1947

Symposium on anti-histamine agents

Thomas Joseph McGuire
University of Nebraska Medical Center

SYMPOSIUM ON
ANTI-HISTAMINE AGENTS.

THOMAS J.McGUIRE.

SENIOR THESIS PRESENTED TO THE
COLLEGE OF MEDICINE,UNIVERSITY OF NEBRASKA.
OMAHA,1947.

TABLE OF CONTENTS

Conditions of altered sensitivity to antigens and haptens are widespread in animals and in man; these include anaphylaxis, the anaphylactoid allergies, and idiosyncrasies.

True anaphylaxis results from the introduction of a specific antigen into a sensitized animal. The symptoms of experimental anaphylactic shock include marked depression of blood pressure, asphyxial convulsion, increased catabolism of protein, edema, urticaria, decreased coagulations of blood, hemorrhage, eosinophilia, and violent contraction of smooth muscle: bronchiolar, uterine, stomach, intestine and bladder. Human beings are less susceptible to these effects than are certain laboratory animals, and the symptoms of clinical anaphylactoid allergy are: pruritis, urticaria, erythema, weakness and in extreme cases, coma. The induced state of hypersensitivity appears only after a latent period, during which the transferred antibody is being fixed in the tissue. Any increase in the quantity of the circulating antibody, as in desensitization, protects temporarily against allergy, by allowing antigen-antibody combination outside the tissue cells. When this combination occurs within the cell, anaphylaxotoxin is liberated.

Peterson (1945) explains the allergic phenomena as a reaction to stimulus differing from the normal only in speed and in intensity. This response against the foreign protein involves the entire vascular system and is reflected clinically by rapid shifts in capillary permeability.

The individual cells of the body exist in a state of unstable equilibrium, pendulating between two poles; activity and rest. The "labile biotonus" of the entire organism is maintained by interplay of many individual balances; for instance, acid-base, water balance, temperature balance, lipoid balance and the calcium-potassium ratio is to mention only a few. "Every energy impact upon the body must be equiliberated and energy effectors are legion. The most common alterations are changes in immediate environment in which we exist. Changes in light, air, cumulative effects of temperature, character of food, work, exercise, and the contact with the world of microorganisms, allergins and toxins." Air hunger too, may be at the root of some diseases. As long as cells are supplied with oxygen they have little dysfunction. Even the acute clinical picture in allergy is said by some to be

basically associated with local anoxia, brought about with the changing tone in smooth muscle or by alteration in cell permeability and the coincident stasis thereby entailed. This period of increased vascular tone is also commonly associated with excitement, cold, trauma and so forth. It is during this phase that tissue anoxia ensues.. Capillary active substances are then formed, histamine and "H-like" in nature, which lowers the blood pressure level and dilates the capillaries.

Clinical conditions such as asthma, hay fever, eczema, urticaria, serum sickness, angioneurotic edema and many others involving the skin, brain, and gastro-intestinal tract have gradually come to be recognized and grouped as diseases of allergy, with a definition common to all: human hyper-sensitivity to ordinarily harmless substances. They represent more or less local anaphylactoid reactions in which tissue antibodies cause reactions varying from mild edema and erythema to the more severe conditions. All types of human allergy show strong familial tendencies which are at least partly due to congenital peculiarities of the tissue protein.

Specific desensitization affords fairly adequate relief. Drugs, chemicals, cosmetics, animal furs, foods and plant substances are to be eliminated when they are

found to be offending. These are the procedures of choice in combating the allergic states. Skin testing for specific antigens, however, has its limitations and desensitization requires time and is not one hundred per cent effective. It is in such conditions as these that the search has leaned in many directions for palliative measures to alleviate the distressing symptoms of allergy, until desensitization occurs or to tide the patient through the season of sensitivity. It is the aim of this report to analyze the physiological approach to symptomatic relief of the anaphylactoid states and to review the clinical and pharmacological data of various medicaments used. The most recently popular drugs Beta dimethylaminoethyl benzhydryl ether hydrochloride and Pyridil N'benzyl N'dimethylethylene-diamine hydrochloride will be thoroughly discussed and evaluated.

Evidence has been quite obvious from the beginning which suggests one substance common in all allergic entities may be responsible for the ensuing reactions.

In 1910 Dale and Laidlow, in experimenting with histamine, noted typical symptoms of anaphylactic shock upon injection of histamine into laboratory animals. The reporting of this consequently stimulated further study to incriminate histamine as the mediator of ana-

phylactic symptoms. Lewis later demonstrated the triple response, displayed after flesh injury by thermal, chemical, physical or allergic agents. This is identical with local reactions produced by intradermal histamine injection. (Lewis 1927)

Best in 1927 furnished a reasonable explanation for the source of histamine in anaphylaxis by demonstrating its presence as a normal constituent of tissue. Five years later, in 1932, Dragstedt demonstrated an increase in blood histamine with concomitant decrease in liver and lung histamine during anaphylactic attacks in dogs. Enough histamine was detected in the inferior vena cava of these dogs to produce the same vascular response as that resulting from administration of intravenous histamine. Seventy to one hundred percent pf normal blood histamine is located in the leucocyte according to the work of Code in 1937.

There has been no valid argument, to date, against the evidence presented in favor of histamine, as a potent factor in the production of the signs of anaphylaxis. Practically all admit that histamine per se cannot explain all the manifestations of the anaphylactoid activity. Apart from the fact that there are multiple

points of resemblance between anaphylaxis and allergy, evidence also enhances the histamine concept of allergy by the results in man. The effect is consistent with many of the phenomena of allergy. Randolph and Racherman (1941) are in agreement with this trend of thought. It was further demonstrated by Cohn and Katz (1941) that in vitro histamine is released from the leucocyte upon addition of the specific allergin. Katz in 1942 observed the release of histamine from human skin by the application of a specific agent. Vast effort is being expanded to control allergic disease in man; based almost entirely upon the fundamental concept that histamine is etiologically related to allergy, Despite the fact that investigators have not yet isolated it in its crystalline purity, this concept is theoretically sound.

With the above view in mind, one might remark "just what is histamine?" Chemically it is beta-imidazolylethyleneamine. Since it is a constituent of ergot the synonym ergomine is less frequently used. It owes its pharmacological activity to its NH, amine group and to

its NH group, the former acting as an anchoring group with the chemical receptors of smooth muscle and the latter as a stimulating agent. (Dragstedt 1945)

In vivo the putrifaction of bacteria plus histidine forms histamine, a constituent of intestine and feces. It is also present in the pituitary gland, liver, striated muscle and other tissue. It may be released from tissue in response to nervous stimulation, giving a basis for the theory that histanergic nerve fibers are present in tissue. The concentration of ergomine in human blood varies from one to eight micrograms per one hundred cubic centimeters. One one-thousandth milligram will drop blood pressure in man with intravenous injections. It is destroyed by the enzyme histaminase, this occuring principally in the kidney. Best and Taylor go on to state that when histamine is introduced into the human skin a characteristic triple response occurs, which consists of:

1. Local dilitation of the minute vessels.
2. Increased permeability of the vascular membrane.
3. Widespread dilatation of the neighboring arterioles.

The first two are due to direct action of liberated histamine on the vessel wall, while the third is due to

local axon reflex mechanism.

