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THE USES AND ABUSES OF ANTIHISTAMINE DRUGS*

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EARLY last year a drug manufacturer estimated that one hundred million dollars worth of antihistaminic drugs would be sold during 1950!¹ Whether or not this prediction proves accurate, it emphasizes the fact that these drugs are being used in tremendous quantities. Since they were first introduced in America only five years ago, first physicians and then the public have been offered such a confusing mass of advertising that a careful appraisal of their therapeutic value is warranted at this time.

Since the discovery of anaphylaxis and the recognition of its relationship to human allergy, many investigators have studied non-specific methods of preventing or controlling anaphylactic shock. In 1932, Hill and Martin² reviewed the results obtained by 165 such methods which were more or less effective in experimental animals; not one of these was applicable to the practical treatment of allergic disease in man.

Many other methods have since been proposed; of these the most successful are based on the concept of histamine as an intermediary between the antigen-antibody reaction and the manifestations of allergy and anaphylaxis. This theory, proposed by Dale and Laidlaw³ in 1910, is supported by many researchers showing that histamine is released in anaphylactic shock and in allergies of the immediate urticarial type and gives rise to many of their chief manifestations. In certain aspects of anaphylaxis, such as the loss of coagulability of the blood in dogs, and in the delayed types of human allergy, such as tuberculin sensitization and contact dermatitis, histamine appears to play no part.

Within these limits, therapy directed at controlling the action of histamine offered the promise of a single form of treatment effective in

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many allergic diseases, without the need of determining the specific causative allergen. The earlier efforts in this direction, employing the enzyme histaminase, injections of histamine in attempts to induce tolerance, and histamine azo-protein (Hapamine) to produce antibodies to histamine, met with no significant success and have been abandoned.

In 1937, Staub and Bover⁴ reported investigations in experimental animals of the anti-anaphylactic and antihistaminic properties of a series of phenolic ethers synthesized by Fourneau. These properties were found to be shown to a significant degree by thymoxyethyl-diethylamine, designated as 929F, which may be considered the first synthetic antihistaminic but was too toxic for clinical use. The ethanolamine portion of its structure is utilized in the modern drugs Benadryl and Decapryn. Subsequently Staub⁵ studied the antihistaminic properties of other synthetic compounds and showed that 1571F, an ethylene diamine derivative, was more potent than 929F, but still too toxic for clinical use. In 1942 Halpern⁶ described a related compound, Antergan, which was 10 times as potent in animals and sufficiently safe for clinical use. This antihistaminic drug showed definite therapeutic effects in allergic rhinitis and urticaria, but was soon replaced by Neoantergan, another ethylenediamine compound which proved less toxic and more potent.

During the past war, while these studies were being made in France, American investigations led to the development of Benadryl, an ethanolamine derivative, and Pyribenzamine, an ethylenediamine compound related to Neoantergan. Both of these compounds had definite therapeutic effects in certain allergic diseases but were sufficiently toxic to stimulate further search for more potent and less toxic agents. During the past five years dozens of such compounds have been produced and screened by the drug industry and seventeen have been marketed, each with its own claims of potency and freedom from toxicity. The average physician is justifiably bewildered by this choice of essentially similar medications and may be comforted by the statement of the Council on Pharmacy that "the number of preparations on the market has served to provide confusion."⁷

The confusion is further increased by the application of both generic and proprietary names to each drug, and in many instances by the fact that the same drug is offered by two or more manufacturers under different proprietary names. For example, chlorcyclizine is marketed by Burroughs Wellcome as Perazil and by Abbott as Di-Paralene. In general,

the proprietary names are the most familiar and will be used in this discussion.

With the licensing of antihistaminic drugs for sale without prescription, many of the familiar drugs are being offered in reduced dosage under a variety of newly coined names. For example, pyranisamine 25 mg., familiar to physicians as Neoantergan, is offered to the public under thirty-two different names such as Kriptin, Anatamine, Macy's Antihistamine, Superhist, etc.

