REVIEW ARTICLE

THE ANTIHISTAMINE DRUGS

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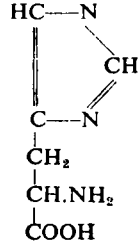
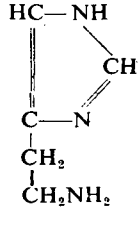
Histamine is a base formed from the amino-acid histidine by the removal of the carboxyl group from the latter substance, which change can be brought about by some bacteria or by prolonged heating with acids. It is present in most cells in the body, but it only becomes



Histidine



Histamine

active when liberated from the cell by trauma or in some other way. It is normally present in large quantities in the intestine from which it is absorbed to some extent, and is destroyed by the enzyme histaminase which is present in particularly high concentration in the intestinal mucosa.

The pharmacological actions of histamine vary according to the experimental animal into which it is injected. Contraction of plain muscle occurs which may be followed by an inhibitory phase. This constricting effect has a striking species specificity. It is mainly to be observed in the bronchioles of the guinea-pig, the muscular tissue round the hepatic veins of the dog and in the pulmonary arteries of the rabbit. Capillary dilatation also takes place, causing a fall in blood pressure and shock, which is particularly obvious in the cat. This action can be demonstrated on the human skin by scratching it through a drop of histamine solution or by liberating histamine from the cells by moderate trauma as may be caused by drawing a blunt pointed instrument firmly across the skin. The characteristic triple response may then be seen: redness, due to dilated capillaries; a weal, due to exudation of plasma from the capillaries under the epidermis; a flare, due to an axon reflex. A higher concentration of histamine will cause itching in addition to the weal formation. Lastly, histamine is a strong stimulant of gastric secretion. This action is used as a clinical test of gastric function and is not antagonised by atropine.

Chemical methods of detecting histamine and of estimating it quantitatively are extremely laborious and difficult, and most of our know-

ledge of its behaviour in the body is based on biological assays, chiefly on isolated plain muscle. Human blood contains only a minute amount of histamine, most of which is present in the granulocyte cells. Attempts to estimate the release of histamine by following its concentration in the general circulation are likely to fail, since any histamine released into the blood will be absorbed before reaching the veins after circulating once round the body. Indeed, sufficient quantities of histamine can be injected intravenously in man to cause marked symptoms, without effecting any detectable increase in its concentration in the venous blood.

Anaphylaxis and Immunity

Anaphylaxis and immunity are probably two stages of the same reaction, since anaphylaxis can only be produced by proteins (antigens) which cause the production of antibodies. It is true that anaphylaxis may occasionally be caused by substances of low molecular weight, such as drugs, which have in themselves no antigenic activity. Landsteiner, however, has demonstrated that drugs can be converted into antigens by being attached to proteins. Like immunity, anaphylaxis is extremely specific. Thus a guinea-pig, sensitised to albumen from a hen's egg, will not respond with an anaphylactic reaction to albumen from a duck's egg.

If an antigen is injected into an animal and its serum is tested at intervals, it is found that the resulting antibodies are present in the blood for some days, during which time the animal is immune to the antigen, and the animal's blood will precipitate it *in vitro*. After a week or two, however, the antibodies are absorbed by the tissue cells. If a fairly large dose of the same antigen is now injected intravenously the serum is found to have lost its power to precipitate the antigen, which now combines with the antibodies inside the tissue cells and an anaphylactic shock results.

That anaphylaxis is due to some reaction in the tissues can be shown by the fact that it can be produced by adding antigen to the isolated plain muscle of an animal sensitised to it. Such a sensitised tissue will only react once to its specific antigen and thereafter becomes insensitive to it, owing to the precipitation of the antibodies which the tissue contains. In this way an animal surviving an anaphylactic shock may become desensitised, and therapeutic desensitisation consists in giving small, repeated doses of the antigen, insufficient to cause anaphylaxis, but sufficient to cause ultimate desensitisation. Apart from intensive desensitisation, which is a highly specialised and rather dangerous clinical technique, ordinary therapeutic desensitisation is a prolonged and laborious procedure, which, even if the correct antigen is found, is by no means invariably successful. The facile methods of desensitisation, so often employed clinically, of giving a few injections, say, of a mixed pollen vaccine a few weeks before the hay-fever season is a concession to psyche rather than a serious tribute to soma.

Fortunately true anaphylaxis is uncommon in man, if reasonable care

is exercised in the administration of serums, but allergy, which probably depends on a similar mechanism, is common. It shows itself in the form of skin rashes—particularly urticaria and angioneurotic œdema—hay fever, paroxysmal rhinorrhœa, drug fever, gastro-intestinal disturbances and many other clinical phenomena.

