produce the protective antibody by desensitization
3. Contract the allergic wheal through vasoconstriction
4. Relieve the muscle spasm through the use of antispasmodics
5. Counteract the histamine

It is the latter method of treatment with which this paper will deal, especially as this method has been applied in the treatment of broncial asthma.

Desensitizing to Histamine

One of the early attempts to break in on the histamine linkage in the allergic chain reaction was di-

rected toward desensitization therapy. Ramirez and St. George (64) treated ten patients with "endogenous" asthma with increasing doses of histamine and obtained temporarily good results in two. Many reports have supported desensitization therapy. However, since the vast majority of patients so treated have received no benefit, this method cannot be expected to be of any use to the present-day allergist.

Histaminase

In 1929, when Best (5, 6) was able to demonstrate the presence of an enzyme capable of destroying histamine in some of the tissues in the body, it was only natural that histaminase be given a therapeutic trial. Ten years of clinical trial have proved the inefficacy of histaminase. Best and Mc Henry pointed out that the physiological basis for the failure of histaminase is that if taken by mouth, the enzyme is destroyed by the acid pH of normal gastric juice. If it escapes this, then it is unable to withstand the assaults of pepsin and trypsin. It must be pointed out that intramuscular injections of histaminase, however, were just as ineffective as were oral preparations. In 1940, the American Medical Association refused to accept Torantil, an

histaminase preparation, for publication in New and Non-official Remedies.

Histamine-Azoprotein or Hapamine

Since histamine itself failed in evoking any immunity, Fell et al (68) decided that histamine bound to a protein (since proteins are powerful antibody-initiating substances) might be useful in immunological procedures. Sheldon (74), in 1941, reported good results in the treatment of ten out of twenty-two patients with asthma, rhinitis, urticaria, and other allergic manifestations. Despite enthusiastic reports by Cohen and Friedman in 1943, 1944, and 1945 (14, 15, 16), these investigators stated that the degree of immunity afforded by this method of therapy is not great. However, they believe that it can be used as an adjunct to other therapy in certain cases of allergy.

At present, the status of histamine azoprotein is still not clear and it would seem that further investigation is needed for the proper evaluation of this procedure in the treatment of allergy.

Biological Antagonists

Another approach to the development of histamine-

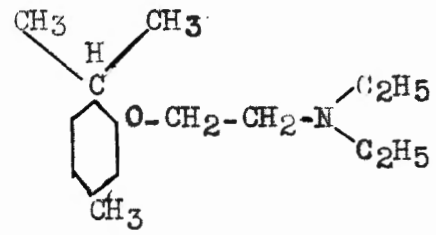
antagoninzing substances has been through the study of compounds which counteract histamine through their own biological activity. Epinephrine is such a drug. However, epinephrine is so potent a biological compound in itself that its therapeutic use should be reserved for extreme circumstances, according to Code (12).

Antihistaminics

The most promising approach to the problem of breaking in on the histamine linkage has been from the point of view of finding compounds which would block histamine without exerting any biological effect. Atropine was shown by Dale and Laidlow to be such a drug. However, the clinically useful dosages were so great as to have more effect on the vagus or on the other parasympathetic nerves than on histamine.

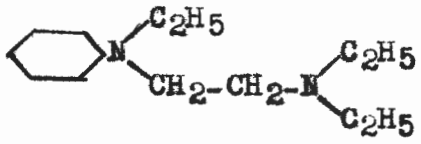
Several amino acids were shown to have antihistaminic properties, but Landau and Gay (48) showed that these compounds were either too inactive or too toxic to be of clinical use.

In 1933, Fourneau and Bovet (33) demonstrated that certain phenolic ethers have antihistaminic properties both in vivo and in vitro. The most effective compound, 929 F, had the following structural formula:



Thymoxyethyldiethylamine
2-isopropyl-5-methyl-phenoxyethyldiethylamine

In 1937, Staub and Bovet (76) investigated the compounds in the Fourneau series for antihistaminic properties. The most promising compound was found to be :

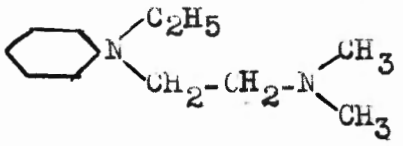


1571 F
N-phenyl-N-ethyl-N'diethylethylenediamine

Both 1571 F and 929 F protected guinea pigs from lethal doses of histamine, inhibited the contraction of isolated strips of smooth muscle due to histamine, and protected guinea pigs from anaphylactic shock. These compounds also showed some anti-acetylcholine action. These results have been confirmed adequately by Rosenthal and Brown (70), Minard and Rosenthal (63), Climenko et al (10), and Wilcox and Seegal (86). However, both of these compounds are toxic and the margin of safety is too narrow to justify their use clincally.