Chemistry: Chemically the twenty antihistaminic drugs more or less familiar to physicians, represent variations on a relatively few basic structures. The most commonly used structure is the ethylenediamine base (Fig. 1). In Pyrrolazote the nitrogen written at the left is included in a phenothiazine radical and that at the right is a pyrrolidine ring. In Antistine the 2nd carbon of the central chain is linked to 2 nitrogen atoms as part of an imidazoline ring, while in chlorcyclizine the 2 nitrogens form part of a piperazine ring rather than a simple chain.

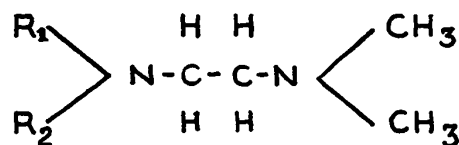


Fig. 1: Ethylene diamine structure. Antergan, Neoantergan, Pyribenzamine, Histadyl (Thenylene), chlorothen (Tagathen), Diatrin, Neohetramine and Thenfadil are represented by this formula with variations in the radicals R_1 and R_2 .

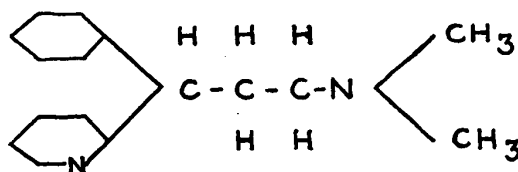


Fig. 2: Aminopropane structure. (Trimeton)

If the nitrogen at the left is replaced by carbon, the ethylenediamine structure is converted to aminopropane, but the antihistaminic activity is preserved, as in Trimeton and Chlor-Trimeton (Fig. 2).

If an oxygen atom or ether linkage is introduced at the same point, the ethanolamine series of antihistaminics, typified by Benadryl and Decapryn, is produced (Fig. 3).

The one chemically unique antihistaminic, Thephorin, has a complex ring structure based on pyridindene but is believed to break down in metabolism to a structure of the ethyldimethylamine type (Fig. 4).

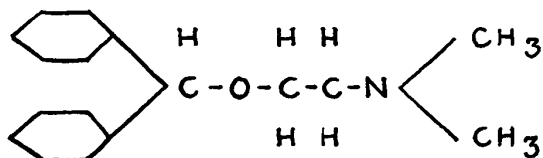


Fig. 3: Ethanolamine structure. (Benadryl)

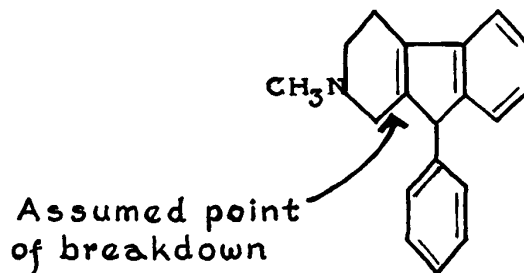


Fig. 4: Thephorin.

All of these are qualitatively similar in their pharmacologic actions, although differing quantitatively in antihistamine potency and toxicity.

Pharmacology: Pharmacologically, an antihistaminic drug has been defined by Bovet⁸ as "a counterpoison having no specific activity of its own on the normal animal, its properties becoming apparent only when it can manifest a detoxifying power against the action of histamine." While the drugs marketed as antihistaminics represent the nearest approaches to this ideal found in screening hundreds of compounds, and all show definite antagonism to the actions of histamine, none can be said to be actually free of activity upon the normal animal.

The antagonism to histamine may be readily demonstrated by inhibition of the effects of histamine in causing contraction of smooth

muscle, capillary dilatation and wheal formation in the skin, hypotension and lachrymation. On the other hand, the stimulation of gastric secretion by histamine is not appreciably affected. The exact nature of the histamine antagonism has not been established but has been assumed to result from blocking the access of histamine to cell receptors.

Presumably through inhibiting the action of histamine as an intermediary, the antihistaminic drugs inhibit anaphylactic shock in guinea pigs, rabbits and dogs; also inhibit the Dale reaction in the isolated smooth muscle of the sensitized guinea pig. In adequate concentrations, these drugs inhibit the specific wheal reaction in the skin of allergic humans.

The other pharmacologic effects, considered as side effects, vary somewhat among the various drugs. Most of the group show a minor degree of atropine-like effect in antagonizing the actions of acetylcholine. The dry mouth of which some patients complain while taking the antihistaminics may be attributed to this action.

