Tuberculosis and Antihistaminics*

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I. General and Pharmacologic Considerations:

Synthetic antihistaminic substances, first discovered in 1933 by Fourneau and Bovet1 while seeking a means of combating the physiologic effects of histamine, have now been used in a large number of fields. The indications have been extended beyond the point of sound pharmacologic judgement and to this day reports are being published which are nothing short of fantastic.

Their mode of action, from the antianaphylactic standpoint, is based on the histamine theory of sensitivity (Lewis2) related in large measure to anaphylaxis, allergy, and to histamine poisoning. There is little doubt that histamine is an important factor in anaphylaxis in animals as in human allergy. In an individual in contact with an antigen to which he has been sensitized, a reaction occurs between antigen and its specific antibody which, liberating histamine or a substance analogous to histamine, provokes anaphylactic shock. Histamine is furthermore a chemical substance present under normal conditions in tissue and it has been shown by Katz3 that all allergic reactions provoke its liberation. In addition the various antihistaminic products react in such a fashion in anaphylactic conditions as to leave little doubt of the role played by histamine in accidents of this type. The still imperfect techniques which are used to measure blood histamine today in patients with allergic conditions do not allow confirmation, although the similarity of results in certain clinical conditions as well as in laboratories are certainly in favor of this hypothesis.

The activity of these antihistaminic substances is demonstrated in certain cases accompanying conditions of capillary permeability of which urticaria, angioneurotic edema, vasomotor rhinitis are examples while in other clinical conditions such as asthma or dermatitis, their indications remain restricted to cases where the allergic origin of the phenomena can be proved readily. In still other clinical states particularly in the area of the nervous system they do not act by virtue of their antihistaminic property but

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rather by those pharmacologic attributes which are apparent in other synthetic substances.

There are three general types of antihistaminic agents which have been recognized and listed by Bovet.4

1) Those products with selective properties related to histamine itself through the mediation of histaminergic substances of the pyridine group:
   a) derived from aminopyridine: neo-antegan, pyribenzamine, histadyl, chlorothene,
   b) derived from pyrimidine: neo-hetramine.

2) Those products which because they are analogous in structure and pharmacologic action are related to sympathetic poisons, and are either sympatholytic or sympathicomimetic:
   a) Phenol ethers: 929 F.,
   b) derived from the aniline group: 1571 F., antergan, diatrine,
   c) derived from the imidazoline group: antistine,
   d) derived from the tetrahydroprydendene group: theophorine.

3) Those products which are antagonistic to acetylcholine with antihistaminic action and severe spasmolytic properties:
   a) Benzyl ethers and its derivatives: benadryl, decaprine, histaphene, antadnil,
   b) derived from the phenotiazine group: phenergan (RP3277), amydril, pyrrozolate,
   c) diphenylaminopropane and derivatives: aspasan, trimetone.

All of these products have varying degrees of toxicity and in many instances are poorly tolerated in humans. The antianaphylactic power of these compounds as well as their action on the Schultz-Dale phenomenon does not parallel their antihistaminic action. Furthermore they all present certain pharmacologic properties which although varying in considerable degree may be summarized as follows:

a) They prevent the spasm of the smooth muscle of the uterus, intestine, and bronchi produced by histamine, through a reaction comparable to atropine but to a considerably less degree.

b) They prevent contraction and relaxation of blood vessels and by this means prevent increased capillary permeability.

c) They have a local anaesthetic action. This prevention of cutaneous reaction to histamine whether provoked by irritants or allergens can not be attributed to an antihistaminic effect if this local anaesthetic action can not be eliminated by other appropriate means (Loew*).

It is readily seen that these substances do not have a strict specificity, but this point is not really appreciated. On the other hand there is as yet no unanimity of opinion regarding the mechanism of antianaphylactic action.
II. *Tuberculous Allergy:*

In view of the efficiency of these different compounds in certain allergic conditions, it was but a short step to attempt their use in tuberculosis. It should be noted that the word allergy, introduced in 1908 by von Pirquet and used in the sense of “altered reaction” produced and continues to produce considerable confusion. Tuberculous allergy may be differentiated from the phenomenon of anaphylaxis on several different points as demonstrated in laboratory experiments. It is actually possible to provoke anaphylaxis to pure tuberculoprotein by injecting it into a laboratory animal free of tuberculous infection. On the other hand it is absolutely impossible to provoke an anaphylactic reaction in any animal already infected with tuberculosis and the reaction will be totally different.

In the normal animal sensitized to tuberculoprotein, an anaphylactic reaction will occur characterized by:

- An immediate acute response within 15 minutes,
- No cutaneous reaction, no Arthus phenomenon (Corper6),
- The reaction may be passively transferred,
- The reaction may be transferred to lineal descendants.