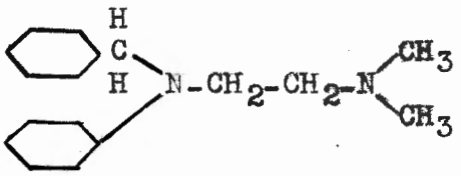
Another series of compounds were investigated by

Halpern in 1942(38). A dimethyl group was substituted for the diethyl group in 1571 F, giving compound 2335 RP.



Dimethylaminoethylaniline
N'- phenyl-N'-benzyl-N-dimethylethylenediamine

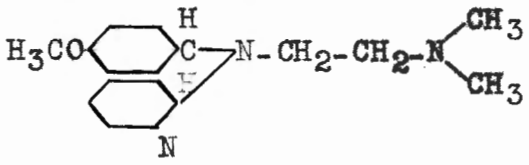
A benzyl group was substitued for the ethyl group in compound 2335 RP giving compound 2339 RP.



Antergan
Dimethylaminoethylbenzylaniline
N'-phenyl-N'-benzyl-N-dimethylethylethylenediamine

Of these compounds, 2339 RP was less toxic and more effective than its predecessors. Good results were reported by Gate' in asthma and other allergic conditions, but Junet and Sciclounoff reported only fair results in asthma, but good reults in hay fever.

Another compound, Neoantergan, has made its appearance in the French literature and is soon to be marketed in this country by one of the prominent drug houses. It has the following structural formula:

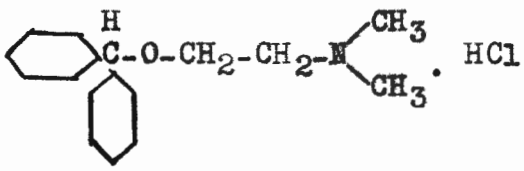


Compound 2786 RP
N-p-methoxybenzyl-N-dimethylaminoethyl-a-aminopyridine

Despite claims of greater effectiveness, the main advantage of this drug is that it is better tolerated than most of the antihistaminics now available. Feinberg (32) states that only twenty per cent of asthmatics were given relief with 2786 RP.

BENADRYL

Using the French compounds as a basis for investigation, work on new antihistaminic compounds began to come out the United States laboratories. Synthesized by Rieveshl and Huber, the Parke Davis product, Benadryl, was first reported on in the literature by Loew, Kaiser, and Moore (53, 54). Benadryl has the following structural formula:



Beta-dimethylaminoethyl Benzhydryl Ether Hydrochloride

Benadryl has three important pharmacological actions. (59) It alleviates:

1. Bronchial constriction due to histaminic or anaphylactic shock (54)
2. Vasodepressor effects of histamine
3. Spasm of smooth muscles

It is fifteen to thirty times more potent than aminophylline in histamine shock. It is six-hundred and fifty times more potent than papaverine in antagonizing histamine. It is fifty times more potent than papaverine in antagonizing acetylcholine. It is one and three-tenths times more potent than papaverine in antagonizing the contractile effects of barium chloride. This suggests that Benadryl's antispasmodic effect has three components (58):

1. Antihistaminic
2. Antispasmodic (anti-barium chloride effect)
3. Atropine-like effect (anti-acetylcholine)

This factor was first described by Yonkman (89) In comparing its antispasmodic action to other drugs, Benadryl ranked as follows (55):

1. Epinephrine
2. Benadryl
3. Demerol

4. Atropine
5. Papaverine
6. Aminophylline

Benadryl potentiates the action of epinephrine. The combination of these two drugs may be efficacious. In addition to the above, main pharmacological properties, Benadryl exhibits several minor properties. Working with sixty normal subjects and two-hundred patients with assorted allergies, Mc Gavach (60) found that Benadryl:

1. Decreases the secretion of gastric acid when given in doses of 150 mg. per day
2. Decreases dermal response to histamine; this is a total abolition if 20 mg. are given intravenously
3. Shows an atropine-like action when applied topically to the eye
4. Produces orthostatic hypotension in eight per cent of the subjects
5. Yields a moderate decrease in capillary permeability in patients getting 300-400 mg. daily

Sherrod and co-workers (75) established the following facts about Benadryl:

1. It decreases the depressor action of histamine and acetylcholine
2. It increases the pressor action of epinephrine
3. It decreases duodenal motility and has no effect on uterine activity

Selle (73), in detailed studies, confirmed the observation of Loew and his co-workers that Benadryl is a potent antihistaminic and antianaphylactic agent. Indeed, his results of experiments on guinea pigs indicated that this was the most potent antihistaminic and antianaphylactic compound studied thus far.