Practically all the antihistaminic drugs act as local anesthetics. Benadryl, Pyribenzamine and Neoantergan are said to be two or three times as active as procaine in this effect. Some authors have recommended the practical use of these drugs for this purpose and it is probable that their antipruritic effect as local applications may be due to action as anesthetics rather than antihistaminics. The relation of local anesthetic and antihistaminic effects is also of interest since procaine and its derivative diethylaminoethanol have been shown to inhibit allergic urticarial reactions. Local anesthetics may be expected to decrease the effects of histamine in the skin by blocking the axone reflexes which take part in the spread of the flare produced. The careful studies of Code⁹ and his associates indicate that the inhibition of the histamine reaction in human skin by Benadryl, Pyribenzamine and Neoantergan is not dependent upon local anesthesia. These three drugs showed greater antihistaminic effects than concentrations of procaine equally effective as anesthetics, and their antihistaminic effect persisted after the local anesthetic effect wore off, while that of procaine did not. Furthermore, when many different antihistaminics were tested, it was found that those most effective as local anesthetics were often least active against histamine.

The actions of the antihistaminics on the central nervous system are among the most important side effects. In experimental animals, the nervous effect is usually excitement, but with ordinary doses in man,

sedation or depression is the usual effect. With the clinical use of the various drugs this may be apparent in 10 to 60 per cent of the patients, the incidence being highest with Benadryl and Decapryn.

Occasional individuals are excited rather than sedated by these drugs and in the case of Thephorin, excitement is the predominant nervous effect. With excessive doses of practically any of the drugs excitement and confusion of psychotic degree may result.

Choice of Drugs: The different antihistaminic drugs show considerable variations in efficacy and toxicity, but no one of them has a sufficiently greater ratio of potency to toxicity to be called the best. There are dozens of statistical reports of therapeutic and toxic effects of the various drugs but attempts to compare them are fraught with error because of variations in dosage used by various authors and differences in evaluation of results. An exact order of efficacy or toxicity cannot be established, but general classifications are helpful as a guide to physicians who can scarcely be expected to be familiar with all of the seventeen drugs that are available. In this grouping, I have borrowed freely from that given by Feinberg, Malkiel and Feinberg in their recent book "The Antihistamines."¹⁰ Among the most potent drugs are Benadryl, Pyribenzamine, Neoantergan, Histadyl (Thenylene), Chlorathen and Decapryn. Of these Benadryl and Decapryn are the most sedative. A second group of drugs which are somewhat less potent but also less toxic includes Chlor-Trimeton and chlorcyclizine (Perazil or Di-Paralene) which also have the advantage of longer duration of action. A third group of drugs less effective but valuable because of low toxicity includes Neohetramine, Antistine and Thephorin.

Such a classification does not accurately predict the reaction on each individual patient, but serves as a guide in selecting a drug for a particular purpose and in choosing a substitute if the one first tried proves ineffective or too toxic. For example, in mild hay fever one does well to choose a drug of relatively low toxicity, such as Perazil or Chlor-Trimeton, while for a patient confined to bed with intolerably itching urticaria, one of the most potent and most sedative drugs such as Benadryl or Decapryn is suitable. If a patient with rhinitis finds Pyribenzamine effective but too sedative, Neohetramine would be a more logical substitute than Benadryl, which is even more depressing.

Dosage Forms: All of the common antihistaminics are readily absorbed from the gastro-intestinal tract and are most commonly given

by mouth. They are marketed in pills or capsules containing one average adult dose which may be 4 to 100 mg. with different drugs. Details of dosage are different for each drug but in general the maximum dose is twice the average dose, repeated three to four times a day. Most of the drugs are also offered in liquid preparations for administration of fractional doses to children. The dosage of preparations offered for sale without a prescription is in general half the average dose offered to physicians.

The average duration of effect is about four hours, but the action of chlorcyclizine and Chlor-Trimeton is reported to last 8-12 hours.

In addition to the oral preparations, Benadryl and Histadyl are available in sterile solutions for intramuscular and intravenous use. These routes give prompter and often more powerful effects than oral administration.

For local application to itching eruptions most of the common antihistaminics are offered in ointments, creams and lotions. A few are offered in drops for ophthalmic or nasal use.