Friedlander and Feinberg (1945) observe similar action and that the skin responds to the various forms of stimuli by liberation of a chemical "H-substance". indistinguishable from histamine in its local action on vessels and nerves. That a variety of clinical syndromes are due to the release of such a substance into the tissue, appears to be well established. Asthma may well be such a manifestation since histamine ca produce a bronchiolar spasm, edema of the mucous membrane, and and increase in secretion of the mucous glands. The mucous membranes reactions of the respiratory tract present in hay fever and in allergiv rhinitis are likewise stimulated by histamine reactions. Elam, Ancona and Kerr in 1945 were able to recover "H-like substance" in the nasal secretion of patients with allergic rhinitis. These extracts were capable of producing a dose response curve similar to histamine. In the skin localized edema manifests itself clinically as urticaria and angioneurotic edema; in the labyrinth as Meniere's syndrome. It is admitted that much more work will have to be done before the exact significance of this and other histamine-like activity can be evaluated.

With these foregoing concepts in mind, the use of anti-histamine substance to counteract the signs of allergy becomes rationalized. These drugs are used clinically to provide temporary relief from anaphylactoid symptoms and are not intended as a permanent cure. In the attempt to evaluate the efficiency of any drug and specifically those used in allergic disease, it must be remembered that symptoms per se, are self-limited. Even in chronic cases, spontaneous improvement may take place at any time in retaliation to the disappearance of inhaled and ingested antigens from the patient's environment. Likewise spontaneous desensitization may occur. Psychogenic factors, too, must be considered, particularly when relief is obtained with placebo.

In our approach to the histamine antagonists two main groups of chemically well defined substances are considered to possess specific antihistamine activities: amino acids like arginine, histamine and cystine; and secondly, certain aromatic derivatives of aminoethanol and ethylenediamine. (Lehman 1942) (Loew, Kaiser and Moore 1945) All of these substances are chemically and pharmacologically closely related. Recently Mayer and his associates (1945) have investigated a group of alpha-aminopyridil and alphaaminopicoline derivatives possess-

ing highly potent anti-histamine activity.

Presumably the clinical action of such a group of drugs could be said to be brought about by one or more mechanisms:

1. By directly opposing the pharmacologic action of histamine through a stimulation of the sympathetic nervous system, as demonstrated by the action of epinephrine.
2. By the direct relaxation of bronchiol musculature.
3. Prevention of histamine release.
4. By direct chemical combination with , and neutralization of the histamine liberated at the site of action.
5. By blocking the action of histamine.

This is in accordance with the description of Friedlander. (1946)

Presuming that a tolerance to histamine could be obtained by repeated administration of the agent, Ramirez and St. George (1924) reported on a group of asthmatics. Temporary favorable results were obtained in two of ten patients with increasing doses of histamine. (Feinberg 1946) Farmer (1941) too claims some efficacy to this management. Ernestine and Banks reported some improvement in half of the cases of urticaria, pruritis and angioneurotic edema treated in this way. Recurrences were marked in all, concluding that no actual diminished sensitivity to histamine was observed.

Wells, Gray and Dragstedt in 1941 further developed this idea after a series of dog experiments using repeated histamine injections. Feinberg (1946) too feels that the effectiveness of this therapy has been widely exaggerated.

Fell and Marshall (1943) attacked this same theory from another angle, by investigating the activity of the histamine conjugate, to stimulate production of specific histamine antibodies. Utilizing an azo linkage they joined histamine to various proteins such as casein and horse serum globulin. Although Cohen reports effective clinical results he gives no substantiating statistical data. Later, in 1945 Cohen and Friedman agree that whatever slight degree of immunity that it may produce is of little value. The committee on Pharmaceutical and Medicaments of Americal Academy of Allergy summarize their information indicating that those who have given histamine azo protein a fair trial report total ineffectiveness per se, or whatever action it may have had is attributed to its non specific action.

As early as 1929 physiologists, as Best, demonstrated the enzyme, histaminase as capable of destroying histamine in vitro. The fad of its clinical use realized widespread favor from 1939 to 1942 with a number of favorable clinical observations in urticaria and vaso-

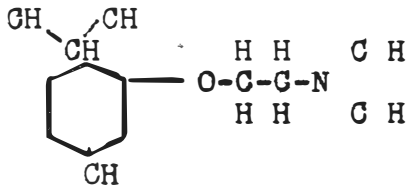
motor rhinits. (Roth and Rynearson 1939) The results in humans have failed to prove effective, as they did in vitro. Best, Alexander and others stated that in study over a long period, histaminase was of no specific value. The Council on Pharmacy and Chemistry of the American Medical Association did not consider its value worth including it in the New and Non-official Remedies.

In Feinberg's (1946) complete treatise on anti-histamine agents he reminds us that it is important to realize the commonly used group; epinephrine, procaine and ephedrine owe their therapeutic value to their vaso-constrictor action. It is not the scope of this paper to include such drugs, since they are not anti-histamine in nature.

Not until 1937 when Edblacher and his co-workers showed that the amino acids histidine, cystine and arginine inhibited histamine contractions of guinea pig intestine, was investigation continued. (Feinberg 1946) Ackermann continued this work in 1939, as did Halpern. More recently Landau and Gay in 1944 noted high rate of fatalities in laboratory animals due to toxic reactions produced in effective doses. Their activity is slight since it requires two hundred and fifty thousand times more arginine than histamine in order to counter-

act the histamine reaction. Mayer (1946) dogmatically states that the amino acids have no therapeutic value in vivo against histamine poison. Finally, experiments in man have failed to produce any effect on the pollen reaction in sensitive subjects.

Feinberg (1946) interprets the work of the French investigators Fourneau and Bovet (1937). They base their conclusions on the synthetic phenolic ethers of amino alcohols. Histamine is counteracted both in vitro and in vivo with this group. The most effective of these was



929F

2-isopropyl, 5 methyl phenokyl diethyl amine often referred to as thymoxyethyl diethyl-amine. This was utilized in dog demonstrations and neither destroyed nor did it antagonize the action of introduced histamine, as a gastric secretory stimulant. (Loew and Chickering 1941) It was found to be very toxic by this group and by Glimenko in 1941.

Wilcox and Segal in 1942 reported on another such group in which they injected doses of compound 1571 F into guinea pigs, previously given six times the minimum

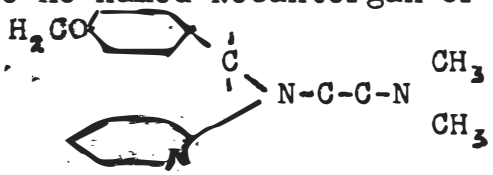
lethal dose of histamine. The drug was ineffective in influencing cutaneous reactions. Primarily it prevents smooth muscle contraction, saving the life of the animal but not preventing the development of manifestations of shock.

Hollenbach (1943) in comparing the compound 1571 F with 929 F states that the former is a more active H-antagonist than the latter. Clinical trial of both the drugs did not support their therapeutic efficacy. The weak action and high level of toxicity was too great to warrant their use as specific antagonists. Loew and Bourque in 1943, and later Ellis confirmed this evidence.