Examining the actions of Benadryl in the light of the effect of histamine as shown in the following table, the dilatation of the nasal mucous membrane in hay fever and vasomotor rhinitis, the skin wheals of urticaria, the over-distention of the membranous labyrinth by edema in Meniere's disease, the vaso-dilating features of certain flushing headaches, and the superficial cutaneous pain of myalgia can all be considered to be due to histamine release.

Table I

Actions of Histamine

SITE OF ACTION	EFFECTS	ORGANS INVOLVED
Capillaries	Dilatation and permeability	Skin and mucous membrane
Glands of external secretion	Secretogogue	Lachrymal, nasal, pulmonary, and digestive glands
Cutaneous endings of pain nerves	Pain	Skin
Smooth muscle	Contraction	Bronchiolar, gut, vascular and uterine muscle

Clinically, Benadryl has shown the following effects:

1. It decreases the cutaneous vaso-dilating action of histamine
2. It alleviates nasal congestion due to the vaso-dilatation caused by histamine
3. It decreases the response of gastric acids and the volume of gastric secretions due to histamine
4. It decreases the wheal and flare response in persons hypersensitive to cold
5. Local application preceding application of a ragweed antigen in sensitive individuals yields marked reduction in whealing

In general, the action of histamine is dependent upon the imine group, NH, and upon the amine group, NH_2; the former acting as an anchoring group with the chemo-receptors of smooth muscle; the latter, as a stimulating agent. The histamine-inhibiting compounds have imine but no amine radicals, bind the chemical receptors, have no pharmacological effect themselves, but do block the effects of histamine. (1)

Rocha e Silva (67) confirmed this by showing that the various histamine compounds which contained masked imine radicals were inactive themselves, but acted as blocking agents.

More specifically, Benadryl (and all of the so-called antihistaminic drugs) and histamine compete for a given site of action or receptive substance. If Benadryl combines with the receptive substance, no particular reaction occurs, since histamine is prevented from combining with the same site and is prevented from exerting its biological effect. This type antagonism is similar to the atropine-acetylcholine system (56), the para-amino-benzoic acid-sulfonamide system, and the ergotoxine-epinephrine system. Benadryl is thought to possess a degree of specificity against histamine comparable to that of atropine in counteracting acetylcholine.

Therapeutic Results with Benadryl

The results with Benadryl therapy in bronchial asthma have been most controversial. Friedlaender and Feinberg (36) found Bendaryl to be effective in urticaria, angioneurotic edema, and the pruritus of various skin conditions, but found it to be without much effect in perennial vasomotor rhinitis and nonseasonal asthma. On the other hand, Mc Gavach (60) observed good results in urticaria, hayfever, angioneurotic edema, and vasomotor rhinitis, and good, but less reliable, results in bronchial asthma, neurodermatitis, dysmenorrhea, and spastic colon.

Todd (79) showed a somewhat better reaction in asthma with rhinitis (thirty-three per cent were completely relieved; fifty per cent obtained partial relief) than in asthma alone (twenty-four per cent got complete relief; fifty-five per cent got partial relief).

Waldbott's (81) percentages of relief were much the same in both seasonal and nonseasonal asthma, about fifty per cent relief was shown in either type. On the other hand, Koelsche and Prickman (46) showed striking differences in the benefits to patients with asthma alone (Twenty-four per cent were completely relieved of symp-

toms) and in the benefits to patients having asthma with hayfever (seventy-four per cent were made symptom-free).

Stroh's (77) results were the least encouraging, showing that only nineteen per cent of those treated were helped, except for another of Friedlaender's series (34) in which no patient with bronchial asthma derived any benefit from the administration of Benadryl.

Levin (49) compared the results obtained with Benadryl in asthmatic adults and asthmatic children and reported about sixty-five per cent benefit in both age groups. Both Waldbott (81) and Logan (57) attest to the fact that Benadryl is strikingly effective in childhood asthma, when given early in the course of an attack and in adequate doses (two milligrams per pound of body weight).

Forty-six per cent of Barnett's subjects were made symptom free and twenty-three per cent reported some relief from symptoms. Epstein (29) showed about fifty per cent relief in the largest series reported in the literature.

Combining the figures from the above sources, we find that of some four-hundred and sixty-three patients two-hundred and eleven (or forty-six per cent) got com-

plete relief; thirty (or six per cent), got partial relief; and two-hundred and twenty-two (or forty-eight per cent) derived no benefits.