Uses: The primary purpose of the development of the antihistaminic drugs was the symptomatic relief of those allergic diseases in the pathogenesis of which histamine was known or believed to play a part, such as allergic rhinitis, asthma, urticaria, atopic dermatitis and serum sickness. Subsequently they have been tried empirically in many other diseases not known to be related to histamine. Such efficacy as they show is always in temporary symptomatic relief; in no disease are they curative. Even in those allergic disorders for which they have proved most useful, their efficacy is often surpassed by that of cortisone and ACTH.

For evaluation of their efficacy in various diseases, a host of statistics are available. When one attempts to consolidate various reports, however, it is apparent that the simple figures do not show the entire picture. In a single disease entity, mild and early cases many prove amenable to treatment while advanced cases are not. Some authors have used an "average dose" two or three times daily while others have prescribed two or three times as much four times a day. In evaluating results some have reported any significant degree of relief as a favorable result, while others have restricted this term to cases essentially free of symptoms. Therefore, we can best speak in general terms and use actual percentages of relief sparingly.

The most extensive clinical evaluation has been in allergic rhinitis.

Here the results obtained vary greatly with the severity and chronicity of the disease. In the acute stage of allergic rhinitis, either seasonal or non-seasonal, with sneezing, rhinorrhea and itching of the eyes and throat, satisfactory temporary relief may be obtained in 60-80 per cent of cases by use of the antihistaminics. On the other hand, the nasal obstruction due to engorgement of the mucosa, which is a prominent feature of long-standing rhinitis, is less susceptible to their action. Advanced rhinitis with polypoid changes in the membrane is only slightly affected. These differences are reflected in the statistics which usually show 60-75 per cent relief of seasonal hay fever and roughly 50 per cent for non-seasonal rhinitis.

In the case of hay fever, it means that patients with mild intermittent symptoms during the pollen season or with a short season caused by one of the tree pollens, may expect considerable relief from these drugs, while those who suffer continuously for 4-8 weeks during the grass or ragweed season will usually obtain only partial alleviation of symptoms. Since no other type of drugs except the recently introduced cortisone and ACTH offers as much symptomatic relief, the choice of treatment lies between the use of antihistaminics and the more elaborate and time-consuming method of prophylactic injections of pollen extract, started six or more weeks before the onset of the pollen season. Statistically the injection treatment is shown to be more effective but symptomatic treatment with antihistaminics has obvious advantages of simplicity and convenience. When the patient is first seen during the hay fever season, there is no opportunity for prophylactic injections and the antihistaminics should be used. The results obtained that season offer a basis for decision as to the choice of treatment in the following year. However, if pollen asthma occurs during the hay fever season, injection treatment is definitely indicated, since its occurrence is not appreciably prevented by the antihistaminics and it tends to become progressively more severe from year to year if other measures are not taken. On the other hand, a suitable course of pollen injections may be expected to relieve pollen asthma in 80 per cent of the cases.

This comparison of the effects of pollen injections and antihistaminics on hay fever does not mean that a choice must be made between them; the best results are obtained by combining both methods of treatment.

In non-seasonal allergic rhinitis it has been indicated that the anti-

histaminics are more effective for relief of acute symptoms than for persistent nasal congestion. Therefore, these drugs are most useful as a temporary measure and long-standing cases should be studied for determination of the causative factors. When the symptoms are due to sensitization to dust, animal danders or other inhalant allergens, much greater relief may be expected from allergic treatment than from continuous use of symptomatic drugs.

In bronchial asthma, the antihistaminics are considerably less effective than in allergic rhinitis. Many studies report 20-40 per cent of all asthmatics benefited by these drugs, but the patients relieved are almost invariably those with mild asthma usually more easily controlled by other oral medications such as ephedrine and aminophylline. In severe chronic asthma, when treatment is a real problem, the antihistaminics are generally useless. Certain proprietary combinations of antihistaminics with aminophyllin or ephedrine are moderately effective for the relief of mild asthma; but on the whole the antihistaminics offer no notable advance in the symptomatic relief of asthma.

