HISTAMINE AND ANTIHISTAMINE SUBSTANCES

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Action of Histamine in the Body

There are three substances to be found in the body which have an action on the cardiovascular system ; the first of these is adrenaline, the second is acetylcholine, and the third is histamine. It is known that adrenaline is liberated from the suprarenal gland and also at the sympathetic nerve endings. It is known that acetylcholine is liberated at the endings of the vagus nerve and of other nerves belonging to the parasympathetic system. What the precise function of histamine is in the body we do not yet know, but it is present in most tissues and in the blood, and there is an enzyme in many organs which can destroy it. Histamine, moreover, can be infused into a vein at a steady rate for a long time without ill effect, provided that the concentration does not exceed a certain limit. Histamine, then, bears all the signs of being a substance with an important physiological function, like the other two substances, but we are still ignorant of what this is. With the exception of the action on the gastric glands, the known actions of histamine are actions exerted by the sudden introduction of a relatively large concentration into the tissues. When injected into a vein, it causes a fall in blood pressure which is largely due to an action on capillaries ; these become widely dilated and their permeability to fluid is increased ; there is also some dilator action on the arteries. None of the fall is cardiac in origin, for histamine stimulates the heart. When a drop of histamine solution is placed on the forearm and the skin is pricked beneath it there is a red flush due to dilated capillaries and later a weal due to leakage of fluid out of them. The weal is a typical urticarial weal. The other action of histamine has often been summarized as being to cause contraction of smooth muscle, and indeed perhaps the most striking effect of histamine in man is to cause constriction of the bronchioles with resulting dyspnoea. It is true also that histamine causes increased intestinal movement, but in the coronary vessels, so far from causing constriction, it causes

dilatation, and its effect on the uterus of the rat and mouse is inhibitory.

Allergic Manifestations

The work of Dale showed that the effects of anaphylactic shock are due to the release of histamine. If a guinea-pig receives an injection of egg albumin, during the next three or four weeks it becomes sensitized, and if then a second injection of egg albumin is given, death follows from anaphylactic shock due to constriction of the bronchioles. If histamine is injected into the guinea-pig, death follows from constriction of the bronchioles. In the dog, on the other hand, anaphylactic shock causes death as a result of the accumulation of blood in the liver due to closure of the collecting venules of the hepatic veins. The injection of histamine in the dog causes death in the same way. In the rabbit, again, both anaphylaxis or the injection of histamine cause death due to constriction of the pulmonary artery so that the animal dies with right-sided heart failure. These similarities led to the view which is now generally accepted that in anaphylaxis there is a union of antigen and antibody within the cells of the sensitized animal which liberates histamine in the blood, so that histamine is responsible for death.

Since the work of Landsteiner, not only anaphylaxis, however, but allergic manifestations in general are thought to be due to the liberation of histamine. Whether the allergy is due to eating some food to which the person is sensitive, or whether it is due to a drug like quinine or aspirin, to which some persons are sensitive, or whether it is merely a skin rash caused by sulphonamides or thiouracil or phenolphthalein in patients who have had these substances administered for too long a time, or who are particularly sensitive to their effects, the signs and symptoms in all cases seem to be due to the release of histamine. Conditions like hay-fever and urticaria must be regarded as essentially similar, that is to say to be produced as a result of the absorption of some substance which after entering the body comes to act as an antigen

and liberates histamine when it combines with antibody in the cells of the tissues.

Antihistamine Substances

It is clear that if histamine is responsible for allergic manifestations, a substance which neutralizes the action of histamine should be of value in treating them. There is now a class of antihistamine substances. Because the first of these to become widely known in this country was benadryl, it is sometimes supposed that the development of antihistamine substances took place in the United States. The credit in fact belongs to French workers, especially to Bovet and his colleagues, who have continued the successful chemotherapeutic work of Fournieu at the Institut Pasteur. It will be remembered, for example, that Bovet, together with the Tréfouëls and Nitti, was responsible for introducing sulphanimide. In 1937, Ungar, Parrott and Bovet were preparing and examining new substances for sympatholytic action, that is to say for their ability to paralyse sympathetic impulses; such substances might be useful in treating hypertension. In the course of this investigation they tested the new compounds to see how active they were in diminishing the action of histamine on the guinea-pig intestine, and discovered that the power to antagonize histamine was in no way related to the power to antagonize adrenaline. Certain substances with no power to paralyse adrenaline were extremely powerful against histamine.