Such a variation in results is distressing. An accurate, objective, therapeutic evaluation of any drug used in bronchial asthma is difficult, because it is well known that asthmatic attacks remit, even without therapy. Because the composite figures above eliminate the extremes of enthusiasm and of disparagement, they may be accepted as being more nearly indicative of the true value of Benadryl in bronchial asthma, namely that some degree of relief of symptoms may be expected in about half of a series of patients.

There are several plausible explanations for the disappointing results with Benadryl in bronchial asthma. "Failure" of oral administration may be due to the fact that insufficient drug reaches the site of action. Waldbott (81) points out that the clinical results indicate that Benadryl acts more effectually on the allergic wheal than on bronchospasm. If this is true, then Benadryl would be the ideal supplement to aminophylline. The striking results in infant asthma bear out the fact that Benadryl is more effective against the allergic wheal, because in infant asthma there is considerable

allergic edema in the lungs.

Epstein (29) believes that the "failure" of both Benadryl and Pyribenzamine is based on the fact that there are several forms of allergic sensitization:

1. Anaphylactic
2. Tuberculin
3. Eczematous

Most cases of hay fever are based on the anaphylactic type sensitization. In allergic rhinitis and asthma, especially of the intrinsic type, bacterial sensitivity is the more important. The antihistamine drugs will help only in the anaphylactic form of sensitivity, because in this type the release of histamine or an histamine-like substance is important in producing the allergic reaponse. In the tuberculin type sensitivity (due to bacterial and other microbic antigens) histamine has little or no role in the mechanism.

The fact that Benadryl will help only one patient in every two, makes it an impractical drug for the ordinary practitioner to attempt to use in bronchial asthma, although it is conceivable that the allergist may find the drug useful in certain selected cases. At any rate, the "failure" of Benadryl does not invalidate the hypothesis that histamine plays a role in the

production of bronchospasm. Indeed, even the small measure of success which the drug has enjoyed is such that should encourage further investigation of new antihistaminic substances in the hope that a drug will be found which will alleviate the symptoms of asthma without producing the unpleasant side effects so common in the currently popular antispasmodics.

Toxicity

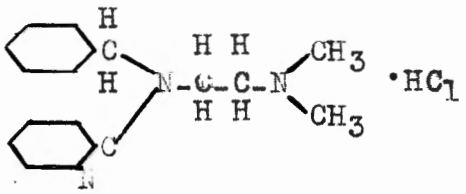
Side reactions have been reported in from thirty to as many as eighty per cent of the patients using Benadryl. Most reactions occur with the initial dose and subside with subsequent doses. Drowsiness, hypotension, gastrointestinal upsets, urinary complaints, dizziness, and dryness of the mouth are among the most frequent side reactions. Barnett (3) has used amphetamine sulfate as a counteractant and this has successfully relieved all of the side effects encountered, including the bladder disturbances.

Lethal doses of Benadryl in test animals lead to violent excitement, convulsions, and respiratory failure.

PYRIBENZAMINE

Following shortly the announcement of Benadryl,

c me the announcement of another American-developed antihistaminic compound, Pyribenzamine. This compound has the following structural formula:



Pyridil-N'benzyl-N,-dimethylethylene diamine

Pyribenzamine has essentially the same pharmacological actions as has Benadryl. Yonkman and Oppenheimer (90) showed that the perfused lungs of guinea pigs could be protected from histamine constriction of their bronchioles by Pyribenzamine. They also demonstrated that in dogs, histamine broncho-constriction is often accompanied by hypotension which is significantly combatted by Pyribenzamine. Mayer (61), using the technique of Langendorf as described by Tainter (78), demonstrated that in dogs the contractile effect of histamine was usually markedly arrested by Pyribenzamine and that its effect was prolonged from forty to ninty minutes or more. Yonkman (89) is preparing a report on the effects of Pyribenzamine on the bronchial muscles, histamine wheals, and anaphylactic hypotension, to be published in the near future.

Arbesman (2) has shown that in addition to a potent anaphylactic activity, when given orally, Pyribenzamine decreases the size of histamine skin wheals and decreases the skin reactivity in allergic patients. Pyribenzamine also yields reduced reactivity of skin sites passively sensitized with serum containing cotton seed reagins.

The effects of Pyribenzamine may be summarized. It enhances the pressor action of epinephrine (75). It gives a slow and more irregular (than Benadryl) protection against both the systemic and the broncho-constrictive effects of parenteral histamine (18). It stimulates uterine and duodenal activity, but does not inhibit the depressor action of acetylcholine (75).