Among the allergic dermatoses, urticaria is the most responsive to antihistaminic drugs. Most statistics indicate that 70-90 per cent of patients with acute urticaria are benefited by these medications. In some cases the "average dose" of the drug selected is effective, but often this must be doubled and repeated three or four times a day. In severe urticaria, intramuscular injections may be more effective than oral use. Relief of itching is often obtained although wheals may persist.

Chronic urticaria is somewhat less responsive than acute but the antihistaminics are still among the most valuable drugs for symptomatic relief. Continuous control may require large doses repeated three or four times daily. As in other chronic diseases, the effect of these drugs is only symptomatic and patients with urticaria persisting or recurring over a period of weeks should be carefully studied to determine the causative factors.

Angioedema or giant urticaria is less susceptible to these drugs but it is also relatively resistant to most other forms of treatment, so a trial of their efficacy is warranted. In acute attacks, large doses of antihistaminics by mouth or injected parenterally may be used concurrently with injections of epinephrine in oil. For prevention of recurrent attacks continuous use of one of the antihistaminics may be advised, but as in chronic urticaria, a diligent search for etiologic factors should be made.

The antihistaminics are of definite value in treatment of serum sickness and similar reactions to penicillin. Relatively large doses are required and intramuscular administration may be more effective. The effects are chiefly in the relief of itching and urticaria; arthralgia and fever are not appreciably affected. In very severe cases, the antihistaminics may prove ineffectual and ACTH or cortisone should be used.

In severe anaphylactic reactions resulting from the injection of heterologous antisera or other biologic products, the effect of the antihistaminics is too slow to be the main therapeutic effort. Epinephrine is more rapid and efficacious, but its action may be supplemented by parenteral injections of Benadryl or Histadyl.

The antihistaminic drugs have been widely used in atopic dermatitis, but estimates of favorable results have been reported by various authors as 0 to 75 per cent. This discrepancy is due to the fact that more than half of the patients treated have some relief of itching but there is no immediate change in the appearance of the skin lesions such as is produced by cortisone and ACTH. However, since itching is one of the most troublesome symptoms of atopic dermatitis and a considerable part of the objective change in the skin results from scratching and secondary infection, control of the itching constitutes an important part of treatment. For this purpose, the antihistaminics are among the most effective systemic medications. When the itching is severe, the drugs having a pronounced sedative effect such as Benadryl and Decapryn are most effective. In addition to oral preparations, many of the drugs are supplied in ointments, creams and lotions for local applications. Such preparations are reasonably effective in the control of itching, either through local anesthetic or antihistaminic actions.

Contact dermatitis, in contrast to atopic dermatitis, is a delayed form of allergic reaction in the pathogenesis of which histamine has not been shown to play a part. However, empirical trial of the antihistaminics, both as oral medications and topical applications, has been found to afford some relief of itching but not to alter the appearance or direction of the lesions. Indeed the antipruritic effect of these drugs is by no means limited to the allergic dermatoses. Itching due to such varied causes as chicken pox, jaundice and Hodgkin's disease may be alleviated to some degree by the local or general use of antihistaminics. Here again, these drugs may be exerting an anesthetic action on the nerve endings and one need not assume that histamine is being an-

tagonized. In pruritus ani and vulvae, moderate relief comparable to that afforded by local anesthetics of the procaine group may be attained.

Trials of antihistaminic drugs in cases of gastrointestinal allergy have given some favorable results but experience in this field is limited. In evaluating the results one must remember that many of these drugs have sedative and anti-cholinergic as well as specific antihistaminic effects.

In the type of headaches classed as histamine cephalalgia, the results are on the whole disappointing. Satisfactory control is rarely obtained with the antihistaminics. Such failures cast some doubt on the diagnosis but it may be recalled that not all known effects of histamine, such as that on the gastric secretion, are prevented by these drugs. Also in migraine attributed to food allergy, the results are generally disappointing.

As in contact dermatitis, the antihistaminic drugs have been applied empirically or illogically to other forms of hypersensitivity in which histamine has not been shown to play a part. For example, these drugs have been administered to patients with pulmonary tuberculosis in an attempt to eliminate the factor of tuberculin sensitization from the pathogenesis of the disease. The clinical results of such therapy are not convincing and most careful studies have shown that the readily observed manifestation of the sensitization, namely the cutaneous reaction to the tuberculin test, is not inhibited by the antihistaminics.