Another group of related agents only slightly differing from 1571 F are described by Halpern (1942) : 2325 RP and 2339 F. The latter proved to be more desirable and was tagged as Antergan. Few if any reports of this compound crept into the English literature until Feinberg (1945) combed the European journals dating from 1942. Urticaria, eczema, hay fever, perrenial vasomotor rhinitis, asthma, migraine, dermatitis and pruritis were all relieved in varying degrees. Halpern is also quoted as stating that he does not believe that the drug prevents liberation of histamine, but he does postulate that the compound does modify the reaction of organs in such a way that histamine is incapable of exercising its customary

effects.

Two years later in 1944 the French investigator Bovet (Feinberg) described another ethylidene derivative he named Neoantergan or compound 2786 R P.



Np Methoxylbenzyl-N-dimethyl amino ethyl alpha amino -pyrine

The European literature professes that this compound is more effective and less toxic than Antergan and is better tolerated.

In seasonal hay fever, the drug was beneficial to thirty-nine of sixty patients, or sixty-five per cent; in one of five, or twenty per cent of asthmatics were relieved. A dose of one milligram per kilogram of Neoantergan protected against seventy-five lethal doses of histamine. Feinberg concludes from his personal experience that the drug is effective and beneficial.

RECENT AMERICAN ANTI HISTAMINE AGENTS I. Benadryl.

Loew who had previously studied various anti histamine compounds has had considerable experience in this field. In his search for more potent compounds he and his associates screened a series of twenty-one benzhydryl ethers and amines by tests which determined the degree of protection each compound possesed against bronchospasm, induced in guinea pigs exposed to an atmosphere of atomized histamine. Three of the benzhydryl ethers were found to posses high anti histamine activity in association with low toxicity. Most promising of these was beta dimethyl-amino-ethyl-benzhydryl-ether hydrochloride, which had previously been synthesized by Rieveschl and Huber (1944). (Feinberg 1946) in the laboratories of the Parke Davis Company. They reported several of these synthetic benzhydryl alkomine ethers to posses anti allergic and antispasmodic activity. In a later publication Loew, Kaiser and Moore (1945) suggested that the new compound was two to four times as active as either 929 F or 1571 F, ~~it~~ is much less toxic and has a distinct and separate pharmacologic action of preventing at least some of the effects of histamine. Early experiments were varied, but the results were consistent. It consistently alleviated bronchiol constrict-

ion, anaphylactic shock and the vasodilating-vasoconstricting action of induced histamine.

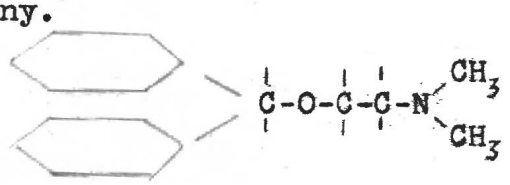
When histamine aerosol was inhaled within a closed chamber the mortality rate in guinea pigs reached one-hundred per cent. Beta dimethyl- amino-ethyl benzhydryl ether reduced this to zero. Comparative studies were then done with effective antispasmodics in histamine-induced bronchoconstriction. The new drug was second only to adrenalin, and then followed demerol, atropine, papavarine and aminophylline. It was found to be thirty times as potent as the latter.

Cohen's (1946) investigations on guinea pig ileum illustrate that the drug is six-hundred and fifty times as antagonistic as papaverine and fifty times more potent than acetylcoline. The effectiveness in decreasing the vasodilating action of histamine in man was dramatic.

PHARMACOLOGY

Through the combined efforts of early investigators, the pharmacology of beta dimethyl aminoethyl benzhydryl ether hydrochloride can be tabulated. It is a white crystalline powder, slightly opalescent in nature and soluble in alcohol and water. Under average conditions of atmospheric pressure and temperature the compound is very stable. (McElin 1945)

Commonly known to investigators as compound A 524, it was later labeled as benadryl by the Parke-Davis Company.



A524

Studies on animals suggest three significant actions. It alleviates:

1. Bronchial constriction caused by histamine or anaphylaxis.
2. The vasopressor effects of histamine.
3. Smooth muscle spasm.

Barnett, Barbas and Gross (1946) respect these activities of benadryl more than any other compound heretofore described.

The mode of action is naturally of interest. Friedlander and Feinberg (1945) presume that the clinical

action could be brought about by one or more of the following mechanisms:

1. By opposing the pharmacologic response of histamine through stimulation of the sympathetic system.
2. By direct relaxation of the bronchial musculature.
3. By preventing release of histamine.
4. By direct chemical combination with histamine, bringing about neutralization.
5. By blocking the action of histamine.

In view of absent peripheral vasoconstriction the sympathetic activity of the drug does not appear plausible. (Dragstedt 1945) Likewise it has been shown that there is little likelihood of preventing the release of histamine unless injury incident to its release is prevented. Wells in 1940 stated that the direct chemical combination between benadryl and histamine is not likely and suggests that its effect is due to the combination at the site of action of histamine, rather than with histamine itself. By so combining, the drug prevents histamine from attaching to this same receptor mechanism, thus preventing it from exerting its pharmacologic effect. In other words A 524 appears to posses a greater affinity for the same receptor site than does histamine. This explanation is well supported

by clinical investigation. The ability of the drug to inhibit a wheal response by prior application at the reaction site enhances the belief that the drug is adsorbed at the site of action. The action is not a reversed one but it does minimize the effect of any further liberated histamine.

The Mayo Clinic Report of 1946 summarizes their work with histamine.

Site of Action	Effect Produced	Some Organs Affected
Smooth muscle	Contraction	Bronchioles, blood-vessels, uterine muscle
Capillaries	Dilatation and permeability	Skin, mucous membranes
Gland of External secretion	Secretogogue	Lacrimal, nasal, pulmonary, and digestive glands
Cut end of sensory nerve fibers	Pain	Skin

Either local or oral administration of benadryl is capable of abolishing the wheal and flare response of the skin to local application of one per cent histamine. Similar inhibition was noted on ragweed sensitive patients.

The effect of benadryl on gastric acidity in normal persons stimulated with histamine bears no consistent results to date.

Moderate lowering of blood pressure is the only effect recorded on the cardiovascular system due to A524. Heart size, pulse rate, circulation time, capillary permeability and electro-cardiographic records are in no way altered in normal persons receiving massive oral doses of benadryl. (Rieveschl and Huber 1944)

When instilled into the conjunctival sac benadryl was well tolerated producing moderate dilatation of the pupil and a consequent interference with accomodation.

Normally the respiratory system is unaffected by A 524. In asthmatics, on the other hand, it causes a decrease in respiratory rate and a rise in the vital capacity in attempting to reach a normal level.

A constant per-centage of histamine acid phosphate, administered parenterally, was counteracted by a given dose of benadryl, regardless of the amount of the former given. When the histamine level was maintained constantly and the benadryl increased, the degree of histamine inhibition rose sharply with a definite ratio curve. Wells, Morris, Bull and Dragstedt (1945) plotted the figures:

1	mgm.	benadryl	antagonized histamine	85.2
4	"	"	"	93.2
16	"	"	"	97.1

and concluded that a rectangular hyperbole is obtained, a curve which closely simulates the formulae for the Langmuir isotherm adsorption equation, indicating:

1. That benadryl is adsorbed at the site of action of histamine, thus giving histamine less opportunity to combine with its receptor site.