Mayer (61) says that there is a question as to whether the drug is antihistaminic or whether it is antispasmodic with an high antihistaminic component. Strong evidence exists to support the former, in that Pyribenzamine counteracts histamine in the same order of magnitude as the histamine present.

Therapeutic Results with Pyribenzamine

Results with Pyribenzamine have been no more encouraging than were results with Benadryl in the treatment of bronchial asthma. Friedlaender (35) reports

that of thirty patients with nonseasonal asthma, two received symptomatic relief with each administration of the drug. Twenty-eight were not helped. Pyribenzamine did help the accompanying allergic rhinitis and did so more effectively than did oral doses of ephedrine. Where there was a complicating nasal infection with purulent secretion, the efficacy of Pyribenzamine was practically nihil.

Feinberg (36) reported that of seventy cases of chronic asthma twenty-four showed improvement on fifty milligrams given on a full stomach four times daily. However, the relief was not as marked as is usual with either ephedrine or epinephrine.

Curry (17) called the results in bronchial asthma unsatisfactory, although forty-six per cent of his series showed definite relief from symptoms. He, too, noted that relief was greater with ephedrine sulfate.

The series of Chobot (9), of Arbesmann (2) and of Epstein (29) showed comparable results. About forty-five per cent of seasonal asthmatics were helped, as were about thirty-five per cent of nonseasonal cases. Feinberg (32) showed that twenty-eight per cent of one of the larger series of cases to be found in the literature were definitely relieved of symptoms.

Toxicity

Both Mayer (61) and Koepf (47) showed that in rats on daily, oral injections of five milligrams of Pyribenzamine, after five months there were no significant changes in the red blood cell count, in the morphology of the red blood cells, in the count and in the morphology of the white cells, and in the differential distribution of the white blood cells.

Mayer (61) showed that in six human subjects, doses up to five-hundred milligrams were well tolerated. One complained of mild sedation; another of pelvic heaviness.

Using three healthy males, one-hundred and fifty milligrams of Pyribenzamine were given daily for eighty days. No ill effects were noted, nor were there any abnormal objective clinical findings. There were no urinary changes, no significant changes in urea-nitrogen blood levels, no alterations in liver function as shown by the tests used, and no changes in the complete blood count, hemoglobin, or hematocrit readings. (47)

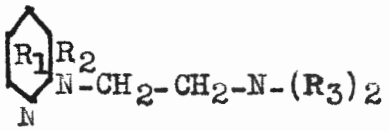
Side reactions occur in from twenty-five to thirty per cent of users of Pyribenzamine. Most commonly noted side effects were drowsiness, vertigo, trembling, nervousness, faintness, fatigue, and gastro-intestinal up-

sets.

CONCLUSION

Benadryl and Pyribenzamine have not been the only products of American research. Winder (87) and Loew (53, 54) have investigated homologues of Benadryl, but have found none which surpasses Benadryl's effectiveness without unwarranted degrees of toxicity. Ellis and Newsome (28) have tested many new antihistaminics in relation to their effectiveness against bronchospasm in guinea pigs. Later publications by these same investigators (27) suggested that Benadryl and its monomethyl and isopropyl derivatives were most effective in preventing histamine constriction in guinea pigs. These compounds also gave added dilatation of the lungs even in the presence of a constrictor dose of histamine.

Huttrer (40) developed a series of compounds more closely related to Pyribenzamine, which showed strong antihistaminic activity. His work was based on Mayer's (62) earlier proposition that secondary amines of the general formula are inactive. The pyridine derivatives which are tertiary amines are very active. The general formula is:



Indeed nearly every major drug house in this country either is working on or is testing new antihistaminics which are to be released soon to the professional outlets.

The French compound, Neoantergan, is soon to be marketed in the United States and from the figures recently published by Winter (88), Neoantergan promises to be one of the more effective of these drugs and certainly offers the least toxicity in the group which Winter tested.

