Section of Experimental Medicine and Therapeutics

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DISCUSSION ON ANTIHISTAMINE DRUGS

Professor W. A. Bain (*University of Leeds*): *The Quantitative Comparison of Histamine Antagonists in Man.*

THIS work, done by a small team[1] at Leeds, is part of a general attempt to apply to pharmacological studies in man methods of a quantitative kind such as have hitherto been applied chiefly to animals and to isolated animal tissues. As a starting-point in this quantitative approach to human pharmacology histamine and the histamine antagonists seemed ideal drugs to use, since histamine produces easily measurable reactions in the most extensive and readily available organ of the body and these reactions, as is well known from much qualitative work, are readily modified by histamine antagonists. A further consideration influencing our choice was the practical desirability of developing methods for assessing the relative merits of antihistaminics: this has now become an urgent practical necessity in view of the bewildering rate at which new drugs of this class are being introduced and the inevitable confusion which this is causing.

Our first task was to determine the dose-effect relationship for histamine when the drug was injected into the skin; and the second to determine in what manner and to what extent this was modified by the oral administration of histamine antagonists. From such observations we were able to devise means for obtaining quantitative comparative information about three of the four most important practical aspects of the actions of these drugs—their relative weight-for-weight potencies, their relative durations of action, and their relative therapeutic efficacies. Only the hyoscine-like side actions were not amenable—or were not subjected—to quantitative study.

Our account is necessarily but a brief summary of what we have done. Results are given mostly as mean values: statistical treatment of the data is omitted and will be presented elsewhere. For information about the various drugs mentioned, and about previous work upon them, the reader is referred to the recent reviews by Halpern (1948) and by Hunter and Dunlop (1948).

The dose-response curve to intradermal histamine and its modification by histamine antagonists.—The two experimental facts which form the basis of the subsequent observations are these: First, if graded doses of histamine are given intradermally to any individual, and the areas of the resulting wheals or flares are measured when at their maximum, then the relationship between the logarithm of the dose and the effect is linear over at least a three-hundredfold dose range—usually from 0·01 μg. to at least 3·0 μg., and in many subjects to as far as 10 μg. or more—after which the slope of the graph increases suddenly. Second, after the oral administration of an adequate dose of a histamine antagonist the log-dose response curve to intradermal histamine shifts so that it occupies at any given time a new position such that, in the conditions of our experiments and as far at least as the wheal response is concerned, there is an approximately equal percentage reduction of wheal area for each of the test doses of histamine over the range from about 0·03 to at least 10·0 μg.

[1]The Author, with Dr. G. Achari, Dr. J. L. Broadbent, Miss M. Robinson, and Dr. R. P. Warin.

These facts are illustrated in fig. 1 which shows the mean results from a set of experiments on five subjects. The upper points show the mean wheal areas resulting from the intradermal doses of histamine indicated on the abscissa, and the graph is drawn through these points by eye. The lower points show the corresponding wheal areas three hours after the ingestion of 25 mg. Phenergan (3277 R.P.).

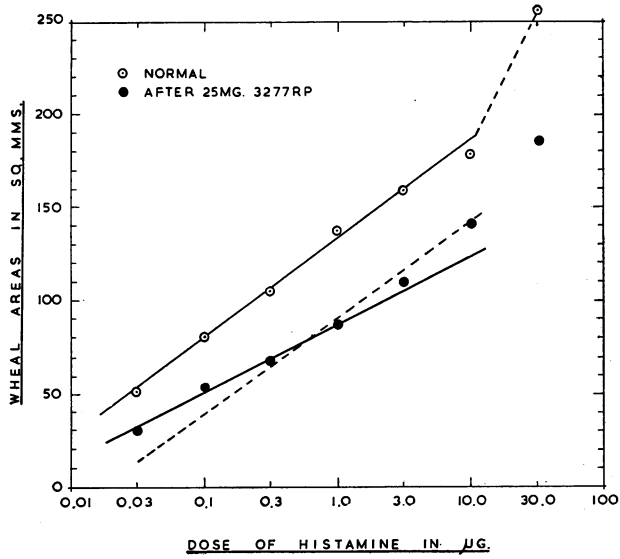

FIG. 1.—To show normal dose-response curve to intradermal histamine and its modification after the oral administration of a histamine antagonist. Mean results from five subjects. Abscissa—dose of histamine base in µg., logarithmic scale. Ordinate—wheal areas in sq. mm. The upper (open) points are normal: the lower (solid) ones were obtained three hours after the ingestion of 25 mg. Phenergan (3277 R.P.). For further explanation see text.

The average percentage reduction in wheal area for all the test doses of histamine was 35·0. The lower solid line is drawn to give throughout its course this same percentage reduction of the values represented by the normal dose-response graph. It fits the experimental points more closely than does the broken line which is parallel to the normal graph.

The comparison of weight-for-weight potencies.—When a histamine antagonist is taken by mouth the antihistamine effect, as gauged by the percentage reduction in the effect of an intradermal test dose of histamine, rises to a maximum and then tails off, the time relations depending on the conditions of the experiment, the drug used, and the individual. This is illustrated in fig. 2 which shows the mean results with various drugs in the same four subjects. It is clear that, other things being equal, the extent of the maximum reduction of the histamine response will depend on the dose of the antagonist, so that in comparing the relative potencies of different drugs it is essential to make the comparisons when the action of each drug is at its maximum, i.e. when the dose-response curve to intradermal histamine is maximally shifted.

If then, in any subject, the maximum shift of the dose-response curve to intradermal histamine is determined for each of several doses of an antagonist, and this maximum shift for each dose of the antagonist is expressed as the mean percentage reduction in wheal area and plotted as ordinate against log-dose antagonist as abscissa, then the relationship between dose and effect for that antagonist in that subject is determined. By making such observations in a group of subjects a mean dose-response curve for that antagonist is determined. By repeating such observations with other antihistaminics in the same group of subjects mean dose-response curves for these other drugs are obtained, and from such data, since the dose-response curves for the various drugs are parallel, the mean relative weight-for-weight potencies can be readily estimated.

Fig. 3 shows the results of such a comparison of Phenergan (3277 R.P.), Anthisan (Neoantergan, 2786 R.P.) and Antistin.

In these experiments the same six subjects were given, on different occasions, oral doses of 50, 100 and 300 mg. Anthisan, 25, 50 and 100 mg. Phenergan and 100, 200 and 300 mg. Antistin respectively, and the maximum reduction of wheal area was determined for each dose of each drug by at least three intradermal test doses of histamine (10·0, 1·0 and 0·1 µg.) given before and at intervals after ingestion of the antihistamine.

The areas of the wheals were obtained by inking the wheal outline on the skin five to ten minutes

after each injection, transferring to millimetre graph paper, and computing directly. The results were calculated from these measurements.

Phenergan is clearly the most powerful of these drugs and Antistin the least so. Thus, while a 50% reduction of wheal area was produced by about 40 mg. Phenergan, it required 275 mg. Anthisan or 600 mg. Antistin to produce the same mean effect. Furthermore, if

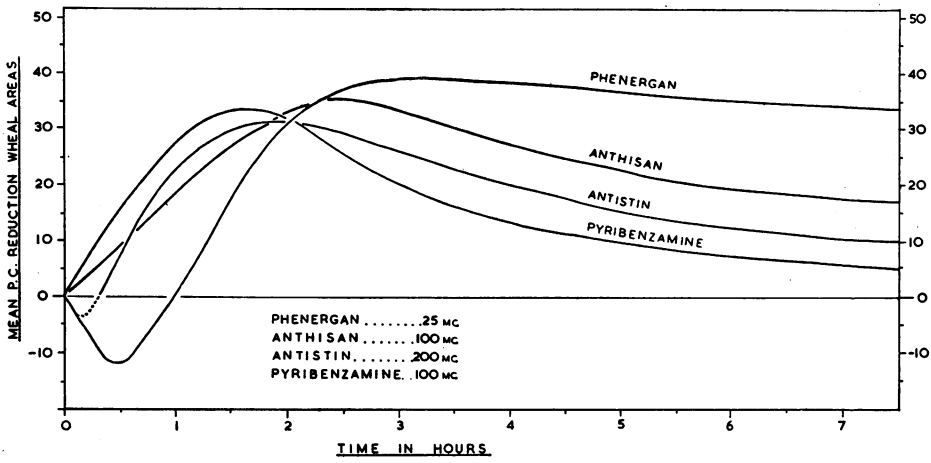

FIG. 2.—To show the variation in the rate of rise and fall of the antihistamine effect of single doses of various histamine antagonists. Mean results from four subjects. Abscissa—time in hours. Ordinate—mean percentage reduction below pre-drug level in wheal areas from intradermal test doses of histamine. The drugs and their doses are indicated on the figure. The individual points from which the graphs are constructed are omitted to avoid confusion.

we assume that the dose-response relationship remains linear throughout its course, then the mean doses of antihistamine theoretically required to abolish the intradermal histamine response are 450 mg. Phenergan, 3,200 mg. Anthisan and 7,000 mg. Antistin respectively—all of them quite intolerable doses.