2. The amount of histamine inhibited bears a consistent relationship to the amount of benadryl administered.

A patient said to be hypersensitive to cold was studied extensively by Horton and McElin (1945). The blood histamine had risen during and immediately after a period of active response to cold, demonstrating that the "H-substance" in this case was definitely histamine. The "triple response" was produced on the patient's forearm by holding an ice cube on the spot for three minutes. Then benadryl was administered intravenously for ten minutes and the ice applied to the opposite arm for a similar period. The response was at least fifty per cent less, producing one of the most definite demonstrations of histamine antagonism ever reported.

The relief in patients is entirely palliative and transient in nature, generally lasting for three to six hours. Results vary in a given group of patients, producing relief on one occasion, and under similar conditions having no effect to the same patient at another

time.

Certain side reactions including drowsiness, nervousness, numbness of extremities, nausea and dryness of the mouth may develop in patients under treatment with benadryl. These may appear at any stage of the treatment and need not bear any direct relationship to the dosage.

Appearing in the Mayo Clinic Proceeding (1946) were results of a study group of one-hundred cases treated with A 524. Side reactions occured with frequency. None of these were intensified enough to warrant discontinuance of the drug. Of these seventy-four presented symptoms:

Cases	Side Effect
44	Sleepiness
12	Dizziness
11	Dry mouth
10	Nervousness
6	Urinary frequency
4	Fatigue
3	Epigastric distress
3	Nausea
3	Difficulty in coordination
Total 74	

The first four cases were considered as noteworthy. Levin (1946) reports similar experience in some two-hundred and thirty-three cases of which sixty per cent experienced side reactions. Several patients slept fifteen to eighteen hours after receiving moderate doses of benadryl. The effect was less marked in children.

Symptoms were severe enough in forty per cent to warrant discontinuance of the drug. Some obtained relief by lowering the dosage to two-thirds. Many of these cases overcame the side reactions and were subsequently able to tolerate larger doses with good therapeutic effect. Williams (1945) and Barnett, Barbos and Gross (1946) reported drowsiness lasting for only one to one and one-half hours in their respective cases. Most patients exhibited a hypotension in association with the drowsiness. Koelishe and Prickman (1945) described drowsiness in fifty-five per cent of their cases and "a feeling of uneasiness or trembling" in many.

Feinberg (1946) states that these side effects are undoubtedly closely related and may be regarded as the result of a depression of the "higher centers". In his experience some fifty per cent of cases treated showed these temporary reactions in various degrees.

The dry mouth is explained by Code as probably due

to bl cking of the secretogogue action of histamine or the atropine-like effect of benadryl.

Amphetamine sulfate or caeffine sodium benzoate is used by many to alleviate the drowsiness. These procedures are limited by the systolic blood pressure. If systolic pressure is below one-hundred and ten, use five millagrams of amphetamine in the morning or in two divided doses. Reports are favorable in overcoming all side reactions including urinary frequency. Nausea is combated by giving a glass of milk before administration of the drug. Temporary reduction in dosage and administration of stimulants such as black coffee or caffeine, too, will alleviate many ill-effects (Zolov 1946).

Numerous animal experiments have been conducted to determine the toxicity of benadryl. In massive doses administered to laboratory animals over long periods of time, nervousness, irritability, cutaneous hyperesthesia and peripheral neuritis become manifest in a few, as a transitory finding. The hemopoetic system of all animals remained undisturbed. Histopathologic studies in these animals revealed no changes in any organ tissue. (Morris, Bull and Dragstedt 1945)

Studies on induced bronchial spasm suggest that benadryl is fifteen to thirty times more toxic than

aminophylline. McElin studied a series of laboratory animals given lethal doses of histamine; violent excitement, convulsions and respiratory failure preceded death. Rieveschl and Gruhzit(1945) reported exactly the same findings. They also studied chronic toxicity in dogs using massive daily doses for six weeks. These showed no changes in the blood count, hemoglobin or non-protein nitrogen. No appreciable change in eating habits or weight of the dogs occured. The highest doses caused nervousness, ataxia, gastro-intestinal reactions and cutaneous hyperesthesia. Autopsy on these dogs revealed no gross pathology. Histologic examination of liver, kidney, spleen, adrenal, cardiac muscle, brain, gall bladder and so forth showed no acute degenerative processes. The central nervous sytem was free from congestion, edema, petechial hemorrhage or necrotic cells. Death of the animals was primarily associated with respiratory failure. The Mayo Clinic (1946) reports observations of non lethal doses in dogs demonstrating violent ataxia and excitement; no visual or mental impairment. They too found no evidence of degenerative changes at necropsy. Unexplained congestion in the choroid plexus, however, was present. There is no available evidence of delayed or cumulative action or

incompatabilities of benadryl.

Horton and McElin (1945) have followed the erthyrocyte, leucocyte and differential blood counts, as well as urinalysis, on a representative group of clinical patients with no associated abnormal findings. One group, placed on high dosage for a considerable period of time, showed no alteration of bleeding time, platelet count or clotting time. Heart disease, hypertension, or renal disease do not constitute contraindications to benadryl therapy. Since A 524 is not a narcotic and posses a wide range of tolerance it may be used for extended periods of time without harmful effects on the patient. There is no evidence indicating that benadryl may be habit forming. A Wide degree of safety is noted in human beings.

Indications for the use of benadryl are:

1. As an anti histamine agent in various allergic states.

2. As an antispasmodic, to a lesser degree, in dysmenorrhea.

3. The effectiveness of the drug in the following has not been fully established but clinical observations indicate its therapeutic usefulness: angioneurotic edema, eczema, asthma, cardio spasm, dermatomyositis, food sensitization, hiccough, migraine, pruritis, spastic colitis, Meniere's syndrome and vesico-urethral spasm.

4. To decrease cutaneous vasodilating action of histamine and nasal congestion due to vasodilating action on the nasal mucosa.

5. Decrease pruritis of eyes or skin.

6. To diminish post nasal drip.

7. To obtain general improvement in congestion of the nose and throat.

8. Relief of pruritis in atopic dermatitis, urticaria, contact dermatitis, and pruritis vulvae prevents secondary infection and delayed wound healing.

The average adult's single dose of benadryl is fifty milligrams. This represents in the average person two milligrams per kilogram body weight. The single oral dose which is lethal in rats is five-hundred and twenty milligrams per kilogram body weight, giving some idea of the wide margin of safety between an effective dose and toxic amounts. Usually cases are begun with basic doses of fifty milligrams each evening before retiring, for three days; this is gradually increased by fifty milligrams, if no associative untoward symptoms occur, until one-hundred and fifty milligrams daily in three divided doses is reached. (Barnett, Barbos, and Gross 1946) Levin (1945) believes that by giving initial dose in the evening the associated drowsiness will not be a serious disability. In severe cases up to four hundred milligrams daily, in eight divided doses, may be necessary to control the condition. When relief is once obtained maintainence doses of fifty to one-

hundred milligrams daily will usually be sufficient to prevent recurrences. The total daily dosage, of course, is best determined by clinical trial and is preferably administered following each meal and before retiring, when more than one daily dose is required. In no instance should a daily dose exceed four hundred milligrams. (Park Davis Company Laboratories)

In the treatment of acute conditions the patient should be instructed to await the effects of the initial dose for at least two hours, since partial to complete symptomatic relief may follow the first dose, a second dose not being required for five to six hours. Some beneficial effect in responsive conditions may be expected within a few hours following oral administration of the drug. More resistant conditions may show minimum response in one or two days, under which circumstance dosage should be elevated. Large doses, over four-hundred millagrims, are usually not well tolerated by most people. (Feinberg 1946)

In infants ten to twenty mill grams have been employed and in children up to twn years twenty-five milligram doses are used. Children up to twelve years may be given one or two teaspoons of the elixir three to four times daily in acute conditions, with a reduced main-

tainence dose following. The elixir contains ten milligrams per drahm (four cubic centimenters). This is supplied in bottles of one pint or one gallon. (Parke Davis and Company) If the elixir is not available for children, the powdered form in twenty-five milligram capsules or part of a fifty milligram capsul may be mixed with syrup or jelly and administered orally. Occasionally if the elixir is retained in the mouth for any appreciable length of time, anesthesia of the tongue and buccal mucosa may be noticed. This is of no significance and wears off rapidly with no residual.