Table II

DRUG	NUMBER OF EXPERIMENTS	AVERAGE PER CENT INHIBITION OF HISTAMINE BY CONTRACTION
NEOANTERGAN	14	81
PYRIBENZAMINE	14	68
3015 RP	16	52
3277 RP	16	45
BENADRYL	13	42
METRAMINE	12	11

Table III

DRUG	NUMBER OF ANIMALS (MICE)	L. D. 50 mgm./ kgm.
NEOANTERGAN	30	102 ± 11[x]
PYRIBENZAMINE	50	68 ± 7
3015 RP	40	140 ± 13
3277 RP	40	190 ± 21
BENADRYL	50	140 ± 13
HETRAMINE	40	76 ± 7

x Standard deviation

The United States Army laboratories are also working on a compound variously known as Aludrine or Isuprel. The story of its discovery by our Medical Corps is rather romantic and certainly provides a white hope for the effective use of antihistaminics in asthma therapy. It was noted that a certain group of German prisoners of war all took pills of the same kind. When an investigation was made, it was found that each of these prisoners was an asthmatic. The pills were Aludrine (the German name for the product which our Army has rechristened Isuprel), an antihistaminic compound capable of preventing attacks of asthma as well as useful in relieving the symptoms once an attack has been initaited. Thus the Germans had been able to field men as line soldiers,

men whom our Army either would have rejected or would have used in limited duty only. What the composition of this compound is and what it will do under the rigorous, controlled, clinical investigations of the Army Medical Corps is unknown, because, to date, there have been no published data available to the interested reader.

It should be understood that administration of antihistaminic drugs does not affect the fundamental reaction leading to histamine release nor will such compounds be effective against symptoms due to the presence of noxious substances other than histamine. With these facts in mind, it can be understood better that each of these drugs will not necessarily be effective in every case of allergy. The very best results which can be expected are the palliative relief of those symptoms which can be ascribed to histamine release. Obviously, ideal therapy is the type which is aimed at the basic mechanism producing a disease. Therefore, it follows that before the ideal therapy for bronchial asthma is found, the holes in our knowledge of the fundamental nature of allergy must be plugged. Then and only then can a rational therapeutic regimen be developed. But until there has been such an advancement in our under-

tanding of the mechanism of allergy, we should attempt to supply the best therapy possible on the basis of existing knowledge. This simply means that in addition to the use of desensitization procedures and antispasmodics, we should strive toward the perfection of an antihistaminic compound which will be effective in asthma therapy, because, according to our present store of knowledge, such a compound should exist.

Therefore, we may draw the following conclusions:

1. Much evidence has accumulated since 1910 which suggests that histamine or an histamine-like substance plays an important role in the production of the bronchospasm of bronchial asthma.
2. The best means to date of attempting to counteract the effects of the histamine or H-substance has been through the use of certain antihistaminic compounds.
3. To date, these antihistaminic compounds have been disappointing in their effectiveness in bronchial asthma, but have proved their efficacy in other allergic manifestation, especially those characterized by the allergic wheal type reaction.

4. The small measure of success which the above discussed compounds have shown in bronchial asthma, the striking results which these compounds have rendered in childhood asthma, and the expectancy of better results through the use of Isuprel all seem to indicate that in future antihistaminic therapy there will exist safe, symptomatic relief from bronchial ashtma, unhampered by the unpleasant side effects of the currently used antispasmodics.

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EXPERIMENTAL BASIS OF THERAPY WITH ANTIHISTAMINE DRUGS

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DEFINITION AND MODE OF ACTION OF ANTIHISTAMINE DRUGS

Antihistamine drugs are specific blocking agents which diminish or abolish the effects of histamine on smooth muscle and endothelial cells.

Antihistamine drugs prevent or diminish the contracting or spasmogenic effect of histamine on the smooth muscle of bronchioles, gastro-intestinal tract and uterus. They may, therefore, relieve hypermotility or spasm provided histamine is an etiological factor. Spasm not due to histamine may not be controlled since antihistamine drugs differ from "spasmolytic" drugs in that they may be devoid of a direct relaxing effect on smooth muscle.

Antihistamine drugs prevent histamine from increasing permeability of capillary endothelium as indicated by diminished extravasation of fluids and dyes into a wheal formed following injection of histamine or allergen.

Antihistamine drugs also diminish the vasodilating action of histamine as evidenced by decreased erythema and diminution of depressor responses to histamine. The ability of antihistamine drugs to diminish vascular actions of histamine probably accounts for their clinical effectiveness in several allergic conditions.

The gastric secretogogue action of histamine is not materially diminished by the antihistamine drugs now available. From the data published thus far, no conclusions can be drawn concerning the effectiveness of antihistamine drugs in diminishing the secretogogue action of histamine on other secretory cells. However, the normal flow of saliva is apparently not materially depressed, since dryness of the mouth is rarely encountered in patients treated with antihistamine drugs.

Antihistamine drugs owe their anti-allergic effects to the fact that they block the effects of histamine. Antihistamine drugs per se have little pharmacodynamic action. Therapeutic doses do not significantly affect the blood pressure, have no effect on the heart and fail to influence consistently the activity of the gastro-intestinal tract. Rather, they protect the organism from the effects of histamine, either injected in various ways or released from its bound form in the tissues.