The results obtained in allergic reactions to drugs are variable as are the mechanisms of these reactions. In general, urticarial reactions in which histamine is presumably a factor, are benefited while other manifestations of drug sensitization such as drug fever, dermatitis medicamentosa and leukopenia, are not. Histamine-like reactions to injections of Diodrast are not prevented by prophylactic use of antihistaminics. Bronchospastic reactions to curare, believed to result from release of histamine, are benefited.¹¹

In view of the similarity of symptoms of the common cold and allergic rhinitis, it is not surprising that the effects of antihistaminics on virus rhinitis were soon tested. In 1945 Troescher-Elam, Ancona and Kerr¹² reported the presence of a histamine-like substance in the nasal secretions of patients with common colds. This study has not been confirmed, but in 1949 Fox and Livingston,¹³ without conclusive evidence, expressed the opinion that allergy to the cold virus played a prominent

part in the pathogenesis of the cold.

Actual use of Benadryl in the treatment of the common cold with apparently brilliant results was reported by Brewster in 1947 in the U.S. Navy Medical Bulletin.¹⁴ This and four subsequent reports by the same author stressed the point that the use of Benadryl during the first few hours after the onset of a cold brought about recovery within twenty-four hours in a large proportion of colds. Murray¹⁵ and also Gordon¹⁶ published similar reports and a more carefully controlled study by Arminio and Sweet¹⁷ indicated that the antihistaminics were effective in the prevention and cure of colds. These reports were analyzed by the Council on Pharmacy¹⁸ and criticized on the grounds of the diagnostic criteria, failure to exclude allergic rhinitis adequately, lack of suitable control groups in most cases, and the methods of compiling statistics. The Council suggested that inoculation of volunteers with a potent strain of cold virus would offer the best basis for a controlled trial.

Such an experimental inoculation study was undertaken by Feller and associates¹⁹ while other groups started carefully controlled observations on natural colds in large groups of individuals. Before the results were obtained, the matter became one of public controversy as well as scientific inquiry. The claims of Brewster were presented to the public in a sensational and uncritical article in the Reader's Digest²⁰ as the long-awaited preventative and cure of the common cold. At about the same time, the Federal Food and Drug Administration permitted the sale of certain antihistaminics without prescriptions and the manufacturers were quick to exploit their use for common colds in spectacular advertising, much of which claimed or implied the approval of not only the Reader's Digest but also the Navy Medical Department and the Food and Drug Administration. In March of 1950 the Federal Trade Commission entered complaints against five of the largest manufacturers of antihistaminic drugs for over-the-counter sales, charging misrepresentation of the efficacy of these compounds in the prevention and cure of the common cold. With millions of dollars of sales at stake and the public having been promised an effective cure of the common cold, the controversy aroused great interest in the press but was settled within a few months with the manufacturers agreeing to advertise that the antihistaminics relieve the symptoms of colds rather than being effective cures.

During the past six months many reports of carefully controlled studies have shown that the antihistaminics have little or no value in preventing or curing the common cold. Experimental inoculations of volunteers with cold virus by Feller and associates¹⁹ showed that these drugs had no effect in prevention of colds. Shaw and Wightman²¹ at Cornell, Cowan and Diehl²² at the University of Minnesota, Hoagland²³ at West Point and a group of workers in the Navy²⁴ all presented careful reports of the treatment of large series of patients with colds with comparable groups receiving antihistaminic drugs and placebos as controls. In every case the results in the antihistamine-treated and control groups were essentially the same. It was a striking find that in every instance the patients given inert placebos reported considerable benefits. Cowan and Diehl reported that one student who returned to the university after graduation specifically to obtain some more of the medication was found to belong to the control group.

The consensus of medical evidence supports the opinion that the antihistaminic drugs are not effective in the prevention or cure of the common cold. The person who takes a pill after the first sneeze or sniffle cannot be sure that he is suffering from a cold infection rather than the effects of a chill, draft or minor allergy and so is not helpful as a part of a scientific experiment. Some of the early symptoms of a cold such as sneezing and rhinorrhea are in many cases relieved partially or completely by the antihistaminics, as they are by atropine, but the progress of the infection is not stopped. Patients with chronic allergic rhinitis and superimposed acute colds may enjoy greater benefit, both directly from relief of the allergic component and indirectly from the fact that the resistance of the mucosa to infection is greater when it is not coincidentally involved with an allergic reaction.