The Parke Davis Company dispenses the fifty milligram capsule, in a pink jacket with its distinctive white band. Capsules with a white body and pink top contain twenty-five millagrams of the powdered form.

Parenteral administration has also been employed in a limited number of cases, with satisfactory clinical response within three to ten minutes and persisting for three to five hours. A sterile solution containing sixty milligrams of benadryl in one-hundred cubic centimeters of physiologic saline is preferable. This form is of particular value when gastro-intestinal symptoms manifest themselves.

Intra muscular injection in solution of ten milligrams per cubic centimeter has been used but the patient

experience local tenderness, induration and erythema at the site of injection.

CLINICAL REPORTS

Hay Fever

Logan (1945) employed benadryl in treating twelve children suffering from hay fever. The optimum daily dose was two milligrams per pound in divided daily doses. Side reactions of drowsiness and vomiting were noted. Excellent therapeutic results were observed in nine of the twelve cases, two of the remaining three received moderate relief, one reported no relief.

A series of eighty-three patients at the Mayo Clinic as reported by Koelsche, Prickman and Carryer (1945) were suffering from hay fever or bronchial asthma. If the patient did not have fifty per cent relief, the results were recorded as of no benefit. Those complaining of hay fever were relieved in seventy-five per cent of the cases, sixty per cent receiving complete relief. The majority of those reporting no relief had stopped routine medication because of unpleasant side effects, drowsiness being the usual complaint.

Many clinicians reduced the dose and administered the drug at bedtime with a consequent alleviation of these undesirable effects.

Signs of improvement include cessation of the nasal discharge and relief of the irritating sensation in the

nose and eyes. This relief was noted by Zolov (1946) within sixty minutes after fifty milligrams of benadryl. His patients reported relief for a duration of six to eight hours. This was prompt and definite within twenty to thirty minutes in sixty per cent of Levin's patients. (1946) He exclaims that side reactions were less frequent in children, but relief was short, lasting three to six hours.

McElin and Horton (1945) report excellent clinical experience in twenty-two of twenty three cases of hay fever treated with A524.

Urticaria

Ben dr controls promptly but transiently the allergic manifestations seen in daily practice. (Williams 1946) Among them urticaria, following liver injections, penicillin or sulfonamide, by parenteral administration, are the most frequebtly seen. It acts more promptly than adrenalin and has fewer undesirable features, less treatment is required, and the effects of medication are more persistent.

Thorough and complete data with followup examination are presented by O'Leary. (1945) He assures us that urticaria is no small problem. Three hundred and sixteen cases of urticaria were seen in the Mayo Clinic dur-

ing 1944, or two and one-half per cent of all dermatology cases seen. They worked diligently and from all angles and concluded that the condition was due to a temporary pathological permeability of superficial vessels, producing extravasation of tissue fluid and resulting in localized edema. The condition is dangerous only when the trachea and larynx become involved, but in any case it is very unpleasant, irritating and frequently incapacitating when hands and feet are involved.

Acute urticaria subsides spontaneously in a few days to a few weeks. The chronic form, however, persists for years and is as yet an etiologic enigma. As inferred the chronic form has thus far been resistant to all forms of treatment. Prompt relief in nine of sixteen cases of the symptoms of acute urticaria (sixteen days duration) occured in twenty to thirty minutes. The lesions were gone in two to six hours. The remaining six patients were improved.

O'Leary also treated thirty five cases of chronic urticaria which averaged four years duration, thirty years of symptoms being the longest. Twenty four of the thirty five had the additional complaint of angioneurotic edema. Common sites of swelling were hands, face, arms, feet, legs and the throat. Only three were

not benefited. Twenty five had complete relief and seven were improved. The dose was one hundred milligrams three or four times daily. Recurrence of symptoms were marked when placebos were substituted for benadryl. The Mayo Clinic group concluded that benadryl is highly effective in relief of urticaria and angioneurotic edema. (1946) This is only palliative and temporary and not curative except in the occasional case.

Approximately ten percent of patients treated with insulin have transient periods of redness, swelling and pruritis at the site of the injection. This may be a le iated with local administration of benadryl, hich can be added to the insulin in the syringe. This should be of considerable aid in diabetic therapy.

Gastineau and Leavitt (1946) discuss a case of insulin-allergic response treated by similar method. Previous methods had failed. The patient had required some sixty-five units of insulin daily; she developed severe edema of the fingers and lips. Benadryl was administered orally in two hundred and fifty milligram doses daily. Results were dramatic. This group preferred the oral route to local application.

Similar reports with parenteral penicillin-allergic

reaction, extensive allergic lesions from barbiturates and other drugs are many. (Hart 1945, Curtis and Owens 1945, O'Leary and Farber 1946, McElin and Horton 1945, Williams 1946)

Todd (1946) finds such therapy of value in:

1. Maintaining the urticarial patient in comfort for a few weeks until specific desensitization becomes effective.
2. In controlling the urticaria and angioneurotic edema of serum sickness.
3. In relief of both allergic and non-allergic urticaria.

He had excellent benefits in forty-seven of fifty-two cases.

Asthma

An impressive case of Woldbott's (1946) is that of a seven month old infant suffering from extremely severe attacks of asthma periodically, always terminating in pneumonitis, etiology unknown. Describing these attacks he reveals the child was in complete shock, unconscious with marked cyanosis. All efforts were without avail. Dramatic relief was procured with one-half gram benadryl orally, within thirty minutes. The pulse rate dropped from an imperceptible number down to ninety; respirations fell from ninety-six to thirty-four. Needless to say the drug afforded definite relief.

Advanced asthma, however, responds far less readily to medication than do hives or hay fever. (Woldbott 1946, Logan 1946) Relief in thirty-three per cent of twelve cases treated with benadryl by Koelsche, Prickman and Carryer (1945) occured with one-hundred milligrams daily. They express their views in that considerable more experience is needed before conclusions can be evaluated pertaining to asthma.

Zolov (1946) on the other hand had excellent therapeutic results in two of four cases treated with A524. Levin 1946) has given the problem much thought and a fair therapeutic trial. Eighty-seven patients, fifteen of them children, were studied. Sixty-six per cent praised the therapy highly. His good results were due to his keen analysis of the cases. He observed that doses up to three hundred milligrams daily afforded no relief in asthmatics who had superimposed colds. Chemotherapy to improv the upper respiratory infection plus the benadryl following this was the answer to the problem. Eyermann (1946) too emphasized that asthma complicated by bacterial infection was not responsive to benadryl therapy. Sixty-five per cent of his patients were re ieved with benadryl, when not complicated by bacterial infection. Horton and McElin (1945) had similar

results. In fourteen of the sixteen selected cases who showed no improvement from benadryl, suffered from bacterial type of allergy for many years.