Thus, the mode of action of antihistamine drugs differs sharply from that of other drugs used in allergy. Aminophylline or epinephrine and related pressor amines combat various responses to histamine by their own pharmacodynamic action which may be diametrically opposed to that of histamine on a particular tissue or organ.

Antihistamine drugs constitute a palliative treatment in allergy since they merely control the symptoms by protecting endothelial and smooth muscle cells from the effects of excess free histamine released under pathologic conditions.

Since the antihistamine drugs are to be regarded as specific blocking agents for histamine, the action of histamine itself and its role in allergy will be briefly discussed.

PHARMACOLOGICAL ACTION OF HISTAMINE

Histamine is one of the most potent pharmacological agents known and is noted for its diversity of action on various tissues. Although the action of histamine is fundamentally the same in animals and man, the degree in which certain of its effects predominate over others is different in different species. Each species reacts to histamine in its own characteristic manner.

Prominent effects of histamine:

1. Spasm of smooth muscle—with the exception of the iris and possibly the arterioles in some locations.

   Bronchiospasm—pronounced in guinea pig, less apparent in rabbit, dog and man.

   Gastrointestinal spasm—in all higher animals and man.

   Uterine spasm—histamine is not used as an oxytocic agent because of its numerous other actions.

2. Dilatation of capillaries and venules, as well as arterioles in certain vascular beds.

   Hypotension is the resultant of vasodilatation — pronounced in dog.

   Myocardial depression only with large doses of histamine.

3. Increased capillary permeability. In systemic reactions, hemo-concentration may result and contribute to the hypotension.

   Wheal formation and attendant erythema are local reactions referable to the increased capillary permeability and vasodilatation. Axon reflexes are also involved in the local cutaneous reactions.

4. Secretory effect on gastric, salivary and lacrimal glands, as well as the mucosal glands of the alimentary and respiratory tract. Of greatest importance is the hypersecretion of the gastric glands induced with minute quantities of histamine. The concomitant occurrence of pylorospasm and hypersecretion are dual factors which may be related to peptic ulcer and other gastrointestinal disturbances.

ROLE OF HISTAMINE IN ANAPHYLAXIS

It is an accepted fact that the antigen-antibody reaction is a fundamental reaction in anaphylaxis and most forms of allergy. The antigen-antibody reaction causes the production or liberation of pharmacologically active humoral substances which account for the major symptoms. Evidence is outlined which constitutes proof that histamine liberated from tissue cells causes the most important symptoms encountered in anaphylaxis.

Release of histamine in anaphylaxis: Histamine is normally present in the tissues of nearly all animals, for the most part in a bound and inactive form which can readily be liberated in an active form. The amount of free or active histamine in blood, lymph and reacting tissues has been closely related to allergic reactions and symptoms, the onset and duration of which coincide with elevated levels of histamine. Thus, the amount of histamine released from the liver of a dog during anaphylaxis is sufficient to account for the severe hypotension and death of the animal.

Failure to detect histamine in blood during anaphylactic reactions is not a valid objection since histamine leaves the blood stream with extreme rapidity and blood levels may not reflect the rise of histamine content in shock tissues where the reactions occur. Furthermore, it has been demonstrated that white blood cells and platelets which contain large amounts of histamine are "screened out" by capillaries of shock tissues, thus localizing the histamine which after

its release from these cells can exert its effect at a time when blood histamine has apparently decreased.

Conspicuous similarity in responses to histamine and to antigen (in sensitized tissue): Without exception, animals of a single species react similarly to both histamine and antigen.

1. Bronchiospasm—is a prominent feature of anaphylaxis in guinea pigs in which histamine causes severe broncho-constriction.
2. Intestinal and uterine spasm—occur regularly in anaphylaxis.
3. Hypotension—is a prominent feature of anaphylactic shock in those animal species which also respond to histamine with a marked fall in blood pressure (rabbit, dog).
4. Local cutaneous reactions—involving vasodilatation and increased capillary permeability are elicited by antigenic substances in sensitized skin as well as by minute amounts of histamine. Differences in type of reaction to histamine and antigen, when existent, are apparently due to factors operating in addition to histamine.
5. Gastric secretion—is augmented when sensitive persons are exposed to light, heat or cold, which suggests that histamine has been released from tissues.

Effectiveness of antihistamine drugs in anaphylaxis: Antihistamine drugs are remarkably effective in preventing and diminishing both anaphylactic and histamine-induced responses in animals. Likewise, these drugs are known to control many allergic manifestations in man. The results obtained with these specific antihistamine drugs in anaphylaxis and allergy may therefore be regarded as further convincing evidence for the major role which histamine plays in anaphylaxis and allergy. The slight degree of atropine-like action exerted by antihistamine drugs (greatest with Benadryl) does not detract from the argument since atropine itself is only of little value in anaphylaxis and allergy.