The antihistamine substances now available (see Fig. 1) are neoantergan, which was made in France, antistin, made in Switzerland, and benadryl and pyribenzamine, made in the United States. Neoantergan is to be sold in this country under the name anthisan. The first of these compounds to be introduced was neoantergan, the properties of which were described by Bovet and Walthert in 1944. In 1945, Loew, Kaiser and Moore introduced benadryl in the United States. Also in 1945, Mayer and others introduced pyribenzamine, which differs from neoantergan in lacking only a $-\text{OCH}_3$ group, and which is inferior to neoantergan in potency. It is thus no new discovery and is probably a substance discarded as less efficient by the French workers. Finally, in 1946, Meier and Bucher described the properties of antistin, which has a structural formula containing a ring similar to histamine. Antistin is the one compound which thus has a logical chemical basis, for the imidazol ring probably ensures that antistin combines with the histamine receptors and so prevents histamine molecules from exerting their effect.

Neoantergan (Anthisan)

Pyribenzamine

Benadryl

Antistin

Privine

Histamine

FIG. 1.

By laboratory tests the substance which is easily the most potent is the first, neoantergan. For example, Friedlaender, Feinberg and Feinberg (1947) compared benadryl, pyribenzamine and neoantergan. They determined the amount of histamine base necessary to kill all guinea-pigs receiving a fixed dose of each substance given intraperitoneally 15 minutes before histamine was injected intravenously. The animals received 3 mg. per kg. of the substance being compared. Controls were killed by 0.4 mg. per kg. histamine. Animals protected by benadryl were killed by 2.0 mg. per

kg. histamine ; this is a five-fold protection. Those protected by pyribenzamine were killed by 15.0 mg. per kg. histamine ; this is almost 40-fold protection. Those given neoantergan were only killed by 50 mg. per kg. histamine, which is 125-fold protection.

A direct test of antistin with neoantergan by this method has not hitherto been published, but Schild (1947) has described a method of comparing antihistamine substances on the isolated ileum of the guinea-pig. By this method it appears that the potency of antistin is less than $1/10$ that of neoantergan, the actual figure depending on the time of contact of the compound with the ileum. For longer periods of contact the potency of antistin is much less than $1/10$ that of neoantergan.

The question has been raised whether the figures for relative potency of these substances obtained in the laboratory can be applied to patients, for if so, neoantergan is clearly the best to use, and benadryl is the weakest. It is dangerous to be dogmatic on this subject, and it is better to admit the possibility that the animal figures may not be applicable. A quantitative comparison is, however, almost impossible in patients unless the same group of patients is used over a long period of time for testing the effect of the different drugs. Unless this has been done it is surely dangerous to doubt the quantitative relations which can easily be established on animals.

The Testing of Antihistamine Compounds

Bovet and Walthert (1944) test antihistamine substances in the following ways. First they determine whether the substances protect guinea-pigs against the lethal effect of histamine given intravenously. In normal guinea-pigs the lethal dose of histamine injected into the jugular vein varies from 0.4 to 0.8 mg./kg. They determine the actual dose in some of the animals they are using. They inject the substances they are testing under the skin. Then they give increasing doses of histamine intravenously to discover the maximum dose which the animal survives. For example, after the injection of neoantergan (anthisan) in a dose of 1 mg./kg., guinea-pigs have survived the injection of 60 mg./kg. histamine, that is to say, about 75 times the normal lethal dose.

The second test is to discover whether the substance protects the guinea-pig against the lethal effect of histamine sprayed into the air of a chamber in which the guinea-pig is sitting. Bovet and Walthert describe conditions in which normal guinea-pigs collapse from constriction of the bronchioles in 2 min. They state that when a dose of 0.05 mg./kg. neoantergan was injected 30 minutes previously, the guinea-pigs remained unaffected by this concentration of histamine for 8

minutes. After the injection of 1 mg./kg. neoantergan (anthisan) the guinea-pigs withstood 10 minute exposures to the histamine concentration during the next three hours.