Curtis and Owens are not encouraged by their efforts in asthma treatment with benadryl. (1945)

errenial Vasomotor Rhinitis

Nasal stuffiness, sneezing and excessive lacrimation are frequently controlled within thirty minutes following a single dose of benadryl. All reports of benadryl therapy is excellent in these conditions, affording ninety per cent relief as an average. (Williams 1945, Zolov 1946, McElin and Horton 1945)

Histamine Cephalgia

Histamine cephalgia, vasomotor rhinitis, hyperplastic sinusitis and Meniere's syndrome are closely related and are due to some fundamental disturbance in the physiological mechanism.

Williams (1946), Zolov (1946), McElin and Horton (1945) find benadryl effective in about fifty per cent of patients diagnosed as having histamine cephalgia. Hart (1946) inferred only moderate value in such a syndrome. He says that it appears to reduce the severity of the

severity of the attacks rather than the frequency, but is not consistent.

Meniere's Disease

In endolymphatic hydrops, overdistension of the membranes by fluid, owing to increased cell permeability produced by histamine, is thought to stimulate the Christi Ampularis of the semicircular canals, resulting in subhective or objective vertigo.

Two cases were improved when treated by McElin and Horton with benadryl. Zolov had similar results in as many cases. Williams had seventy-five per cent relief with two patients, but suggested tha benadryl be used in conjunction with niacin and potassium nitrate.

From this data it appears that benadryl therapy is useful in physical allergy of the head and is deserving of a more extended trial.

Trifacial Neuralgia

Reports are few and results non-conclusive. Williams (1946) treated one case with benadryl and procured relief, "at times".

Migraine

A case is cited in which intravenous benadryl was

administered to a patient with migraine and superimposed grand mal seizures. In five minutes the attack of migraine was terminated. All procedures which had previously precipitated attacks failed to produce them for the remaining twenty-four period. Levin (1946) also treated three children and fifteen adults. Sixty-six per cent or eleven were relieved. Two showed aggravation of symptoms.

Myalgia of the Head

A condition in which tender regions appear in muscles as a result of physiological or emotional stimuli is known as myalgia of the head. There is a tendency toward reference of pain to a distant area. When myalgia occurs in the head or neck it is usually referred to by the patient as sinus headache. In a series of five patients Williams (1946) gave benadryl orally every day for one week and reported fifty per cent relief of both headache and muscular tenderness.

Generalized Non Specific Pruritis

This condition is said to be precipitated during routine skin testing. Williams (1946) found that benadryl lowers the excessive distribution of histamine in

the tissues; usually occuring after a number of positive reactions. Subsequent skin tests are more clear cut and specific. The Mayo Clinic Report by McElin and Horton (1945) summarizes its findings of eighty-one cases treated with benadryl:

Diagnosis	Cases	Results			
		Excellent	Good	Fair	Poor
Hay fever	22	19	2	1	
Vasomotor rhinitis	8	5	2		1
Meniere's synd.	6	3			
Angion' edema	4	4			
Asthma	3	1			3
Histamine ceph.	8		4	2	2
Tension Headache	4	4			
Dysmenorrhea	1				
Atypical face pain	4				4
Migraine	3				3
Recurrent contact dermatitis	2			2	
Trigeminal Neur.	1			1	

This chart is by no means representative of all opinions and reflects only the data of an isolated group.

In neurodermatitis and atopic dermatitis therapy was

directed toward combating the pruritis and preventing trauma of the skin by scratching. Wolbott (1946), Friedlander (1946), Feinberg (1946), Williams (1946) and all the investigators report favorable therapy. The pronounced relief in pruritis vulvae is of considerable value. The results in contact dermatitis were less striking.

Friedlander and Feinberg (1946) sum up their observations. The clinical value of benadryl is only palliative and symptoms invariably recurred after withdrawal. In the present series the clinical efficacy of the drug was best demonstrated in hay fever, urticaria and vasomotor rhinitis. It was possible to relieve many intractable cases of urticaria of years duration in which other measures had proved of no avail.

II. Pyribenzamine

More recently Mayer (1945) reported the anti histamine activities of compound 63 C. Rennick and his cohorts in studying the pharmacology of the drug found it to be very similar to benadryl in activity. (Rennick, Chess, Hayes, Mathieson, Mayer, and Yonkman 1945) The toxic dose was found to be many times the effective dose, in animals. This finding rationalized its therapeutic use without fear of danger, at least for short periods of time.

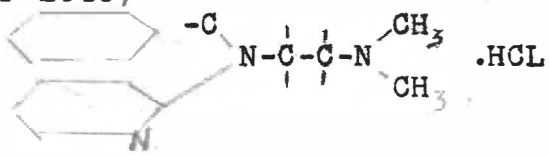
Using five dogs of the same breed, Koefp, Arbesman and Munafo (1946) investigated further, 63C. Two were given one hundred milligrams orally every day; two were given fifty milligrams daily for one year; the remaining dog acted as control.. There were no apparent changes in physical signs, all remained in good health and exhibited normal activity. At no time was drowsiness or fatigue present. Kidney function test, liver function, bromsulpthalein tests in addition to icteric index, prothrombin and blood urea nitrogen tests indicate that 63C in therapeutic doses can be administered for long periods of time without liver or kidney damage.

Yonkman (1945) experienced slightly different results. In his work on guinea pigs, toxic doses produce

excitation up to a point of convulsive seizures. Concentrated solutions injected hypodermically produce local tissue necrosis. He also noted that in dogs gradual hypertension developed in high doses, simultaneously respiration increased, suggesting a central action in this instance. The anti cholinergic action of 63C, however, may explain such reactions.

Since 63C is so recent in its discovery the reports are limited. The few other investigations on laboratory animals demonstrated the same consistent findings as in similar experiments with benadryl.

The mode of action of 63C is unknown, but theory offers the explanation that it acts similar to benadryl. This is strongly supported by experimental findings. (Mayer 1946)



(63C) is N'pyridl-N'benzyl-N'dimethyl ethylene diamine hydrochloride

or commercially name pyribenzamine by the Ciba Laboratories. It posseses definite oxytoxic activity but its anti histamine action is much greater. The protection by pyribenzamine against allergic states is very temporary, acting as long as it is present in the blood

stream or in tissue cells. Slight antispasmodic action has been noted by Mayer. (1946) He adds that the anti histamine action is several million times more active than the amino acid group.

Such limited studies as are reported in man are not by any means exhaustive. Koepf, Arbesman and Munafo (1946) experimented on three healthy male patients, giving one hundred and fifty milligrams of 63C for eighty days. At no time was their state of well being altered and no significant alterations in physical signs, weight or blood pressure were noted. Routine urines, blood examinations, liver and kidney function tests were done weekly.

In another group four hundred and ninety-five private patients were chosen in the allergy clinic of the Buffalo General Hospital. All patients were seen frequently to insure complete cooperation, but due to the many variables encountered in any series of experiments, obvious difficulties were presented in enough cases to render evaluation questionable. They found that the dosage varied with the individual and the allergic states. The average established dose was the same as A524, one hundred to four hundred milligrams daily, one-half this for children. At times as much as twelve

hundred milligrams of pyribenzamine were administered in twenty-four hours without any serious untoward effects. The medication was always given orally and in four divided doses. Relief was produced in those who were consistent in taking their medication, within fifteen to twenty minutes and lasted from three to twelve hours. Aside from the infrequent side reactions results were similar to benadryl therapy.