Failure of antihistamine drugs to block effects of histamine and thus alleviate symptoms in some cases of allergy does not detract from the histamine theory of anaphylaxis. Overwhelming amounts of histamine may not be blocked by therapeutic doses of these drugs. That histamine is probably not the only cause of symptoms may possibly be demonstrated by the diagnostic use of antihistamine drugs.

THERAPY WITH ANTIHISTAMINE DRUGS

Margin of safety: The antihistamine drugs available possess a large margin of safety. The toxic (lethal) doses in animals (mouse, rat, guinea pig, dog) are from 10 to 50 times greater than those (therapeutic) doses which are effective in blocking the action of histamine. Very large single doses of antihistamine drugs cause stimulation of the central nervous system, tremors and convulsions in which the animals may die. Antihistamine drugs have been administered daily in relatively large doses to dogs over extended periods of time without producing any toxic manifestations.

Effects of therapeutic doses: In man, therapeutic doses of antihistamine drugs exert little, if any, pharmacodynamic effects. There is no significant effect on the vascular system; some investigators found a slight decrease in blood pressure during treatment with antihistamine drugs. The functions of the gastro-intestinal tract are not materially affected. Some of the drugs (Neoantergan, Pyribenzamine) may have a tendency to increase motility, others (Benadryl) to decrease it slightly. It is curious to note that in contrast to their stimulatory effects on the central nervous system in animals, antihistamine drugs frequently have a sedative effect in man.

Antihistamine drugs are effective when taken by mouth. They are rapidly absorbed. The duration of the effect of the usual therapeutic dose (25 to 50 mgm.) is about 4 to 6 hours. Therefore, if prolonged effects are desired, medication should be repeated after 4 or 6 hours. Doses in children are correspondingly smaller. It has been recommended not to exceed an amount of 2 mgm. per pound of body weight in a single dose in young children.

The metabolic fate of antihistamine drugs in the body is as yet unknown. When administered at proper intervals, antihistamine drugs have no cumulative effects. Habituation has not been encountered.

No specific contra-indications are known for the therapy with antihistamine drugs. Other anti-allergic drugs may be administered while the patient is treated with antihistamine drugs. Obviously, antihistamine drugs should not be given whenever a diagnostic skin test is intended.

Side-effects: Fortunately, the side-effects encountered with therapeutic doses are not of a dangerous character and seldom inconvenience the patient to such an extent that medication has to be discontinued. Untoward reactions will stop promptly after withdrawal of these drugs. A temporary decrease in the dose is often sufficient to overcome unpleasant side-effects.

The majority of the side-effects involve the central nervous system. A mild degree of sedation expressed by sleepiness and drowsiness is the most frequently encountered side-effects. The drowsiness which appears to occur more frequently with Benadryl than with Pyribenzamine can be relieved by caffeine, ephedrine or amphetamine. Disturbances of the gastro-intestinal tract are less frequently observed; vomiting is a rare side-effect.

Side-effects include (in order of frequency observed):

(1) Drowsiness
(2) Dizziness
(3) Nausea
(4) Headache
(5) Dry mouth
(6) Intestinal cramps and diarrhea
(7) Vomiting

INDICATIONS

In view of their mode of action, antihistamine drugs are indicated in those conditions in which histamine is or may be assumed to be a causative agent.

Thus, treatment with antihistamine drugs has yielded excellent results in urticaria, pruritus, dermographism and drug reactions. It is not surprising that antihistamine drugs have been less reliable in the treatment of other skin afflictions, such as atopic dermatitis and eczema, in which the causative connection with histamine is less well established.

Acute allergic manifestations on the mucous membranes, like vasomotor rhinitis and hay fever, respond readily to treatment with antihistamine drugs, whereas the benefit derived from these drugs in gastro-intestinal allergy is less consistent.

It should be pointed out that the efficacy of antihistamine drugs in asthma is relatively small. Severe asthmatic attacks can seldom be controlled by antihistamine drugs, an indication that bronchial asthma may be caused by a variety of causes in which histamine may not play a major part.

Obviously, the indication of antihistamine drugs is dependent on the appreciation of the mechanism and a more concise knowledge of the underlying causes of many supposedly allergic diseases. The use of antihistamine drugs for diagnostic purposes has already materially contributed to the elucidation of certain allergic manifestations especially in the field of drug sensitization.