Such comparisons of relative potency are, of course, facilitated by the fact that the regression lines for the different drugs are parallel, so that there is a simple ratio relating the mean dose of any two antagonists to give equal mean responses. Thus from the results shown in fig. 3 it is evident that about seven times the amount of Anthisan, or fifteen times the amount

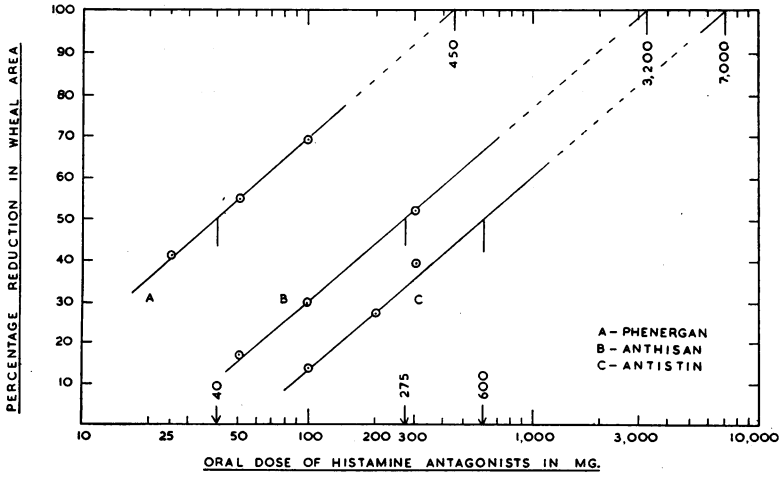

FIG. 3.—To show relationship between dose and maximum antihistamine response for Phenergan Anthisan and Antistin. Mean results from six subjects. Abscissa—oral dose of drug in mg. on logarithmic scale. Ordinate—mean percentage reduction in wheal areas. Graphs A, B, and C are for Phenergan, Anthisan and Antistin respectively. Mean doses to give 50% reduction in wheal area are indicated on lower abscissa, and theoretical doses to produce 100% reduction on upper abscissa. For further explanation see text.

of Antistin, is required to produce the effect of a given dose of Phenergan. We can express these differences by saying that, in relation to the maximum effect produced by a single dose, Phenergan is seven times more active, weight for weight, than Anthisan, and fifteen times more active than Antistin. Phenergan, indeed, is by far the most powerful drug of this class which we have encountered and is thus a suitable standard with which the potencies of others can be compared.

Since this method of determining and comparing equi-potent doses of histamine antagonists is of general applicability it is convenient to express the relative potencies of Phenergan and any other antihistamine in terms of what we propose to call the "Mean Potency Quotient" (M.P.Q.), and to define this as the quotient obtained when, for any particular antagonist, the mean dose required to produce a given effect at the time of maximum action is divided by the mean dose of Phenergan required to produce the same effect. The M.P.Q. of Anthisan is thus approximately seven, signifying that, as far as the maximum antihistamine effect of single doses upon the skin capillaries is concerned, seven times as much Anthisan is required to produce the same effect as a given dose of Phenergan, or that Anthisan is weight for weight one-seventh as potent as Phenergan, or that Phenergan is weight for weight seven times more potent than Anthisan. Similarly, the M.P.Q. of Antistin is fifteen. It should be noted that this method of expressing relative potencies states how much more potent Phenergan is than the drug with which it is compared. This convention is adopted in order to avoid fractional quotients. The reciprocal of the M.P.Q. expresses, of course, the potency of any drug as a fraction of the potency of Phenergan.

Comparison of durations of action.—From a practical point of view differences in potency among histamine antagonists are probably of less importance than differences in the durations of action; for it is on this latter property that the frequency of administration will depend, and this is an important matter in a class of drugs the use of which is so often associated with unpleasant or disconcerting side-effects and where such effects are usually most evident for a period following the absorption of each successive dose. Fig. 2 gives some idea of the marked differences in the duration of action of some of these drugs; but our problem was to obtain a measure of the relative durations of action such that the differences could be expressed in a fashion analogous to that which we have used for expressing differences in potency. It is evidently impossible to estimate the relative times for the disappearance of the action and so our comparisons have been made by estimating the times taken for the maximum antihistamine effect of single approximately equi-effective doses of the different drugs to be reduced by 50%.

The experiments were carried out on groups of from 4 to 11 subjects. The normal response to intradermal histamine was determined by at least three injections of 1·0 or of 3·0 μg. histamine. The drug was then taken with a cup of coffee two or more hours after a light breakfast. The onset and disappearance of the antihistamine effect was determined by duplicate injections of the test dose of histamine at suitable intervals. It was thus possible to estimate graphically for each subject both the degree of maximum effect and the time for establishment of this, together with the time for its reduction by half. The graphs in fig. 2, already referred to, were obtained in this way. They are the average results in four subjects and represent a single experiment. Fig. 4 shows the mean results from three such experiments for the drugs Phenergan, Anthisan and Antistin respectively. In this the times to maximum and to half maximum action are indicated on the graph for each drug.

There is, of course, great individual variation among the results, but the mean values from different experiments are remarkably consistent. Thus while the mean times from ingestion to half action are about 1,360 minutes for Phenergan (1,375, 1,320 and 1,375 minutes) and about 430 minutes for Anthisan (400, 510, 390 minutes) the range among individual subjects is from 700 to 1,800 minutes for Phenergan and 250 to 1,000 minutes for Anthisan.

It will be seen from fig. 4 that Anthisan and Antistin reach full action in about two hours and Phenergan in just over three, and that the mean times from full to half action in these experiments are thus 1,170 minutes (19 hr. 30 min.) for Phenergan, 310 minutes (5 hr. 10 min.) for Anthisan and 210 minutes (3 hr. 30 min.) for Antistin.

As this method of determining and comparing the half-action times after oral administration is applicable to any histamine antagonist, and as Phenergan is by far the longest acting of the drugs we have studied, it is convenient to express the relationship between the half-action time for Phenergan and that for any other antagonist by what might properly be called the "Mean Half-action Quotient", but which we propose to call the "Mean Duration Quotient", or M.D.Q., which we define as the quotient obtained when the half-action time for Phenergan is divided by the half-action time for the drug with which it is compared. This relates the half-action time of any particular antagonist and Phenergan by expressing the half-action time of Phenergan as a multiple of the half-action time of the drug with which it is compared. This convention avoids fractional quotients.

Thus the M.D.Q. of Anthisan is 3·8, signifying that the maximum effect of a single dose

of Phenergan takes about three and three-quarter times as long to be reduced by half as does the maximum effect of an approximately equi-potent dose of Anthisan, or that the maximum effect of a single dose of Anthisan is reduced by half in about a quarter of the time required for the same degree of reduction after an equi-potent dose of Phenergan. Similarly, the M.D.Q. of Antistin is 5·6.