Feinberg (1946) noted fairly common side effects, but they were neither severe or serious. Of the five hundred and ninety-eight patients he observed, twenty-three per cent admitted side effects. In the order of frequency these were, drowsiness, dizziness, nervousness and dryness of the mouth. Other less common and less consistent complaints were: headache, palpitation, burning on urination, gastric irritation and hypotension. The dose had been fifty millagrams four times daily.

Pyribenzamine is well tolerated by man, since between two hundred and five hundred milligrams by oral route have been used in five subjects for eight to ten days without undesirable symptoms.

Seasonal Allergic Rhinitis

In thirty four cases reported by Arbesman, Koepf and Lenzner (1946) using 63C to combat rhinitis due to

grass pollen, eighty-five per cent were benefited. Twenty-three of twenty-four who had no previous treatment were relieved. The remaining ten had unsatisfactory pre-seasonal desensitization. Relief was obtained in seven of these. Feinberg (1946) reports eighty-two per cent relief of the typical symptoms of rhinorrhea, sneezing, nasal occlusion and itching. The results in perennial vasomotor rhinitis were definitely less frequent. Ninety three of these one hundred and eight cases were resistant to desensitization; of the remaining forty-five who had no previous treatment thirty-seven were relieved with 63C; fifty-eight percent relief in all. Feinberg (1946) reported more favorable results in the same syndrome, approaching sixty-five per cent benefit. Feinberg also hails the excellent response to pyribenzamine in the treatment of hay fever, in a limited group of patients.

Asthma

The per-centage of cases relieved of their symptoms varies widely with the clinicians. As with papers written on A524, this variability is probably due at least partially to technique of the clinician.

The complete and rapid response produced by epi-

nephrine is not mirrored by pyribenzamine. (Feinberg 1946) Twenty-eight per cent of his one hundred and twenty-one cases reported only moderate relief. Arbesman, Koepf and Lenzner (1946) studied sixteen cases, all of which were treated with pyribenzamine; twelve were markedly relieved. Seven of these had complete relief. This appears to be much more impressive than the previous investigators' results.

Dermatitis

The relief of pruritis is responsible for the benefit in pruritis vulvae and pruritis ani by reducing secondary infections from scratching.

Urticaria

Friedlander and his associates (1946) had better results and similar action with 63C than with A524. The greatest effect being noted when the drug is applied locally, preventing the wheal phenomenon induced by histamine or by specific antigens. Arbesman and associates (1946) report ninety-three per cent of the patients relieved of acute urticaria. Seventy-five per cent of the patients with chronic urticaria were completely rid of symptoms when 63C was employed.

In miscellaneous conditions pyribenzamine produced some benefit in migraine and in food allergies. These results included too few cases and were too inconsistent to be of much value.

It is quite obvious that the clinical experience with pyribenzamine thur far is limited. Apparently 63C does not produce either the frequency or degree of drowsiness associated with A524, despite its closely allied activity.

CONCLUSION

In comparing the therapeutic value of the more promising anti histamine compounds, antergan, neo-antergan, benadryl and pyribenzamine are the most valuable ones described by current investigators. Clinical evidence points toward greater benefit associated with less toxicity in the latter two. Benefits with benadryl and pyribenzamine are practically equal, the latter being better tolerated with fewer side reactions.

For the present it is clear that A524 and 63C are drawing together a widely diversified group of clinical conditions, the common denominator being some abnormality of histamine metabolism. Permanent relief is the therapeutic aim of the clinician, but it is not always possible to determine or eliminate the etiologic factors. The anti histamine preparations A524 and 63C are of definite value in the temporary relief of pruritis, urticaria, rhinorrhea and nasal congestion and has potential value in the relief of other allergic manifestations.

The indiscriminate use of anti histamine agents by physicians is not to be encouraged, since severe side

reactions of confusion,drowsiness and loss of judgment may prove deleterious.

The recently investigated anti histamine agents, A524 and 63C, are not only of inestimable value in the treatment of acute allergic phenomena, but will henceforth give the allergist an opportunity to search for the fundemental etiologic factor in hope of securing permanent relief.

Since attention will be focused on anti histamine agents in the future a detailed investigation of the available literature semmed appropriate at this time.

The possibility of a universal treatment for allergy has been frowned on by many clinicians. It is advisable then for the allergist to evaluate the indications for and the limitations of, any anti histamine preparation.

Literature Cited

Alexander,H. 1940 Treatment of allergic disorders with histamine and histaminase. J. Lab. & Clin. Med., v.26, pp. 110.

Arbesman,C., Koepf,F., & Lenzner,A. 1946 Clinical studies with N'pyridil N'benzyl dimethyl ethylene diamine monohydrochloride. J. Allergy, v. 5, pp. 275.

Barnett,S., Barbos,F. & Gross,S. 1946 Benadryl in hay fever, asthma, and vasomotor rhinitis. J. Mich. M. Soc., v.45, pp. 771.

Best,C, Dale,H., & Dudley,A., & Thorpe,W.V. 1927 The nature of the vasodilator constituents of certain tissue extracts. J. Physiol., v.62, pp. 397.

Best,C. & McHenry,E. 1930 The inactivation of histamine. J. Physiol., v.70, pp. 349.

Bourque,J. & Loew,E. 1943 The effect of histamine antagonists on gastric secretion. Am. J. Physiol., v.138, pp.341.

Butler,S. & Thomas,W. 1945 Intravenous histamine in the treatment of migraine. J.A.M.A., v.128, pp.173.

Climenko,D. 1941 Pharmacology of thymoxyethyl diethylamine. J. Lab. & Clin. Med., v.27, pp.289.

Code,C. 1937 The source in the blood of the histamine-like constituents. J. Physiol., v.90, pp.349.

Code,C. 1945 A discussion of benadryl as an anti-histamine substance. Proc. Staff Meet. of Mayo Clinic, v.19, pp.15.

Cohen,M. 1944 The immunologic management of a patient with allergy. J. Allergy., v.15, pp.274.

Cohen,M. & Friedman,H. 1945 Histamine azo protein in treatment of allergy: paper read before academy of allergy. (Feinberg,S. 1946 Anti histamine agents J.A.M.A., v.12, pp.704.)

Curtis,A. & Owens,B. 1945 B-dimethylaminoethyl benzhydryl etherhydrochloride in treatment of acute and chronic urticaria. Univ. Mich. Hosp. Bull., v.11, pp.1.

Dale,H. & Laidlow,P. 1910 They physiologic action of B-imminazolylethylamine. J. Physiol., v.41, pp.318.

Dragstedt,C & Gebauer-Feuelnegg,E. 1932 Studies in anaphylaxis. Am. J. Physiol., v.102, pp.512.

Dragstedt,C. 1945 Significance of histamine in anaphylaxis. J. Allergy., v.16, pp.69.

Dragstedt,C. 1945 The role of histamine in various pathological conditions and the methods of controlling its effects. Quart. Bull., Northwestern Univ. M. School., v.4, pp.303.

Dragstedt,C. & Morris,H. 1945 The anti histamine effects of immidazol. Soc. Exper. Biol. & Med., v.59, pp.311.