Aside from their use in the common cold, antihistaminic drugs have been found to have unforeseen uses in certain diseases unrelated to allergy. Dramamine, a derivative of Benadryl, attracted such attention as a remedy for motion sickness that its use as an antihistaminic has been neglected. Subsequent studies have shown that Benadryl itself is equally effective in the relief of motion sickness and that Neoantergan is also beneficial. Dramamine has also been used but with less definite results in Ménière's disease and in nausea and vomiting due to pregnancy and many other causes. Benadryl has been found beneficial in the relief of Parkinson's disease and several of the other antihistaminics have been

shown to have palliative effects comparable to other available drugs.

Isolated reports have described various antihistaminics as being of value in dysmenorrhea, irradiation sickness, ulcerative stomatitis, bee stings and snake bite. In most of these cases the evidence presented is scanty and confirmation lacking as yet.

Untoward Effects: As previously mentioned, no drug yet developed is purely antihistaminic in its activity; all show other pharmacologic actions which are undesirable side effects. The best known of these is the sedative effect produced in 10 to 60 per cent of patients by ordinary doses. This effect is most marked with drugs of the aminoethanol group such as Benadryl and Decapryn, less marked with Thephorin and Neohetramine. The undesirability of this action must be weighed against the severity of the symptoms for which the drug is given. Not infrequently the patient may consider the treatment worse than the disease. It is particularly important since many of the conditions for which antihistaminics are used are not disabling and the patient remains ambulatory and employed during treatment. Thus drowsiness may lead to serious errors of judgment in business or failure of performance in operating automobiles and other machines. On the other hand, in patients confined to bed with intolerable itching, mild sedation may be helpful.

With gross overdosage, the usual mental effect is confusion and excitement rather than somnolence. In severe cases this may result in an acute toxic psychosis with hallucinations and delusions. Several fatalities have been reported in children.

In idiopathic epilepsy and seizures due to focal lesions of the cerebral cortex, Benadryl and Pyribenzamine have been shown to increase the frequency of seizures.²⁵ In the absence of specific data on the other drugs of the group, it is apparent that all antihistaminics should be used with caution, if at all, in patients with convulsive seizures.

Since many of the antihistaminics have a mild atropine-like effect, some patients will complain of dryness of the mouth and throat. Gastrointestinal irritation, manifested by nausea, vomiting, diarrhea or abdominal cramps, is not uncommon when large doses are given between or before meals. In many cases, this may be avoided by administration after meals, in others a different drug of the group may be substituted.

Prolonged administration of large doses of antihistaminics of the ethylenediamine group has occasionally resulted in leukopenia or agranu-

locytosis. A half-dozen such cases have been reported, most of which have followed the use of Pyribenzamine. However, since this is one of the oldest and most widely used drugs of the group, it would appear that the predominance may be due simply to more extensive use. While the danger of this type of reaction does not appear to be great, prolonged use of full doses should be avoided if possible, and if the need persists, the blood should be examined periodically.

Drug rashes from the oral use of antihistaminics have been reported but are rare. On the other hand, contact dermatitis from local application of these drugs to the skin is relatively common if use is continued for more than one or two weeks. With most topical antihistaminic preparations an incidence of sensitization of 2 to 5 per cent may be expected.

SUMMARY

The available antihistaminic drugs are all essentially similar in their action and side effects although varying both in potency and toxicity. No one drug may be said to be the best. These drugs are of value for symptomatic relief in allergic rhinitis, urticaria and serum sickness and for the control of itching. In no disease do they have a curative effect. In asthma, their efficacy is less than that of older drugs. In the treatment of the common colds they do not alter the course of the infection but may afford some symptomatic relief. The commoner side effects are drowsiness and nausea. Long continued use occasionally leads to leukopenia or agranulocytosis. Contact dermatitis not infrequently results from their topical use. On the whole, these drugs represent a definite contribution to therapy but there is still room for newer compounds with greater potency and less toxic effects. In most of the allergic diseases, their efficacy is surpassed by that of cortisone and ACTH.

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