The remarkable similarity between the half-action times for Phenergan and Anthisan when administered orally, and the corresponding ones obtained when the drugs are infiltrated locally

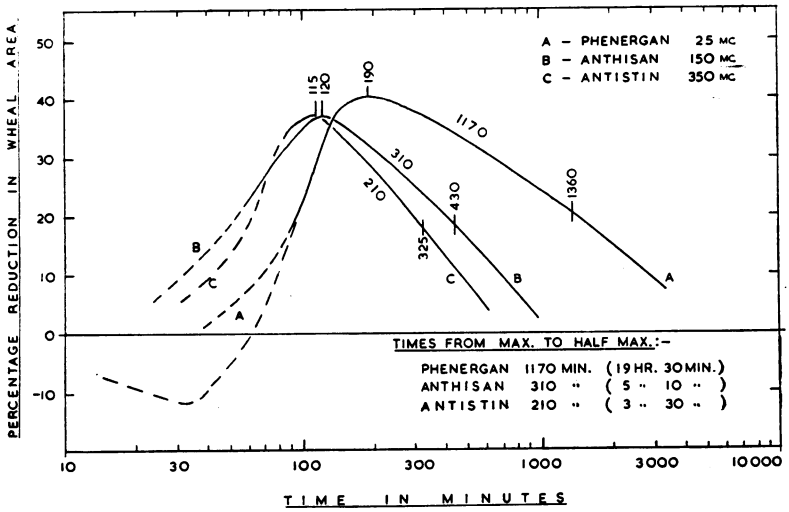

FIG. 4.—To show mean time relationships between onset and disappearance of antihistamine effect with approximately equi-effective doses of different antihistamines administered orally. Mean results from three experiments, each on four or more subjects, with each drug. Abscissa—time in minutes on logarithmic scale. Ordinate—mean percentage reduction in wheal area. Curves A, B, and C are for Phenergan, Anthisan and Antistin respectively. Times to maximum and to half maximum action are indicated for each drug. For further explanation see text.

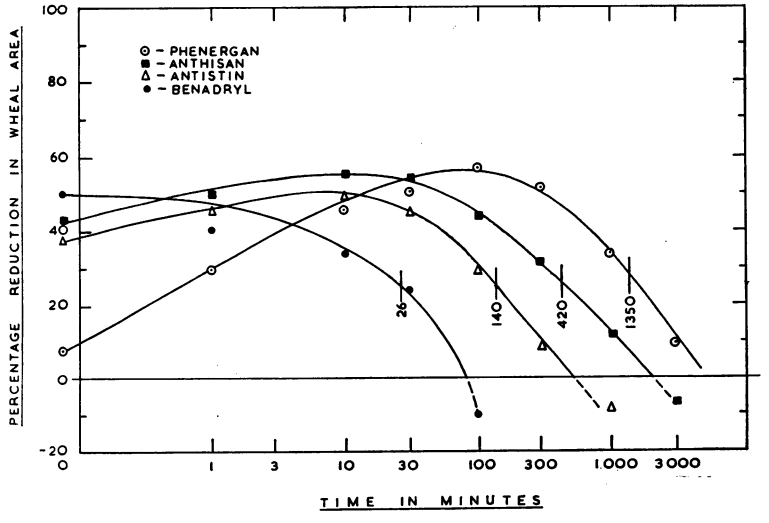

FIG. 5.—To show mean time relationships between onset and disappearance of antihistamine effect when the antihistamine drugs are administered locally to the skin and the test doses of histamine are injected to these infiltrated areas. Results from 14 subjects. Dose of antihistamine—0·2 ml. of 0·1% w/v. Test dose of histamine—1·5 μg. base in 0·05 ml. Injections at zero time—i.e. of histamine and the antagonist simultaneously, were of 0·2 ml. containing 0·1% w/v of antihistamine and 1·5 μg. histamine base. Indicated on graphs are the times from administration to half-action of the various drugs. For further explanation see text.

to the skin, in the manner briefly described in a previous paper (Bain, Hellier and Warin, 1948) and extended and reported on in more detail by Achari *et al.* (1948), is worthy of note. The results of these experiments are shown in fig. 5. It will be seen that the mean times for maximum action to be reached in these circumstances were about 100 minutes for Phenergan and 10 minutes for Anthisan, while the mean times from maximum to half-action were 1,250 minutes (20 hr. 50 min.) for Phenergan and 410 minutes (6 hr. 50 min.) for Anthisan. In view of the similarity of the figures derived from these two different types of experiment it is difficult to escape the conclusion that both the absolute and the relative durations of action of these two drugs are dependent mainly upon their duration of fixation by the tissues on which they act rather than upon, for example, differences in their rates of excretion. Some antihistaminics, however, give markedly discrepant results in the two types of experiment, indicating that such a view is not generally applicable to this class of drugs. Thus some may show a moderate half-action time when administered by mouth, and only a very short half-action time when administered locally. The most striking example is Benadryl, which has an oral half-action time somewhere between that for Antistin and that for Anthisan, but which, on local application (*see* fig. 5), has a half-action time of under 30 minutes. In such instances, where the drugs are not firmly fixed by the tissues, their duration of action must presumably depend mainly on their duration of sojourn in an active form in the extracellular fluid and thus ultimately on their rate of inactivation, or of excretion, or both.

The foregoing comparisons show clearly that histamine antagonists differ markedly in their relative potencies and durations of action. Thus Phenergan is about seven times more potent than Anthisan and about fifteen times more potent than Antistin: the time from full to half-action for Phenergan is about three and three-quarter times greater than that for Anthisan and over five and a half times greater than for Antistin. It is evident that both these factors must be taken into account in assessing the relative merits of both existing and proposed new histamine antagonists.

A further important factor is, of course, the relationship of side-effects to antihistamine activity, for it is the side-effects which at present constitute one of the chief limiting factors in the usefulness of these drugs. We have discussed elsewhere (Bain, Hellier and Warin, 1948; Bain, Broadbent and Warin, 1949) the difficulties associated with the assessment of the incidence and severity of side-effects, and have stated earlier in this paper that we have not dealt with these in a quantitative fashion. We hope, however, that it may be possible to devise a semi-quantitative treatment of side-effects by applying to them a system of "scoring". The "scores" obtained in the same group of subjects by different drugs could then be used to derive a "Mean Side-Effect" or "Mean Toxicity Quotient". Determined on equi-potent doses of different drugs this might indicate the relationship, if any, between the most interesting side-actions—those which are so similar to the effects of hyoscine—and the specific antihistamine effect itself. But from the clinical point of view it would also be important to compare equi-therapeutic as distinct from equi-potent doses and this would clearly give a different quotient, the difference depending to a large extent on the relative durations of action of the drugs compared. This will be evident from the observations about to be described.

Comparison of therapeutic potencies.—We have so far been able to make a therapeutic comparison of only two drugs—Phenergan and Anthisan. As details of this comparison are presented elsewhere (Bain, Broadbent and Warin, 1949) only a summary will be given here.

In 20 patients with chronic urticaria the reaction to intradermal test doses of histamine and, when present, the dermographic reactions to various stimuli, were measured by Dr. Warin before and at intervals after the institution of therapy with Anthisan, and compared with the progress of the urticaria. The Anthisan was given two, three, or four times a day, as was found necessary. After a rest period the control observations were repeated and the patients put on Phenergan. In view of the long duration of action of this drug it was given in a single dose at night. Given in this way we hoped that the drowsiness which it often causes would but contribute to sleep and that any other side-actions would pass unnoticed, whereas the antihistamine effect would continue throughout the following day. An attempt was made to adjust the dose of Phenergan so as to give the same therapeutic effect as with Anthisan in the earlier period of treatment: we hoped to be able in this way to establish the approximately equivalent therapeutic doses.