Histamine as a Cause of Anaphylaxis

There is little doubt that anaphylaxis is due to the damage produced by the combination of antigen with antibody inside the cells of the body. Some of the resulting symptoms may be directly due to the damage itself, but most are due to the release of toxic substances from the damaged tissues. In 1910 Dale and Laidlaw first pointed out that the symptoms of anaphylactic shock closely resembled those produced by an injection of histamine, even to the extent of exactly stimulating the varying manifestations resulting from an injection of histamine in different animals. Thus anaphylaxis in the guinea-pig causes death from bronchial spasm, in the dog from a fall in blood pressure consequent on arrest of blood in the liver, and in the rabbit from heart failure due to inability of the right ventricle to force blood through the constricted pulmonary arteries—all the same effects as are produced by histamine in these animals respectively. There is also much experimental evidence in animals to show that histamine is actually released during anaphylaxis. There is, for instance, during anaphylaxis a fall in the histamine content of the lungs of guinea-pigs and the livers of dogs, and a rise in the histamine content of the perfusate of sensitised guinea-pigs' lungs and dogs' livers when antigen is added. Much work has been done by such methods, and there is now no doubt that histamine plays a part in the manifestations of anaphylaxis in animals. There is no reason to suppose that man differs from the brute in this respect, though the evidence is not so conclusive, owing to the difficulty and danger of the experimental study of anaphylaxis in the human subject.

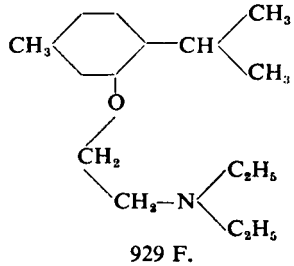
Histamine, though the most important, is not the only toxic substance released in anaphylaxis. There is, for example, an increase in the clotting time of the blood due to the release of heparin, and another substance is also produced, known as "the slow reacting substance" because of its slow action on plain muscle. The phenomenon of anaphylaxis is, therefore, a more complex one than can be accounted for by the simple release of histamine; damage to tissue, heparin, "the slow reacting substance" and possibly other products play a subsidiary role, but there is overwhelming evidence to suggest that a release of histamine is the dominating factor.

Antihistamines

Ever since it was established that histamine was intimately concerned in the production of anaphylaxis and allergy many attempts have been made to find a drug or form of treatment which would counteract these states. In recent years efforts have been made to desensitise patients to histamine by means of histamine injections, histaminase and histamine

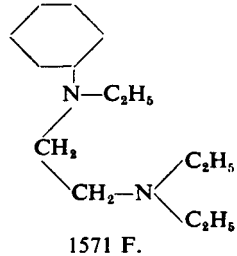
azoprotein. There may still be a future for work along these lines, but up to the present the benefits of such treatment have not been striking and no-one who has had considerable experience of the use of histamine azoprotein, which may produce some clinical benefit, can think it is the philosopher's therapeutic stone in dealing with allergic disorders.

From 1933 onwards French workers had been systematically searching for synthetic antihistamine drugs, and between 1937 and 1939 certain active compounds were actually discovered which would protect guinea-pigs against anaphylactic shock and lethal doses of histamine, but which were, however, too toxic for human use. The first of these substances, thymoxy-ethyl-diethylamine was discovered by Staub and Bovet and



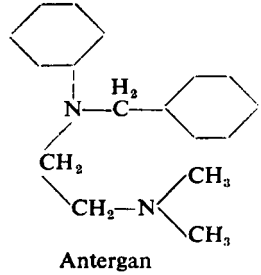
929 F.

labelled 929F. in their series, and the second discovered by Staub was another Fourneau compound containing an ethylenediamine radical labelled 1571F.



1571 F.

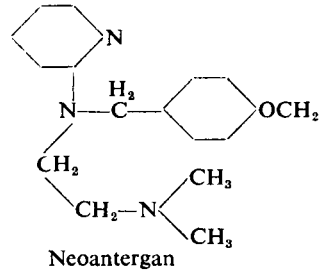
In 1942 antergan (2339 R.P.)—a phenyl-benzyl-dimethyl-ethylene-diamine compound—was introduced by Halpern, and soon the results of



Antergan

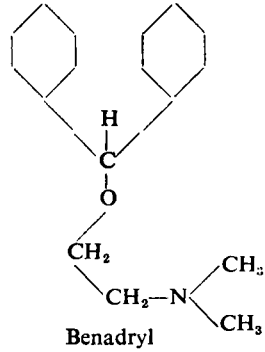
its experimental and clinical trial began to appear in the French literature. Such was the chaotic state of Europe at that time, however, that Hal-

pern's discoveries did not become generally known till after the liberation of France, by which time neoantergan (2786 R.P.) had also been introduced.