The third test of an antihistamine substance is to determine its power to abolish the stimulant action of histamine on the isolated intestine of the guinea-pig. The fourth test is to study its power to abolish the depressor action of histamine on the blood pressure of the dog. Finally the fifth test is to study the power of the substance to diminish or abolish the capillary reactions caused by pricking the skin through a drop of histamine solution. Antihistamine substances also protect guinea-pigs against anaphylactic shock. Thus if the animal is injected intraperitoneally with 20 mg. egg albumin, after three weeks the intravenous injection of 0.04 mg. causes death from constriction of the bronchioles. If, however, the antihistamine substance is given 30 minutes previously by the subcutaneous route, the injection of the same dose of antigen has no effect. If the horn of the uterus is taken from a sensitized guinea-pig and suspended in a bath, the addition of a very small amount of antihistamine substance prevents the contraction otherwise caused by adding the antigen to the bath. Similarly in the dog, an antihistamine substance prevents the fall of blood pressure due to blocking the exit of blood from the liver which would otherwise occur when a second dose of antigen is given to a sensitized dog.

These, then, are the characteristic properties as described by Bovet and Walthert, who note that these substances have little antagonistic effect on the action of histamine on the guinea-pig uterus, and none on the action of histamine on gastric secretion.

Clinical Uses

The clinical applications of antihistamine substances are similar to one another. The most important use is in chronic urticaria, and in pruritus. The other uses are in hay fever and other forms of allergic rhinitis, and to some extent in asthma. Related to the use in urticaria is the use in various kinds of dermatitis and in skin reactions due to serum sickness, digestive disturbances, penicillin or liver extract.

The majority of clinical reports have dealt with benadryl, which has probably been most widely advertised. It has been given in doses of 50 mg. four times a day, more than this not being tolerated by most patients. Of those with urticaria, benadryl has been found to benefit 80 per cent. Varying results have been obtained in hay fever ; Koelsche (1946) stated that 75 per cent. of his patients improved and Logan (1945) gave similar figures ; Friedlaender, however, found no im-

provement in 19 cases. There have been contradictory findings in asthma, for Friedlaender said it was not affected, but Eyermann (1946) found improvement in 65 per cent.

Like benadryl, pyribenzamine has been used in urticaria, atopic dermatitis, asthma, allergic rhinitis, and hay fever. Its advantage over benadryl has been that it is tolerated in much larger doses, as 100 mg. can be given at a time without ill effect. Urticaria, dermatitis, and pruritus have again been the conditions most improved by pyribenzamine, but it has also been effective in rhinitis and hay fever (Feinberg and Friedlaender, 1947). The results with asthma have not been good, only 28 per cent. of 121 patients receiving benefit. Feinberg (1946) states that the relief obtained with oral pyribenzamine in asthma is only moderate compared with that afforded by hypodermic adrenaline.

Antistin has been given in doses of 300-600 mg. orally, but this drug can also be given by slow intravenous injection when an immediate effect is desired, and in this case a single dose of 50-200 mg. can be given, repeated on the third day (Schindler, 1946). For urticaria antistin can be injected subcutaneously, 300 mg. being given daily in doses of 50-100 mg. The results in urticaria, pruritus, eczema, and other dermatites, have been good, and some cases of asthma have responded to treatment.

Bovet and Walthert (1944) report on the therapeutic uses of antergan and neoantergan, and have also found the best results in urticaria and various kinds of dermatitis, and in skin reactions due to serum sickness or digestive disturbance, etc. They state that good or very good results were obtained in about one-third of asthma cases, since a good many cases of asthma are probably not due to histamine at all. Neoantergan has been used by Hunter (1947) in the treatment of urticaria. Eight cases of chronic urticaria and angioneurotic oedema, and six cases of acute urticaria which were mainly the result of sensitization to penicillin, were benefited, two of the latter being controlled even while penicillin was being administered. Hunter suggests an initial dose of 0.1 g. three times a day, increasing as required to a maximum of 1 g. daily. Feinberg *et al.* ('New Antihistamine Drugs in Hay Fever and Other Allergic Manifestations,' in press) found neoantergan of benefit in 39 out of 60 hay fever patients, in eight of ten perennial rhinitis patients, and in one of five asthma patients. Arbesman, Koepf and Lenzer (1946) and Hunter and Hill (1947) have found that antihistamine drugs are useful for patients with pernicious anaemia who are sensitive to liver preparations such as anahaemin, neo-hepatex, etc.