While Anthisan had usually to be given three or four times a day the nightly dose of Phenergan controlled the urticaria in all the patients throughout twenty-four hours. Only 3 patients were completely free from side-effects with Anthisan against fourteen on the nightly dose of Phenergan. The only side-effect noticed with Phenergan was morning drowsiness, but in only 5 patients did this persist throughout treatment. 14 patients preferred Phenergan, 5 had no preference and only one

preferred Anthisan ; the high preference for Phenergan was clearly based on the relative absence of side-actions with this drug. Thus with Phenergan in nightly doses the appreciated incidence of side-effects, and the severity of these when they occur, is much less than with equi-therapeutic doses of Anthisan given, as it usually has to be, several times a day : hence it should be possible to obtain adequate therapeutic effects by easily tolerated nightly doses of Phenergan in patients unable to tolerate the necessary divided doses of Anthisan.

A diagrammatic representation of the type of data obtained from some of the patients is given in fig. 6. In this case it is evident that the effect of 50 mg. Phenergan lies between that for 600 and for 900 mg. per day of Anthisan. In making the quantitative therapeutic comparison, however, 10 cases have had to be excluded; 8 because the dose of Phenergan used produced a greater therapeutic effect than did the Anthisan in the earlier period of treatment; and 2 because in them the urticaria was not abolished. In the remaining 10 cases the therapeutic effect of a given dose of Phenergan was produced by a total daily dose of Anthisan from eight to eighteen times greater: the average figure was fourteen. Thus, on the average, 25 mg. Phenergan per day is the approximate therapeutic equivalent of 350 mg. Anthisan per day, or of three divided doses each of about 115 mg. Similarly, a nightly dose of 50 mg. Phenergan is the equivalent of about 700 mg. Anthisan per day, or of three divided doses each of about 230 mg.

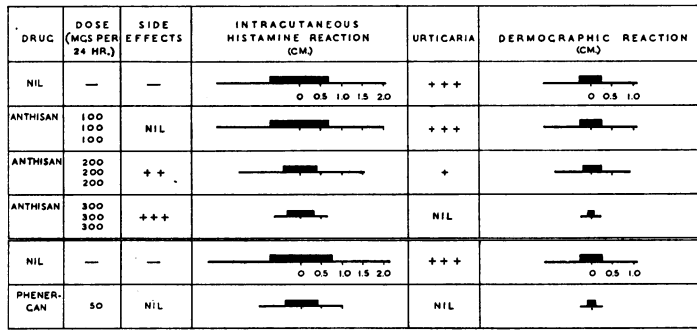

FIG. 6.—To show the type of result obtainable in the clinical comparison of histamine antagonists. Subject W. H., male, aged 23, urticaria present for two years, associated with dermographism. Urticaria: +, occasional wheal; ++, a few wheals; +++, moderate number of wheals. Side-effects: +, slight symptoms on questioning; ++, complaint of mild symptoms; +++, complaint of moderate symptoms. Mean diameter of wheals (thick lines) and flares (thin lines) in cm. Histamine reaction from 0·05 ml. of 0·01 % w/v histamine acid phosphate. Dermographic reaction from various traumatizing stimuli (mean of 4 measurements). In this subject 50 mg. Phenergan per day had an effect between that of 600 and that of 900 mg. of Anthisan per day.

With such a relationship between these dose values it is perhaps justifiable to express the relative therapeutic potencies of Phenergan and Anthisan—and, when the information is available, of Phenergan and any other histamine antagonist—in terms of the average ratio between the equi-effective twenty-four hour doses. This "therapeutic ratio" cannot be so called because of the varied connotations which already attach to the expression, and we propose the clumsier "Mean Therapeutic Quotient" or M.T.Q. This can be regarded as stating in respect of the total dose in twenty-four hours, (1) how much more powerful Phenergan is than the drug with which it is compared, or (2) by how much, on the average, a given dose of Phenergan must be multiplied to find the daily dose of the other drug likely to produce the same therapeutic effect as the Phenergan.

The M.T.Q. of Anthisan is about 14. Thus while Phenergan is only about seven times more potent than Anthisan when compared in terms of the single doses required to produce the same intensity of effect (M.P.Q.), it is almost fourteen times more potent than Anthisan when compared in terms of the relative doses per day required to maintain a similar level of antihistamine activity (M.T.Q.). It is clearly the difference in the duration of action of the two drugs, expressed as the Mean Duration Quotient, which is the main factor determining the difference between the mean potency and mean therapeutic quotients.

Concluding remarks.—The differences so far noted among the various drugs are differences of degree. But in our first experiment on the duration of action of Phenergan (illustrated in fig. 2) the initial effect of the drug was to potentiate the intradermal histamine response in all four subjects. In subsequent experiments this phenomenon was seen only in some subjects, and the mean curve did not fall below the zero abscissa. These different results are indicated in fig. 4, where alternative routes for the onset of the antihistamine effect of Phenergan are indicated by broken lines. (No other histamine antagonism has exhibited this effect, with the

possible exception of Antistin: but with this the only evidence was indirect—the somewhat late rise of the curve (*see* fig. 2) from the zero line.) A similar potentiation of the intradermal histamine response has often been noticed—but again only in some subjects—when Phenergan and histamine have been injected to the skin in experiments of the kind illustrated in fig. 5. The effect was most commonly seen when the two drugs were administered simultaneously.

We sought to account for this phenomenon by the hypothesis that Phenergan might antagonize histaminase. Some support is perhaps given to this view by the work of Kapeller-Adler (1949) who has shown that Phenergan and Antistin inhibit the action of histaminase *in vitro*, but that none of the other histamine antagonists investigated do so.

If the primary potentiation of the intradermal histamine response with Phenergan is due to partial inhibition of histaminase then it is clear that the fixation of the drug by the enzyme occurs very quickly, in marked contrast to the rate of fixation by the capillaries. But to what total extent histaminase may be inactivated by therapeutic doses of Phenergan, or how long the effect may persist, it is impossible from our experiments to say, because the effect itself, manifested by the potentiation of the wheal response, becomes quickly masked by the establishment of the specific antihistamine action of the drug. However, if Phenergan is potent as an inhibitor of histaminase it is possible that therapeutic doses of the drug in persons relatively resistant to the antihistamine effects might produce an exacerbation of any symptoms due to histamine release; such untoward effects could presumably be countered by increasing the dose.

It is generally assumed that histamine antagonists act by receptor competition—that they become fixed, in varying degree and with varying firmness, to receptors on the tissues on which histamine acts, and, by this preferential fixation or competition, partially exclude or block the access of histamine to these receptors (Gaddum, 1948). The failure of histamine antagonists to diminish histamine-induced gastric secretion may be due to a difference in the histamine receptors in the gastric glands such that the antagonists fail to become fixed to them. Of the actions of histamine which are influenced by histamine antagonists those due to injected (exogenous) histamine are usually held to be more readily affected than those due to histamine released by the tissues (endogenous histamine). Furthermore, Dale (1948) distinguishes between histamine which is released by the cell on which it reacts and that which when released acts only upon more remote structures: the former he calls intrinsic and the latter extrinsic histamine. In man the antihistamine drugs are usually much less effective against intrinsic than against extrinsic actions of endogenous histamine. They are—assuming the role of histamine in these conditions—less effective, for example, in bronchial asthma, where the histamine is liberated by the reacting structure, than in chronic urticaria where it is not. But it may be that the relative failure of histamine antagonists to block intrinsic actions is due simply to the difficulty, with the agents at present available, of reaching an effective drug level at the site of histamine release with doses of the drugs which are tolerable. In chronic urticaria, on the other hand, the histamine does not act upon the cells from which it is liberated but upon the capillaries with which it subsequently comes in contact through humoral channels. Histamine antagonists are thus regarded as effective in urticaria because the liberated histamine acts in a fashion analogous to that of histamine injected from outside.

Nevertheless it may be wondered how antihistamine drugs can abolish urticaria when, according to the pharmacological data summarized earlier in this paper, very large doses may be required to produce a 70% reduction in the intradermal histamine wheal response and quite intolerable doses are theoretically required to abolish it. Nor is it only when histamine antagonists are administered orally that we have failed to abolish the intradermal histamine response, for we have failed equally to do so when the drugs are administered locally to the skin. The average maximum percentage reduction obtained by local administration, even of Phenergan, was about 60% (*see* fig. 5) and the maximum individual reductions seldom exceeded 80%.