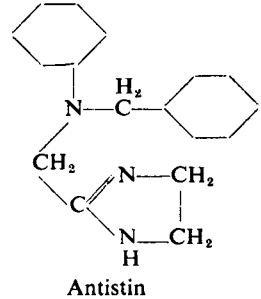
Neoantergan

It differed from antergan in the replacement of a benzene by a pyridine group and the addition of a methoxy group to the benzene ring, and was a more potent, specific and less toxic antihistamine. In 1945 pyribenzamine and benadryl were introduced in America, in which country both drugs began to be widely used therapeutically, though for some time benadryl was the only antihistamine to be generally employed in



Benadryl

Britain. Pyribenzamine differs from neoantergan in the absence of a methoxy group on the benzene ring, and benadryl is dimethylaminoethylbenzhydryl ether hydrochloride.



Antistin

In attempts to produce more potent and less toxic antihistamine drugs new derivatives of these compounds have been studied recently. Antistin is closely related to antergan, but the dimethylamino linkage is replaced

by an imidazole ring, while hetramine is the pyrimidine analogue of pyribenzamine. Two further compounds—α-naphthyl-methylethyl-β-chlorethylamine and β-2-biphenyloxyethyl-β-chlorethylamine are halogen derivatives of neoantergan. They are of interest because they antagonise the action of adrenaline, whereas all the earlier antihistamines, with the exception of the original one, 929F., potentiate the action of adrenaline. The search for more potent and less toxic antihistamines continues, and it may well be that we have as yet only touched the fringe of new developments.

Potency. The potency of antihistamine substances has been tested in a number of ways. The lethal dose of histamine injected intravenously is determined for a group of guinea-pigs, which usually varies from 0·4 to 0·8 mg./kg. of body weight. The antihistamine to be tested is then injected subcutaneously and increasing doses of histamine are thereafter given to determine the maximum dose which the animal survives, and therefore the protective effect of the antihistamine. The second test is designed to discover the protective action of the antihistamine against the lethal effect of histamine inhaled by a guinea-pig. The third test determines the power of the antihistamine to prevent the action of histamine in causing contraction of the guinea-pig's isolated intestine. The fourth test determines its effect in preventing the depressor action of histamine on a dog's blood pressure, and the fifth test measures its power to abolish or diminish the size of the weal caused by an intradermal injection of histamine.

The relative antihistamine activity of the drugs which have been commonly employed in clinical practice has been tested by these animal experiments. Using such tests it was found that benadryl and the old-fashioned French preparation, antergan, were less effective than pyribenzamine, and all of them very much less effective than neoantergan The relative clinical effectiveness of the various drugs is, however, not nearly so divergent in human beings as the experiments on laboratory animals would have led us to expect, though it does seem that neoantergan is at present the most potent and specific antihistamine which we possess.

Mode of Action. A knowledge of the mode of action of this group of drugs is necessary if they are to be used efficiently. It is apparent that they might act in a number of ways: they might prevent the release of histamine from the tissues; they might abolish its action by entering into some inert chemical combination with it; they might set up a directly antagonistic pharmacological action; or they might block the action of histamine by competing with it successfully for the tissue receptors. If they acted by preventing the formation of histamine they would have no effect on the production of the typical skin weal when histamine is injected subcutaneously, but they do have a striking effect in this respect. Further they would prevent the stimulating action of histamine on the gastric secretion, which, as we shall see, does not occur. There is no evidence whatever that they destroy histamine or render it inactive by

entering into chemical combination with it. The only type of pharmacological antagonistic action to histamine which is at all likely would be the potentiation of adrenaline, but as some potent antihistamines antagonise rather than potentiate adrenaline it is impossible to believe that there can be any relationship between the sympathomimetic and antihistamine properties of the others. Thus, by a process of *reductio ad absurdum* we come to the conclusion that antihistamines act by blocking the action of histamine by combining with its tissue receptors.