This reaction then is a humoral response due to circulating antibodies in blood and body fluids producing an immediate response. In the animal infected previously with tuberculosis there will be an allergy characterized by:

- No acute intoxication, requiring hours to produce a fatal reaction and appearing only after one, six or 24 hours,
- A definite positive cutaneous reaction,
- The allergic state is not passively transferred,
- The allergic state is not an inherited characteristic.

In the latter situation this is more of a tissue response, the antibodies present being fixed to the cell structure producing a delayed reaction. There are obviously two dissimilar reactions in tuberculosis. While the anaphylactic type of sensitization can be established through the injection of pure tuberculoprotein in a virgin organism, this same substance is a chemically extracted toxic material and does not produce the same reaction as the tubercle bacillus in vivo. The special allergic type of sensitization can be established only in an organism previously exposed to a bacillary infection and must be considered as a type of bacillary sensitization.

Certain investigators seem to consider these reactions as similar and believe that there is a common principle basic in these phenomena. It is felt that the different forms of sensitivity are effects resulting from the interreaction of antigen and antibody under
different physiopathologic conditions but probably liberating a homologous toxic substance. It is possible but not proved and up to this time not demonstrated that in the tuberculin reaction there is actually a liberation of histamine. If antihistaminic agents can have any effect in clinical tuberculosis it must be therefore by some other mechanism.

From what has already been presented it seems impossible at this time to say that there is a type of tissue or cell other than involuntary muscle or vascular endothelium which can be directly sensitized to an antigen-antibody reaction. This must be similar in all respects to those produced by direct action of histamine or a similar substance on the same organs in an anaphylactic reaction (Dale and Laidlow, and Rich). In tuberculosis, a type of bacillary sensitivity can exist in the total absence of all anaphylactic sensitivity to tuberculin. That is why one may say that in bacillary sensitization, involuntary muscle as well as vascular endothelium are not sensitized, a fact well proved in vitro and in vivo and that the antibody is bound up intimately in the individual cells. Therefore any tissue which does not have a good capillary bed can be sensitized to the action of the specific antigen in the bacillary type of sensitization but will not respond to the action of antihistaminics. On the other hand anaphylactic phenomena are produced only in tissues where a larger blood supply is present and will respond to the administration of antihistaminic substances. This may explain why in bacillary sensitization the circulating antigen in the blood can induce an inflammatory process, necrosis, or hemorrhage in any area of the organism which is involved and the focus of infection will show a "focal reaction," a rare occurrence in anaphylaxis described, however, by Arthus and explained by him as due to the use of an impure material.

Many authors feel that under certain circumstances in clinical tuberculosis a typical anaphylactic reaction to tuberculin may occur during infection, superimposed on the bacillary type of sensitization. Corper as well as others believe that this concept is only of academic interest in tuberculous animals as well as humans and is of so little importance as not to be worthy of too lengthy discussion.

Such a situation actually may be observed under the following circumstances:

1) In massive dissemination.
2) In pulmonary cortical types adjacent to pleura, a tissue extremely sensitive itself and with a large absorbable surface.

A considerable depression in cutaneous sensitivity may be produced, probably due to some effect on the vascular or inflamma-
tory response of the organism rather than to autotuberculinization or tuberculin autointoxication, for the liberation of tuberculin in the body has never been proved. This latter point is of considerable clinical importance and has not been too well recognized. These types of depressed reaction especially following massive dissemination are generally of short duration, followed as a rule by a temporary increase in tuberculin sensitivity, probably due to the mobilization of large numbers of tubercle bacilli. By virtue of their action on vascular tissue, antihistaminics may have some value in this area during the acute stage (vascular blockade?). However, recent experiences of Halpern and Reber on the influence of antihistaminics on the evolution of experimental microbial infection tend to prove that such employment of antihistaminics, in paralyzing the organization of local inflammatory defenses, favor microbial dissemination. This would tend to contraindicate the use of antihistaminics in local or focal infections. Actual experimental data in animals, infected with Salmonella typhimurium and treated with phenergan (RF3277), showed a mortality through septicemia three times higher than that in control animals.