Chronic urticaria is in fact abolished, however, when the area of the intradermal wheal response is reduced by, on the average, about 50% with a range of individual values from 30% to about 80%. On the other hand, the average percentage reduction in the dermographic wheal response at the stage when urticaria is cleared is of the order of 90% (range 86–96%). This type of difference is illustrated in fig. 6 where, with the 50 mg. dose of Phenergan, the dermographic wheal response is reduced by about 90% and the intradermal histamine wheal response by 70%. Unfortunately we have but few observations of this kind on the dermographic response. Nevertheless if this sort of result can be confirmed and the quantitative differences between the effects of the drugs on injected and on liberated histamine respectively can be shown not to be due to the different circumstances attending the production of the two types of reaction, then it will be difficult to escape the conclusion that, in the relief of chronic urticaria the histamine antagonists may be exhibiting a dual modality of action—

by antagonizing the action of histamine on the capillaries, by a receptor competition mechanism, on the one hand, and by diminishing the release of histamine from the tissues, by some unknown mechanism, on the other. We have evidence, indeed, from other lines of work that histamine antagonists may in certain circumstances act in this latter fashion. But much further work is needed before any discussion of the various possibilities concerning the mode of action of histamine antagonists can be justified on the basis of experimental work on man; the view just expressed is therefore to be regarded as little more than a speculation.

SUMMARY

(1) Methods of comparing the weight-for-weight potencies, relative durations of action, and relative therapeutic efficacies of histamine antagonists are described, but statistical treatment of the data is omitted.

(2) The outstanding potency and duration of action of Phenergan (3277 R.P.) suggests its suitability as a standard against which these properties of the others can be compared.

(3) Relative weight-for-weight potencies are expressed in terms of the "Mean Potency Quotient" obtained by dividing the mean dose of the drug under test which produces a given mean antihistamine effect, by the mean dose of Phenergan which produces the same effect. The quotient states how much more powerful Phenergan is than the drug with which it is compared, or by how much the dose of the drug under test must be multiplied to give the same effect as a given dose of Phenergan. The M.P.Q. of Anthisan is about 7 and of Antistin about 15.

(4) Relative durations of action are expressed in terms of the "Mean Duration Quotient", obtained by dividing the time from maximum to half-maximum action for Phenergan by the corresponding time for an approximately equi-effective dose of the drug under test. This expresses the half-action time for Phenergan as a multiple of the half-action time of the drug with which it is compared. The M.D.Q. of Anthisan is 3·8 and of Antistin 5·6.

(5) Relative therapeutic efficacies in chronic urticaria may be expressed in terms of the "Mean Therapeutic Quotient", obtained by dividing the daily dose of the drug under test by the daily dose of Phenergan required to produce an equal therapeutic response. This expresses the therapeutic potency of Phenergan as a multiple of the potency of the drug with which it is compared, or states by how much the daily dose of Phenergan must be multiplied to give the equivalent daily dose of the other drug. The M.T.Q. of Anthisan in chronic urticaria is about 14.

(6) A possible qualitative difference between Phenergan and the other drugs is noted, and some aspects of the probable mode of action of histamine antagonists are briefly discussed.

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REFERENCES

ACHARI, G., BAIN, W. A., BROADBENT, J. L., and ROBINSON, M. (1948) Communication to British Pharmacological Society, July.

BAIN, W. A., BROADBENT, J. L., ROBINSON, M., and WARIN, R. P. (1948) Communications to British Pharmacological Society, July.

——, ——, and WARIN, R. P. (1949) *Lancet* (ii), 47.

——, HELLIER, F. F., and WARIN, R. P. (1948) *Lancet* (ii), 964.

DALE, H. H. (1948) *Brit. med. J.* (ii), 281.

GADDUM, J. H. (1948) *Brit. med. J.* (i) 867.

HALPERN, B. N. (1948) *in* Acquisitions Médicales Récentes. Flammarion, Paris, p. 251.

HUNTER, R. B., and DUNLOP, D. M. (1948) *Quart. J. Med.*, **17**, 271.

KAPELLER-ADLER, R. (1949) *Biochem. J.*, **44**, 70.

Dr. H. O. Schild: *The Experimental Evidence for the use of Antihistamine Drugs in Allergic Conditions.*

The following experimental facts form the basis for the use of antihistamine drugs in allergic disease:

(1) Histamine is released in anaphylaxis.

(2) Antihistamine drugs abolish the actions of histamine on plain muscle.

(3) Antihistamine drugs diminish or abolish the anaphylactic reaction in the whole animal and in isolated sensitized plain muscle.

When these drugs are used in allergic conditions in man, however, certain inconsistencies appear which are difficult to explain at first sight. For instance, antihistamine drugs are almost inactive in bronchial asthma, and are most active in capillary conditions such as urticaria and hay fever (Hunter and Dunlop, 1948). When, however, histamine is injected into the blood-stream its bronchoconstrictor effects are readily abolished by antihistamine drugs, more readily indeed than its vasodilator effects.

Dale (1948) distinguishes between the actions of intrinsic histamine and those of extrinsic histamine. The former are actions produced by histamine on the tissues from which it is released; the latter are actions on tissues to which histamine is carried after release. Obviously antagonism by an antihistamine drug may be very different in the two cases. The actions of extrinsic histamine might be expected to correspond closely to those of injected histamine. It can be shown, in fact, that the action of histamine released from tissues

corresponds in every respect to that of synthetic histamine, and that both are equally antagonized by antihistamine drugs.

Many inconsistencies would be explained if it could be assumed that in those instances where the antihistamine drugs are most effective extrinsic histamine is concerned. For instance, in hay fever histamine might be released from epithelial cells and thence diffuse to the blood-vessels. In this way its action on blood-vessels might be easily antagonized. Unfortunately we lack direct evidence that histamine is released from tissues in human allergy, as is the case in experimental anaphylaxis. The problem is essentially technical owing to the difficulty of demonstrating the presence of minute amounts of histamine in plasma and tissue fluids. Positive results might possibly be achieved by using techniques based on diffusion of histamine from sensitized tissues into Ringer's solution containing the antigen (Schild, 1939). These techniques might be applied to slices of tissue removed during operations from patients exhibiting some specific allergy.

The effects of antihistamine drugs on intrinsic histamine are more difficult to appraise. When histamine is released in anaphylaxis the total quantity released can be measured, but the effective concentration at the cell membrane at the time of release is unknown. It is therefore impossible to estimate how much antihistamine is required to antagonize these actions.

In general the anaphylactic reaction of plain muscle is more difficult to suppress than the reaction to extrinsic histamine (Loew, 1947). For instance, equal concentrations of antagonist are needed to antagonize the actions of 500 μg./ml. extrinsic histamine and of 5 μg./gramme intrinsic histamine on bronchial muscle (Schild, 1936*a*). This might be due to a hundredfold concentration of intrinsic histamine at the cell membrane, but other experiments indicate a qualitative as well as a quantitative difference. For instance, the isolated uterus of a sensitized guinea-pig can be made completely irresponsive to extrinsic histamine and yet continue to respond to the specific antigen (Schild, 1936*b*).

This experiment is illustrated in fig. 1. In this case the antihistamine drug used is histamine itself, in some ways the most specific antagonist of histamine (Barsoum and Gaddum, 1935), since when present in excess it presumably blocks all the "receptors" for histamine. Why is it that the muscle still continues to respond to the specific antigen? Granted that histamine is released from the uterus during the anaphylactic reaction (Schild, 1939), how does intrinsic histamine reach the receptors which are already blocked? Is it that intrinsic histamine reaches certain intracellular receptors which cannot be reached by histamine added from outside? This explanation is rendered less likely by the finding that histamine added from outside diffuses readily into the cell interior (Schild, 1949). Whatever the explanation of the experiment shown in fig. 1, its significance lies in the fact that it shows that in principle anti-anaphylactic and antihistamine actions can be separated.

