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 Martin[2] 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 Laidlaw[3] 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

* Read at The New York Academy of Medicine, November 3, 1950 in the 25th Series of Friday Afternoon Lectures.

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 Bovet[4] 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 Staub[5] 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 Halpern[6] 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.

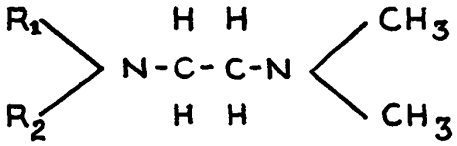

Fig. 1: Ethylene diamine structure. Antergan, Neoantergan, Pyribenzamine, Histadyl (Thenylene), chlorothen (Tagathen), Diatrin, Neohetramine and Thenfadil are represented by this formula with variations in the radicals R_1 and R_2.

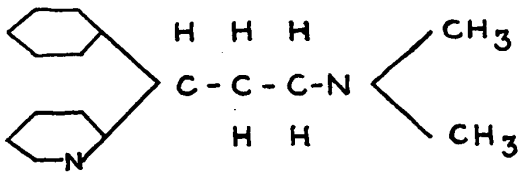

Fig. 2: Aminopropane structure. (Trimeton)

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).

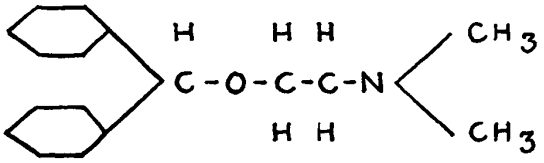

Fig. 3: Ethanolamine structure. (Benadryl)

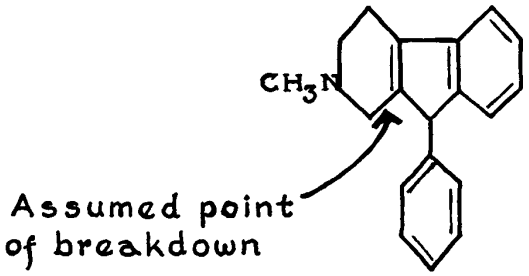

Fig. 4: Thephorin.

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 Bovet[8] 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 Code[9] 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,

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