If this theory is correct it is apparent that the underlying allergic or anaphylactic tendency persists in spite of the use of antihistamines since the abnormal production of histamine is not interfered with, and, therefore, the administration of the antihistamine in clinical practice has to be continued either indefinitely in a few cases or at least till the allergic or anaphylactic tendency has subsided spontaneously, or as the result of artificial or natural desensitisation. It is thus important to realise that the use of these drugs does not absolve the physician from considering the advisability of specific desensitisation in certain cases, though such desensitisation may be frequently impossible, undesirable or unnecessary.

Other Effects. Few drugs have only one property. Most of them produce—perhaps to a lesser degree—effects additional to that for which they are principally prescribed in therapeutics. Antihistamines are no exception to this rule, for, besides abolishing the effects of histamine, they have many other actions, some of which are inconvenient when they are used in clinical practice. In addition to their antihistamine activity, they have to a varying extent anti-acetylcholine, local anæsthetic and sympathomimetic or sympatholytic properties. Antispasmodic, analgesic, and quinidine-like actions have also been demonstrated by some members of this group. Benadryl has, even in therapeutic doses, a pronounced atropine-like action, causing dryness of the mouth and some dilatation of the pupil, an analgesic action causing drowsiness and some slight spasmolytic effect. These properties are shared, but to a less extent, by neoantergan and pyribenzamine. As we have seen, however, some of the newer antihistamines and 929F. are sympatholytic drugs. Antihistamines are local anæsthetics. Neoantergan, benadryl and antistin, for instance, are 3·3, 2·5 and 1·5 times as potent as procaine. When taken by the mouth, however, they do not produce a demonstrable local anæsthetic effect on the skin. Their power as antihistamines has nothing to do with their local anæsthetic effect, since the latter wears off in about an hour's time, whereas their antihistamine action lasts for at least four hours. Neoantergan has been found to be twice as powerful as quinidine on the auricle of the rabbit, but this effect has not been demonstrated in the human subject. Thus, as Burn has pointed out, antihistamines "join the group of other substances which include spasmolytics like trasentin and syntropan, analgesics like pethidine and papaverine, local anæsthetics like procaine, and atropine-like substances. None of these can be sharply distinguished from one another. Probably each possesses

every property in some degree." The common properties of all these drugs suggest that their site of action must be a similar one.

Dosage and Administration. Antihistamine drugs are usually given by the mouth in tablets or capsules. Benadryl and pyribenzamine are prescribed in doses of 50 to 100 mg., with a maximum daily dose in the case of benadryl of 400 mg. and in the case of pyribenzamine of 600 mg. Neoantergan and antistin, being less toxic, can be given in bigger doses of 100 to 200 mg. with a maximum daily dose of 800 mg. Children tolerate the drugs well, and over the age of twelve can be given the adult dose, with appropriately smaller doses under that age. The drugs are quickly absorbed and fairly quickly excreted in the urine. The effect of a single dose does not last for more than six hours, so that in order to maintain a satisfactory concentration, dosage should be well spaced, the drug being given at least three times a day. In severe cases four doses should be administered—the last one as late as possible at night so as to "cover" the hours of sleep. The tablets or cachets should be swallowed whole and not chewed as they have an unpleasant taste, and if brought in contact with the mucous membrane of the mouth or pharynx will have a marked local anæsthetic effect. Neoantergan and antistin are not spasmolytics like benadryl, and their use may, indeed, produce increased motility of the alimentary tract in experimental animals. In consequence they may occasionally cause nausea if given on an empty stomach, and should, therefore, be taken after food. Tolerance to antihistamines does not seem to take place.

Benadryl is procurable in a purified solution containing 10 mg. of the drug per ml. for intravenous use and its administration in this way has been recommended for anaphylactic emergencies, but otherwise the parenteral use of antihistamines is unnecessary and may, indeed, cause on occasion rather alarming symptoms of collapse. As might be expected from the mode of action of antihistamines, no effect, apart from diminishing skin irritation, is produced on established lesions, which will subside spontaneously, though new lesions are prevented from occurring. Thus antihistamines, even if given intravenously, will have little effect on an established allergic emergency such as swelling of the tongue or œdema glottidis, for which adrenaline is the drug of choice.

Antihistamines may be used in a suitable base for local application in some of the itching dermatoses, and may be applied locally to the nose in cases of allergic rhinorrhœa. For this latter purpose antistin is the most suitable preparation.