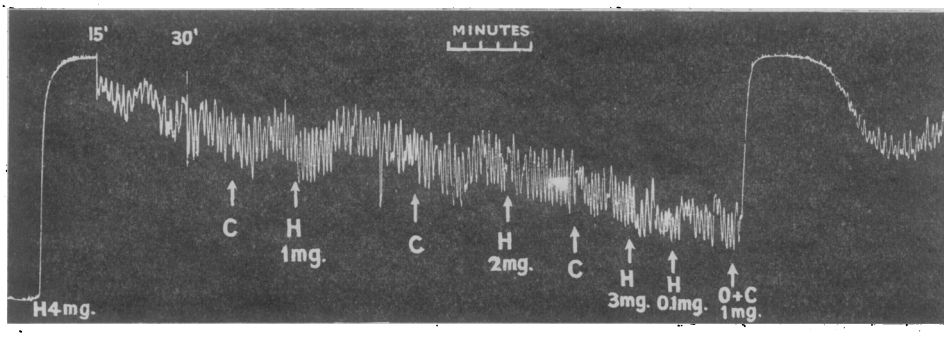

FIG. 1.—Contractions of the isolated uterus of a guinea-pig which had been previously sensitized to egg albumen. Uterus suspended in 20 c.c. bath in Ringer's solution. Addition of histamine to the bath at first produces contraction, but gradually the muscle relaxes in spite of the continued presence of histamine, and shows no more response to further additions of histamine acid phosphate (H), or sodium acid phosphate (C). When, however, the specific antigen, egg albumen (O), is added, it contracts maximally. This experiment shows that it is possible to abolish the response to extrinsic histamine and yet preserve the anaphylactic response of plain muscle.

Antagonists of histamine may thus be expected to relieve readily those pathological conditions in which histamine acts at some site in the body different from the original site of release, but they may be expected to be rather less active, and possibly, in some cases, inactive, at the site of the primary allergic reaction itself.

In some cases the beneficial effects of antihistamine drugs may not be due at all to antagonism to histamine, but to some independent pharmacological action. Antihistamine drugs, like all antagonistic drugs, are not entirely specific. In low concentrations they antagonize only histamine, but in higher concentrations they antagonize the actions of acetylcholine (Schild, 1947) and presumably of other stimulant agents. Although none is completely specific, some antihistamine drugs are more specific than others. Reuse (1948) has shown that 3277 R.P. (Phenergan) besides being a very powerful antagonist of histamine also strongly antagonizes acetylcholine. Benadryl, though weaker, also possesses both actions. By contrast Neoantergan (Anthisan) is a very strong antagonist of histamine but only a weak antagonist of acetylcholine. Halpern (1948) has shown that antihistamine drugs affect capillary permeability. They counteract increases in capillary permeability produced not only by histamine but also by other capillary dilators. 3277 R.P. (Phenergan) is particularly active in this respect.

To summarize: We now possess drugs with extremely powerful antihistamine action (except on gastric secretion) and in some cases with remarkable activity against the anaphylactic response. It is probable, however, that the two actions do not run strictly parallel. Furthermore, it is doubtful whether the anaphylactic reaction in animals can be wholly equated with human allergic reactions. It follows that antihistamine drugs, like all drugs, cannot be completely assessed by animal work. The preliminary work must of necessity be done in the laboratory, but the eventual appraisal of each individual drug can only be made by assessing it in patients exhibiting the disturbance against which the drug is to be used.

REFERENCES

BARSOUM, G. S., and GADDUM, J. H. (1935) *J. Physiol.*, **85**, 1.
DALE, H. H. (1948) *Brit. med. J.* (ii), 281.
HALPERN, B. N. (1948) *in* Acquisitions Médicales Récentes. Flammarion, Paris. p. 251.
HUNTER, R. B., and DUNLOP, D. M. (1948) *Quart. J. Med.*, **17**, 271.
LOEW, E. R. (1947) *Physiol. Rev.*, **27**, 542.
REUSE, J. J. (1948) *Brit. J. Pharmacol.*, **3**, 174.
SCHILD, H. O. (1936*a*) *Quart. J. exp. Physiol.*, **26**, 165.
—— (1936*b*) *J. Physiol.*, **86**, 51P.
—— (1939) *J. Physiol.*, **95**, 393.
—— (1947) *Brit. J. Pharmacol.*, **2**, 189.
—— (1949) Unpublished results.

Dr. Ranyard West (*Edinburgh*): *Bronchospasm and Antihistamine Drugs.*

The antihistamine drugs have been so named because, under certain conditions of administration, they antagonize many observed actions of histamine. The conditions of successful administration of these drugs are not always easy to determine: and certain actions of histamine, notably that of gastric secretion, remain unopposed by all existing "antihistamine" drugs. It is therefore impossible to say of a histamine-like effect: "Because this action is not antagonized by Neoantergan or Benadryl or Antistin, therefore it is not due to histamine".

When the fame of the antihistamine drugs was experimentally established and they came to be considered as safe therapeutic agents, there was naturally enough a rush to exhibit them in asthma, since in some animals bronchospasm is an observed action of histamine and it had frequently been suggested (though it was as frequently denied) that the bronchospasm of asthma might sometimes be due to the liberation of histamine or a histamine-like substance in the bronchial tree of asthmatics. On the whole we may say that the results of such treatments, although not entirely negative in the hands of some workers (Waldbott, 1947; Herxheimer, 1948) were disappointing (Hunter and Dunlop, 1948). Up to date it cannot be said that antihistamine drugs abolish or prevent the bronchospasm of asthma, under well-controlled conditions of administration, with any constancy or even with results which suggest that success is just round the corner. That fact has created a disappointing situation in the field of therapy.

But apart from clinical asthma there is another condition of bronchospasm in which histamine-liberation has been invoked as the effective bronchoconstrictor agent. I refer to curare-bronchospasm. Curare-bronchospasm was first described in 1935 as an irregularly occurring complicating action of crude curares. The action appeared to vary from one specimen of curare to another and to show a species variation, being particularly marked in rodents and not uncommon in dogs, while it was more rarely found (though it could occur) in the cat (West, 1935). At that time our chemical collaborators, Dr. Harold King and Mr. A. Stephens, were constantly providing us with new, impure alkaloidal fractions from crude curares, and plant material from British Guiana was yielding increasingly pure chemical material for pharmacological trial. Some of these fractions possessed a greater power of causing bronchoconstriction than did others; and at one time we were inclined to think

that we were merely dealing with an impurity separable from the alkaloids which caused the classical curare action of myoneural paralysis.

It so happened, however, that the only reasonably pure (though never definitely crystalline) alkaloid with which Dr. King was able at that time to supply me in any considerable quantity had both a strong "curarizing" action and also showed this action of variable bronchoconstriction, with species variation towards rodents and dogs but also affecting man. This alkaloid was calabash "curarine". Boehm, 1895, obtained in this case direct from the bark of *Strychnos toxifera*, an accepted ingredient of Guianese curare.

In man curare bronchospasm produced by calabash "curarine" occurred as an occasional sudden severe bronchoconstriction when curarine was given in subparalytic doses to cases of tetanus, spastic paraplegia and post-encephalitic Parkinsonism (West, 1936). It could occur in patients who appeared to be only lightly curarized. Its analysis was undertaken in the hope that curare derivatives would find a useful place as "lissive" agents in removing pathological muscular rigidities in diseases of the nervous system (West, 1932).

In curare "asthma" it is necessary to separate the two elements of active and passive bronchoconstriction. Passive bronchoconstriction is produced by the classical action of curare upon the respiratory muscles, with a resultant fall of intrapleural suction (or "negative pressure") during inspiration. It leads ultimately to a passive collapse of the lungs. Active bronchoconstriction is due to a maintained contraction of the circular muscle of the bronchi in response to a local stimulus. It is impossible to speak with confidence of bronchospasm in connexion with any curarizing drug unless this separation has been made.

Active curare bronchospasm, thus separated from passive components, can be demonstrated in animals as follows: (1) by directly observing the intact exposed lungs in guinea-pigs; (2) by recording minimal distension pressures of the exposed guinea-pig lung; (3) by perfusing an isolated strip of bronchial muscle in a water-bath.