Drake,C., Earl,G. & Ulrich,H. 1946 Benadryl. Minnesota Med., v.29, pp.711.

Elam,E., Ancona,G. & Kerr,W. 1945 Histamine like substance present in nasal secretions of the common cold and allergic rhinitis. Am. J. Physiol., v.144, pp.711.

Ellia,F. 1945 The effects of some new spasmolytic agents in perfused guinea pig lungs. Fed. Proc., v.4, pp.117.

Ernestene,A. & Banks,B. 1933 Use of histamine in the treatment of pruritis. J.A.M.A., v.100, pp.328.

Eyermann,C. 1946 Clinical experience with a new anti histamine drug. J. Allergy., v.17, pp.210.

Farmer,R., Laurence,E. & Kaufman,R. 1942 Histamine in the treatment of nasal allergy. Laryngoscope., v.52, pp. 225.

Feinberg, S. 1946 Antihistamine agents. J.A.M.A., v.12, pp.702.

Fell, N., Rodney,G., & Marshall,D. 1943 Histamine azo protein. J. Immunol., v.47, pp.237.

Friedlander,S. & Feinberg,S. 1946 Histamine antagonists. J. Allergy, v.13, pp.129.

Friedlander,S. & Feinberg,A. & Feinberg,S. 1946 Comparative study of benadryl and pyribenzamine in histamine and anaphylactic shock. Proc. Soc. Exper. Biol. & Med., v.6, pp.65.

Gastineau,C. & Leavitt, 1946 Treatment of allergy to insulin with benadryl. Proc. Staff Meet. Mayo Clin., v.17, pp. 316.

Hallenbeck, G. 1943 Studies on the effect of thymoxyethyldiethylamine (929F) and N-diethylamine ethyl N-ethylaniline on gastric secretions in the dog. Am. J. Physiol., v.139, pp.329.

Hart,C. 1945 Toxicity of benadryl. Proc. Staff Meet. Mayo Clin., v.20, pp.423.

Katz,G. 1942 Histamine allergic reaction. Proc. Soc. Exper. Biol. & Med., v.49, pp.272.

Katz,G.& Cohen,S. 1941 Experimental evidence for histamine release in allergy. J.A.M.A., v.117, pp.1782.

Koelsche,G, Prickman,L. & Carryer,H. 1945 Treatment of bronchial asthma and hay fever with benadryl. Proc. Staff Meet. Mayo Clin., v.20, pp.432.

Koepf,G., Arbesman,C. & Munafo,C. 1946 Chronic toxicity of N'pyridil N'benzyl dimethylethylene diamine monochloride (pyribenzamine). J. Allergy, v.5, pp.271.

Landau,S & Gay,L. 1944 Influence of certain amino acids on histamine reactions and anaphylactic reactions in intestinal strips of guinea pigs and in intact guinea pigs. Bull. John Hopkins Hosp., v.74, pp.55.

Levin, S. 1946 B-dimethyl amonoethyl benzhydryl ether hydrochloride (benadryl) and its use in allergic disease. J. Allergy, v.17, pp.145.

Lewis,T. I927 The blood vessels and their responses Shaw & Sons Ltd.,ppI33.

Loew,E. & Chickering,O.I94I Gastric secretions in dogs treated with histamine antagonist thymoxyethyl-diethylamine,929F. Soc.Exper.Biol.&Med.,v.48,pp 68.

Loew,E. & Kaiser,M. I945 Alleviation of anaphylactic shock in guinea pigs with synthetic benzhydyl alkamine ethers. Proc. Soc. Exper. Biol.& Med., v.58,pp235.

Loew,E. Kaiser,M. & Moore,V. I945 Synthetic alkamine ethers effective in preventing fatal experimental asthma in guinea pigs exposed to atomized histamine. J.Pharm.& Exper. Med., v.83, ppI20.

Logan,G. I945 The use of benadryl in treating some of the allergic diseases of childhood. Proc.Staff. Meet. Mayo Clin. v.20, pp436.

Mayer,R. I946 Anti histamine substances with special reference to pyribenzamine. J.Allergy, v.I7,ppI53.

Mayer,R. Huttner,C. & Scholz,C. I945 Anti histamine and antiphylactic activity of some alpha pyridine-ethylenediamines. Sci., v.I02, pp.93.

McElin,T. & Horton,B. I945 Clinical observations on the use of benadryl: a new anti histamine substance. Proc. Staff. Meet. Mayo Clin., v.20, pp.4I7.

O'Leary,P. & Farber,E. I945 Ben adryl in the treatment of urticaria. Proc. Staff. Meet. Mayo Clin., v.20, pp.249.

Peterson,W. I945 The organic state in the problem of allergy. Ann. of Allergy, v.3, pp.348.

Randolph,T. & Rackermann,F. I94I The blood histamine level in asthma and eosinophilia. J.Allergy, v.I2, pp.450.

Rennick,B. Chess,D. Hays,H. Mathieson,D. Mayer,R. & Yonkman,F. I945 The anaphylactic and anti histamine activity and toxicity of N'Pyridil N'Benzyl N'dimethylethylinediamine hydrochloride. Fed. Proc., v.4, pp.I33.

Rieveschl,G. & Gruhzit,O. I945 Atoxicologic study of the histamine antagonist beta dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Fed. Proc., v.4, pp.I50.

Rose,B. I94I Studies on blood histamine in cases of allergy J.Allergy., v.I2, pp.44I.

Roth,G, & Rynearson,E I939 The use of histamine and histaminase in treatment of allergic reaction to insulin. Proc.Staff. Meet. Mayo Clin., v.I4, pp.335.

Todd,L. I946 Symtomatic relief of the allergic reaction with the anti histamine drug benadryl. North Carolina Med. J., v.7, pp.308.

Wells,J. Gray,J. & Dragstedt,C. I94I An investigation of the problem of histamine tolerance. J.Allergy, v.I3, pp.77.

Wells,J. &Morris,H. I945 Observations on antagonism of histamine by beta-dimethylamino ethyl benzhydryl ether (benadryl). Fed. Proc., v.4, pp.I40.

Wells,J. Morris,H. Bull,H. & Dragstedt,C. I945 Obsrvations on the nature and antagonism of histamine by beta-dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) J. Pharm. & Exper. Ther., v.85, pp.I22.

Wilcox,H. & Seegal,B. I942 Influence of ethylenediamine derivitives on histamine intoxication and anaphylactic shock in the intact guinea pigs and in isolated guinea pig ileum. J. Immunol., v.44, pp.2I9.

Williams,H. I946 The syndrome of physical or intrinsic allergy ergyof the head, vasomotor rhinitis, and vasodilating pain syndrome. Proc. Staff.Meet. Mayo Clin., v.2I. pp.58.

Williams,H. I945 The use of benadryl in the syndrome of physical allergy of the head. Proc. Staff. Meet. Mayo Clin., v.20, pp.434.

Waldbott,G. I946 Clinical results with benadryl., v.3, pp. I42.

Yonkman,F. Hays,H. & Rennick,B. I946 The protective action of " pribenzamine" (63C) against horse serum anaphylaxis in dogs. Fed. Proc., v.4, pp.I44.

Zolov,B. I946 A new anti histamine agent in allergic disease. J.Maine Med. Assn., v.37, pp.I26.