Side Effects.—No deaths or toxic effects leading to organic change have occurred as the result of the administration of antihistamines, even though they have been administered to some patients for years. Side effects are, however, very common, and in about 5 per cent. of cases may be sufficiently distressing to necessitate discontinuing their use. A full dose of benadryl or antistin will cause effects in about 50 per cent. of cases. Pyribenzamine and neoantergan are less toxic, but cause side

effects in about 30 per cent. of cases. The practical superiority of neoantergan, and to a less extent pyribenzamine, over benadryl lies in the fact that they are not only more active antihistamines milligramme for milligramme, but can be tolerated in larger doses and may thus benefit some patients for whom the necessarily smaller dose of benadryl had proved ineffective. The great majority of the side effects of antihistamines only occur when the drugs are first administered and tend to wear off in a few days.

The principal side effect of all antihistamines, but particularly benadryl, is sleepiness, fatigue or dizziness. In some patients on first taking the drug this hypnotic effect may be very marked indeed, and may in a few cases persist even after they have been taking the drug for a long time. Patients should be warned about this effect before they are given antihistamines, and, until their reaction to the drug in this respect has been ascertained, should not take their first few doses before undertaking work requiring skilled judgment. It is wise also to start treatment with a small daily dose and gradually to increase it till the optimum effect has been obtained, as in this way the patient usually becomes quickly tolerant to any hypnotic effect which may be present. Alternatively, 5 mg. of amphetamine may be administered coincidently in the morning and at mid-day for the first few days of treatment till the hypnotic effect of the antihistamine wears off. Owing to the fact that antihistamines often produce soporific effects when they are first taken, the coincident use of hypnotics and sedatives should be prescribed with care. On the other hand, a curious sensation of tension, nervousness and unreality is occasionally produced by antihistamines, and these sensations may lead to insomnia rather than to sleepiness.

As benadryl has a strong atropine-like action, it is not surprising that patients frequently complain of dryness of the mouth as the result of its use. Pyribenzamine, neoantergan and antistin may also produce this side effect, but less commonly and to a less extent. Atropine and its congeners should not, therefore, be prescribed along with these drugs, though there is no contra-indication to the coincident use of sympathomimetic preparations.

Other side effects have occasionally been noted as the result of the therapeutic use of antihistamines, but they are rare and unimportant.

Therapeutic Uses. It might be anticipated that drugs which antagonise histamine would have a wide range of therapeutic application. Their value in treatment, however, is actually somewhat limited to allergic conditions characterised by vascular reactions in the skin and mucous membranes resembling the effects produced by the local application of histamine. Thus they may be claimed almost as specifics in cases of acute and chronic urticaria or angioneurotic œdema, and in many of the urticarias encountered when a patient becomes sensitive to drugs such as penicillin, liver extract and insulin. The itching of pruritus

vulvæ and ani is often greatly ameliorated by the use of antihistamines, while they either cure or very much alleviate some 75 per cent. of cases of hay fever and a somewhat smaller proportion of cases of perennial vasomotor rhinitis.

The administration of histamine does not cause bronchospasm in healthy persons, but it has this effect in asthmatic subjects, just as it has in guinea-pigs, and this artificially produced bronchospasm can be prevented by antihistamine drugs. These observations do not *prove* that naturally occurring asthma is due to a simple release of histamine or that it can be prevented by antihistamine drugs, but they encouraged the hope that such drugs might be of some value in the prevention and treatment of the condition. The results of their clinical trial in asthma are, however, extremely conflicting, and much of the work claiming antihistamines to be of value in the disorder is based on poorly controlled evidence. It is at any rate certain that the benefits to be derived from the use of antihistamines in asthma, if they exist, are in no way comparable to their value in the allergic reactions in the skin and mucous membranes mentioned above.

It is almost certain that histamine is the natural stimulant of gastric secretion. It might be expected, therefore, that antihistamine drugs would be of value in the treatment of hyperchlorhydric dyspepsia and peptic ulcer. All clinical and experimental evidence unfortunately goes to show that they are of no practical use in these conditions and have no significant effect in modifying gastric secretion. The drugs have also been tried in a great variety of other allergic states with negative results.

In summary, then, antihistamine drugs are of great value in superficial allergies, in the treatment and prevention of which they constitute a major therapeutic advance, but they are of little or no value in the treatment of the more deep-seated visceral allergies in the human subject. It may be that histamine does not play a part, or a predominant part, in the production of some of these visceral disorders and that this may account for the failure of antihistamines to influence their course favourably. We do know, however, that histamine does stimulate gastric secretion, and that in spite of this antihistamine drugs have no influence on this action of histamine. It may be, therefore, that in some visceral allergies histamine is released in such intimate contact with the effector cell that antihistamines are impotent to block its action.