Method 1.—By this method, in which the guinea-pig is pithed, the diaphragm incised and ventilation maintained by positive pressure with a pump, calabash "curarine" produced a reduction of lung movement, but never, even with very large doses, did it produce the instant abolition of lung expansion which is characteristic of histamine given by injection. The lungs also became more cyanosed, giving the impression that effective oxygenation ceased at a lesser reduction of lung movement with curarine than with histamine (West, 1938).

Method 2.—Apart from such direct observation active bronchospasm can be recorded by measuring the "minimal distension pressures" of the guinea-pig lung, or alternatively the shunt of air to a side tube which is produced when the air-space of the exposed lung is diminished by bronchoconstriction, the record being made either with a water manometer or a tambour. The author used a water manometer recorder and by it found that "curarine" produced a rise of seven to ten times the initial distension pressure by a bronchoconstrictor effect which was abolished by adrenaline. The effect could not be increased by raising the dose of "curarine". Small doses of histamine always produced a greater bronchoconstriction than did curarine. Its effects were also removed by adrenaline; but with histamine increased dosage proportionately increased the severity of the bronchospasm (West, 1938).

Method 3.—The reaction of the bronchial muscle can be studied more intimately by adding the drug to a water-bath containing a strip of muscle attached to two or three rings of the trachea suspended from a reflecting mirror recorder. This is a classical pharmacological experiment in which histamine produces an instant bronchospasm. Curarine in high concentrations also produces a severe bronchoconstriction, but only after a delay of about eight minutes, which suggested to us even at that time that some progressive reaction must be under way in the water-bath between the "curarine" and some substance within the muscle fibres of the trachea. As with histamine the spasm is readily and instantly removed by adrenaline (West, 1937).

Among methods of measuring bronchial narrowing which may confuse active bronchospasm with passive bronchoconstriction are those which involve the creation of an artificial pneumothorax. This may be done in two ways. In one of them, useful in the guinea-pig, a pointed metal cannula with perforated sides is thrust through the posterior mediastinum to a point where at least one perforation transmits a freely swinging pressure, or suction, from the pleural cavity to a connected tambour (Jackson, 1917). In larger animals, such as rabbits and cats, a small pneumothorax may be induced, as in man, by a hollow needle thrust between the ribs and attached to a water manometer to record intrapleural pressures (West, 1938). With either method it is necessary to realize that, where the bronchoconstriction of a curarizing agent is under examination, the effect of partial curarization will be recorded as a "fall" of negative intrapleural pressure and thus oppose the recording of any active bronchospasm which "increases" by suction the negative pressures in the closed recording system. By a combination of active bronchospasm and passive bronchoconstriction it is possible for a severe collapse of the lung to occur without a greater change in the intrapleural pressures than may occur with deep ether anæsthesia. Without great care in handling and analysis, therefore, the results of such methods of recording are unsuitable to the estimation of bronchoconstriction produced by curarizing drugs.

In a valuable investigation of curare bronchoconstriction in dogs an infant resuscitator has been used by Landmesser (1947). In these experiments the diaphragm was paralysed by spinal anæsthesia in order to obviate the confusing effect of passive bronchoconstriction, the histamine controls were effective, and the author was satisfied that he demonstrated active bronchospasm from the use first of "intocostrin" and later of pure *d*-tubocurarine and "curarine chloride". The element of inconstancy of the reaction is emphasized by his results: for though "intocostrin" caused bronchoconstriction in five cases out of five, *d*-tubocurarine produced bronchoconstriction only seven times out of ten, and bronchodilatation in two of the remaining three. "Curarine chloride" (impure calabash "curarine"?) was rather more prone to cause bronchospasm than was *d*-tubocurarine. Repeated small doses of the curare preparations had diminishing effects, while a subsequent large dose might cause increased bronchoconstriction. Landmesser made the additional observation that such curare bronchospasm in dogs is both preventable and removable by the antihistamine drugs Pyribenzamine and Benadryl (Landmesser, 1947). More recently Mahfouz (1949) has examined the action of *d*-tubocurarine chloride on the exposed guinea-pig lung, using the air-shunt method. He reported bronchoconstriction as present, not constantly, but in 9 of 16 consecutive cases. He has so far observed no alternative bronchodilatation. The bronchospasm is both removable and preventable by Neoantergan. Mahfouz adds that bronchospasm is much less likely to occur in this preparation if the injection of *d*-tubocurarine is given slowly. After curare bronchospasm has occurred, second doses of *d*-tubocurarine are ineffective, while injected histamine remains as effective as before.

The investigations described in the foregoing paragraph were undertaken because of the introduction (Griffith and Johnson, 1942) and extensive use of curare extracts in anæsthesia in recent years and the occasional reports of fatalities due to alleged bronchial spasm (Whitacre and Fisher, 1945; Holoday, 1946). Though all such cases involve the difficult separation of active bronchospasm—which may itself occur from reflex causes unconnected with the use of curare (de Takats *et al.*, 1942)—from passive collapse of the lung, when curare is employed these two conditions may occur together and reinforce each other. It does now appear reasonably certain, however, that at least one pure alkaloid of curare much used in anæsthesia, namely *d*-tubocurarine chloride, is capable under certain conditions of producing active bronchospasm, though it may do so with less readiness than some other curare derivatives.

With regard to the method of production of curare bronchospasm, we have first of all the evidence that perfusing curare (including calabash "curarine") through voluntary or cardiac muscle will liberate histamine in rapidly diminishing quantities until the muscle store is depleted (Anrep and Barsoum, 1935; Alam *et al.*, 1939), and that this also applies, under certain conditions and at least in certain species, to the tissues of the bronchial tree (Schild, 1948). Though the amounts of histamine recoverable from the perfusates may be small, we do not know the histamine concentration at the actual site of liberation; nor do we know the dose of histamine required for muscle contraction when this substance is released in effective proximity to an appropriately sensitive smooth muscle. Histamine is subject to attack by histaminases just as acetylcholine is by cholinesterase; and as it proved with acetylcholine as an excitor of normal voluntary muscle, so may the endogenous liberation and action of histamine (whether it be in intestine, heart or lung) be of so intimate and transitory a nature as continuously to elude detection until some necessary development and improvement of technique has taken place. By the same token antihistamine drugs must not be confused with histaminases. Their action may be more like that of atropine upon the mediation of muscular contraction by acetylcholine, effective only at certain sites and under certain limited conditions. They are not specific antagonists, and the term "antihistamine" is, in a sense, a misnomer.

Landmesser has concluded that curare probably causes bronchoconstriction where it does so by liberating histamine locally in the muscles of the bronchial tree. The evidence for this is cumulative—the similarity of action, the progressive discovery of histamine in curare perfusates, a diminishing efficacy of action comparable to the diminishing curare-liberation of histamine found (Alam *et al.*, 1939) in dogs, a certain inconsistency of the findings which is characteristic of physiological effects produced by histamine, and antagonism by "antihistamine" drugs. Not one of these pieces of evidence is conclusive; many different drugs have similar actions, the presence of histamine may be incidental, "antihistamine" drugs have other actions, among them an antagonism to acetylcholine. Cumulatively the presumptive evidence that something very like histamine pursues its pharmacological effects upon the bronchi when it has been locally released by an action of curare on muscle may now be considered to be fairly strong. Such a presumption is strengthened and not weakened by the "histamine reactions" of the skin following intracutaneous and intra-arterial injections of *d*-tubocurarine reported by Comroe and Dripps (1946) and their prevention by antihistamines (Grobb *et al.*, 1947).