The latter authors gave 300 mg. anthisan one hour before the intramuscular injection of liver extract into patients who were sensitive. The degree of sensitivity was estimated by intradermal injections of serial dilutions of liver extract, and there was a significant reduction in sensitiveness during treatment with anthisan. They found a similar reduction in sensitivity to insulin in patients who were sensitive.

Undesired Effects

Antihistamine substances have properties in common with several other alkaloids. Thus they are to some extent like atropine and can inhibit the action of acetylcholine. It is for this reason that they cause dryness of the mouth. Dews and Graham (1946) have shown that neoantergan has a local anaesthetic action like procaine (novocain), and an action on cardiac muscle like that of quinidine; it also has a slight analgesic action in rats, and a general narcotic effect in large doses after subcutaneous injection. There can be no doubt that all antihistamine substances possess these properties, and Code (1945) has described the local anaesthetic action of benadryl. As a consequence of these different properties it is not surprising that antihistamine substances produce many undesired effects. These effects are essentially the same for each drug; namely drowsiness, fatigue, dizziness, dryness of mouth and nose, flushing, nausea, gastro-intestinal upset, palpitation, burning on urination and tightness of the chest. Antistin causes a sensation of heat on injection. However, the variation in degree of reaction is important. Fifty per cent. of patients receiving benadryl develop unpleasant reactions, of which some are serious enough to stop treatment. There have been reports (*J.A.M.A.*, 133, 392-4, 1946) of coma, severe disorientation and complete lethargy following benadryl. With pyribenzamine, 25 per cent. of patients are affected, and very few of the symptoms are severe enough to cause concern. Antistin is said to cause no serious ill effects at all, but the reports on this drug are few. Neoantergan (anthisan) seems to be the least toxic of the drugs, Hunter noting slight drowsiness, headache, nausea and dizziness but not as a rule severe. This author observed a severe toxic reaction following parenteral therapy in one patient, and suggested that at present the drug should be given by mouth only. A leading article in the *Lancet* for May 17, 1947, p. 678, states: 'In view of these rare but alarming manifestations it is well to remember that histamine acid phosphate, in doses of 0.5 mg. intravenously, is a specific antidote to benadryl,' and to other antihistamine substances.

Antistin and Privine

A word should be added concerning the combination of antistin-privine now advertised by the Swiss firm Ciba. Privine is also a compound containing the imidazol ring found in histamine, but it has no considerable antihistamine action. Some such action is evident, however, on the isolated ileum of the guinea-pig. Privine, the formula of which appears in Fig. 1 beside that of histamine, is a substance which causes a rise of blood pressure when injected intravenously, and acts like ephedrine on the nasal mucous membrane causing vasoconstriction and shrinkage when the membrane is congested. Privine has been used alone for this purpose with results which have been serious. Thus Feinberg (1945) states that when the vasoconstriction wears off, the vessels are then extremely dilated. Gollom (1944) describes 30 patients addicted to privine. Its application gives instant relief from the congestion of a cold in the head, but to maintain the relief it must be applied oftener and oftener. Some patients have used it every two hours night and day. When application is discontinued, there is a feeling of suffocation, and congestion becomes chronic. The absorption of privine into the system from nose drops has had a sedative action in children (Waring, 1945).

This evidence indicates that privine itself is a substance which requires very careful supervision in its use and which should not be put into the patient's hands for him to use as he feels. The Swiss firm Ciba are now recommending a solution containing antistin 1 in 200 and also privine 1 in 4,000 for use in hay fever. It is pointed out that this amount of privine is small, the suggestion being that the doctor need not fear the untoward effects described above. Fredenhagen (1946) has

described 56 cases and obtained good results with 3-4 instillations a day; congestion was relieved while secretion and sneezing were reduced.

A second use of this antistin-privine combination is for allergic conditions of the eye, in which lachrymation, photophobia and itching occur together with inflammation. Bourquin (1946) states that when the solution was instilled, examination became possible without the use of cocaine. It is still too early to know how uniformly successful and how free from undesired effects the combination antistin-privine will prove to be.

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