If bronchospasm of histamine origin is in fact occasioned by injected curare, this substance joins with peptone shock and anaphylactic phenomena generally in a demonstration that the power of histamine can be exercised upon the human body with very little to show that it is the activating agent concerned. Histamine would have to enter the blood-stream in considerable excess for its presence to be detected in blood or urine, since normally histamine in circulation is rapidly destroyed both in man (Weiss *et al.*, 1932) and animals (Dragstedt and Mead, 1935). Curare bronchospasm may be taken as one more piece of evidence towards the possibility that true bronchial asthma may be caused by local histamine liberation. The similarity would consist in the release of histamine at a specific site in the body—the lungs—in quantities usually insufficient to produce general symptoms or to be detectable in the blood or urine, but highly effective in exciting a bronchospasm which yields to adrenaline and to some degree to atropine.

The possibility of the release of an entirely different, hitherto undiscovered, substance, or of a joint release of histamine and acetylcholine in asthma cannot, of course, be ignored; the successful potentiation of bronchospasm in asthmatics by injections of histamine (Weiss *et al.*, 1932; Curry, 1946) does not prove that a local accumulation of histamine alone is the cause of asthmatic bronchoconstriction. But if such should be the case the findings of Weiss are very interesting. They include not only the potentiation of asthma in bronchial asthmatics, bronchitics and emphysematous patients, but also the precipitation of bronchospasm in cases of "cardiac asthma", and in "normal subjects" increases of intracranial pressure and changes in the electrocardiogram of a type suggesting either deficient coronary circulation or faulty nutrition of the heart muscle. Such actions of injected histamine, if they also potentiated local releases of histamine in diseases of these organs, would allow for a variety of other "histamine-release illnesses" besides that of bronchial asthma. Such may be the case. It would not be unreasonable to suppose that with histamine, as with acetylcholine, the injected drug only produces a faint and diffuse shadow of its highly specific actions when it is released at an effective spot, such as the lung, heart, intestine, or skin.

It may thus be that our present antihistamine drugs, by lacking the potency to reach histamine at its point of action within the cell, withhold from us a weapon, not only in asthma, but in many other diseases as well. In the meantime, however, we shall be wise to remember that the substance which histamine potentiates in the asthmatic lung still remains essentially "x"; and the "antihistamine" drugs have, besides the limited actions against histamine which gave them their names, an action against acetylcholine and possibly also other actions, yet to be discovered and utilized.

BIBLIOGRAPHY

ALAM, M., ANREP, G. V., BARSOUM, G. S., TALAAT, M., and WEININGER, E. (1939) *J. Physiol.*, **95**, 148.

ANREP, G. V., and BARSOUM, G. S. (1935) *J. Physiol.*, **85**, 409.

BOEHM, R. (1895) *Arch. Exp. Path. Pharmak.*, **35**, 16.

COMROE, J. H., and DRIPPS, R. D. (1946) *Anesthesiology*, **7**, 260.

CURRY, J. (1946) *J. clin. Invest.*, **25**, 785, 792.

DE TAKATS, G., FENN, G. K., and JENKINS, L. (1942) *J. Amer med. Ass.*, **120**, 686.

DRAGSTEDT, C. A., and MEAD, F. B. (1935) *Proc. Soc. exp. Biol.*, **32**, 1435.

GRIFFITH, H. R., and JOHNSON, E. (1942) *Anesthesiology*, **3**, 418.

GROBB, D., LILIENTHAL, J. L., and HARVEY, A. M. (1947) *Johns Hopk. Hosp. Bull.*, **80**, 299.

HERXHEIMER, H. (1948) *Lancet* (i), 667.

HOLODAY, D. A. (1946) *Anesthesiology*, **7**, 428.

HUNTER, R. B., and DUNLOP, D. M. (1948) *Lancet* (i), 474.

JACKSON, D. E. (1917) Experimental Pharmacology, p. 196. London.

LANDMESSER, C. M. (1947) *Anesthesiology*, **8**, 506.

MAHFOUZ, A. (1949) Communication to the Society of Anæsthetists of Edinburgh, January 11.

SCHILD, H. O. (1948) Unpublished comm. to Brit. Pharmacol. Soc. July, *J. Physiol.*, **95**, 393.

WALDBOTT, G. L. (1947) *J. Amer. med. Ass.*, **135**, 207.

WEISS, S., ROBB, G. P., and ELLIS, L. B. (1932) *Arch. intern. Med.*, **49**, 360.

WEST, R. (1932) *Proc. R. Soc. Med.*, **25**, 1107.

—— (1935) *Proc. R. Soc. Med.*, **28**, 565.

—— (1936) *Lancet* (i), 12.

—— (1937) *Arch. int. Pharmacodyn.*, **56**, 88.

—— (1938) *J. Physiol.*, **91**, 437.

WHITACRE, R. J., and FISHER, A. J. (1945) *Anesthesiology*, **6**, 127.

Dr. H. Herxheimer: *Antihistamines in Bronchial Asthma.*

As the beneficial effect of antihistamines in bronchial asthma has been doubted, attacks of bronchial obstruction and bronchial asthma were induced by inhalation of histamine, mecholyl or allergenic extracts, and the protective effect of antihistamines was studied. Respiration and vital capacity during the attacks were recorded by a recording spirometer. It was found that in a number of normal and asthmatic subjects bronchial obstruction and

mild bronchial spasm could be effectively prevented by Phenergan or Anthisan given beforehand. An example is given in fig. 1. If a severe attack was induced, no protection was achieved. This is in accordance with clinical experience. The antihistamines have no influence in violent asthmatic attacks, but they are often able to protect the patient from recurrent nocturnal attacks in the mild chronic asthmatic state. The individually effective antihistaminic substance and its dosage must be found in each case by trial and error. When it has been found, night doses of antihistamines can be combined with day doses of ephedrine, whilst superimposed acute attacks can be checked by aleudrin. This combination has been used successfully in a number of patients who have been rendered fit for regular employment.

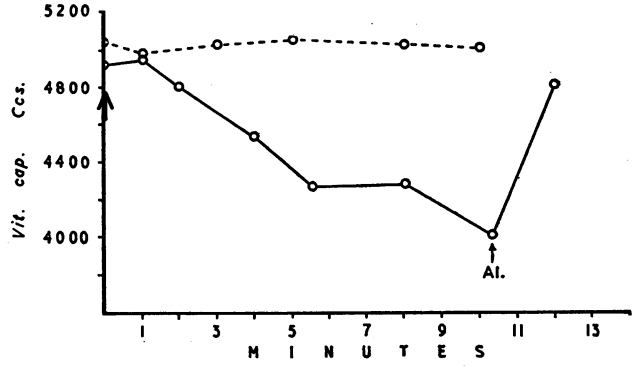

FIG. 1.—Case of mild asthma. At ↑ mixed pollens were inhaled for 5 seconds.
Full line: vital capacity falls after inhalation of pollen extract and asthma attack develops which is terminated by inhalation of aleudrin at A1.
Interrupted line: 25 mg. of Phenergan were given ninety minutes beforehand and the same experiment repeated. No symptoms of asthma developed; vital capacity unchanged.

[*May* 31, 1949]

JOINT MEETING WITH THE MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES

Recent Advances in the Study of Venereal Disease.[1] [*Abstract*]

By JOSEPH EARLE MOORE, M.D.
(*Baltimore, U.S.A.*)

THIS communication is a report of recent American advances in venereal disease research.

The prophylaxis of gonorrhœa.—Two United States Navy studies have shown that penicillin, orally administered, is of value in the prophylaxis of gonorrhœa. A single oral dose of 0·2–0·25 mega units, administered two to fifteen hours after potentially infectious exposure, reduces the incidence of gonorrhœa two to twelve fold from that in a control group.

Aureomycin, orally administered, is of value in the treatment of gonorrhœa.

SYPHILIS

Multiplication time of T. pallidum *in vivo.*—Two groups of independent workers have shown that the multiplication time of *T. pallidum* in the rabbit is thirty to thirty-three hours per single division.

Cultivation of T. pallidum *on artificial media.*—Actual cultivation of the virulent

[1]From the Johns Hopkins University and United States Public Health Service Venereal Disease Research and Post-Graduate Training Center. These investigations were supported by various grants-in-aid from the Research Grants and Fellowships Division, National Institutes of Health, United States Public Health Service.
The original article is to be published in the *British Journal of Venereal Diseases.*