Can one say then that in chronic forms of tuberculosis any type of desensitization is possible through the use of antihistaminics or by any other method? Desensitization as a form of treatment has been tried and continues to be utilized by a few clinicians. Utilizing Besredka's technique of injecting patients with progressively increasing doses of tuberculin, it has been possible to give as much as 10 cc. of undiluted tuberculin (Bauer10), an amount many hundreds or thousands of times that which the patient would have reacted to before sensitization. Is this however a true desensitization? It is rather an extreme tolerance because if desensitization with tuberculin produces an inhibition or alteration of sensitizing antibodies, this does not free the body of its bacilli which will resensitize the tissue as soon as treatment is discontinued and sometimes will provoke a much greater sensitivity in the immediate future. Actual tissue necrosis may occur at the site of tuberculin injection. The obvious importance of focal reactions, considered as a valuable feature in treatment in the past, need not be discussed here. If antihistaminics possess a similar desensitizing effect, should they not similarly be feared, rather than utilized?

III. The Use of Antihistaminics in Tuberculosis:

Although numerous investigators have utilized the antihista-
minic compounds: Rolland11 with antergan, Vallery-Radot, Hamburger and Halpern12 with phenergan, no real benefit from treat-
ment has been reported in France to date. In 1943 Boquet and Breton in their experimental trials were unable to demonstrate in guinea pigs a negative tuberculin response after prolonged subcutaneous injections of the earlier antihistaminic agents. Guyl was unable to obtain any effect in five patients by the use of large doses of pyribenzamine by mouth. Crip, Levine and Aaron could not influence the Mantoux reaction in tuberculous animals using pyribenzamine and rutin by oral route, intradermal injection, iontophoresis or the injection of a mixture of tuberculin and pyribenzamine.

The cutaneous reaction to tuberculin is obviously too variable to be considered as a precise test. It is influenced by meteorologic variations, the state of the peripheral vessels, the acquired sensitivity of the skin and many other factors. On the other hand, the antihistaminics having a local anaesthetic action may in themselves upset further the value of the test. For all these reasons the actual test result may be questioned.

The only optimistic report to date which does not accept within its framework the foregoing physiopathologic concepts, is that of Judd and Henderson presented before the American College of Allergists in April 1949. These investigators used benadryl, pyri-benzamine, theophorine and neohetramine in the different forms of tuberculosis both pulmonary and extrapulmonary. In the latter group there were cases of lymph node involvement, larynx, and one case complicated by erythema nodosum. Doses were given of 50 mgm. three times daily, increasing gradually up to a maximum of 500 mgm. according to the patient's tolerance. The patients were followed by tuberculin test, x-ray, pulse, weight, appetite and other subjective symptoms. A dramatic improvement was noted in the x-rays in some patients after a short period of treatment, and it was similarly possible to demonstrate the return of the pathological lesion if treatment was stopped with return of improvement as soon as treatment was again instituted. The sputum also was decreased and the cutaneous reaction seemed less positive throughout the period of treatment. The best results were apparently obtained in the exudative lesions while the fibrocaseous responded less well paralleling the action of streptomycin.

In some cases the antihistaminics were used simultaneously with streptomycin and the authors felt sure that the results with the combined drugs were better than if they were used separately. In the discussion Wittich indicated that other workers had found that neohetramine was effective for the protection of animals against experimental tuberculosis in approximately half the cases, although no specific action against the bacillus had been de-
monstrated in vitro. We have no personal knowledge of this quoted work. The hypothesis was projected that through the suppression of tuberculin sensitivity or some other product of the bacillus, the normal defenses would be better capable of combatting the infection.

In view of this enthusiastic report, through the cooperation of Merck and Company, the following combination of antihistaminic drugs were tried on 30 patients with tuberculosis; neo-antergan and the new product phenergan (RP3277) described by Halpern and Ducrot in 1948, whose action is considerably greater than that of all known antihistaminic substances and much more prolonged. This product had already been tried in France in 1947 by Vallery-Radot, Blamoutier and Halpern in tuberculosis without any influence on the allergic manifestations of tuberculosis or on the intradermal reaction to tuberculin.

No attempt was made in this study to choose special cases for treatment and among those included were cases with far advanced lesions while others had lesions of less importance either exudative or fibrocaceous.

The following dosage schedule was used: Three hundred mgm. of neo-antergan were given daily, divided into fractional doses through the day. In addition 25 mgm. of phenergan was given at bed-time because of the sedative and hypnotic effect noted in the use of this product. The patients noted almost immediately that sleep was considerably better since the use of the antihistaminics.

The compounds were well tolerated generally although there were occasional complaints of drowsiness, dizziness, headaches and dryness of the mouth. In two instances it was necessary to discontinue medication because of vomiting, nausea, vertigo, and in one, a severe tremor.

We have chosen to evaluate the treatment in our cases with the following criteria: X-rays, volume of sputum, sedimentation rate, weight, and subjective complaints. We have not used the skin reaction for the reasons of variability noted previously. The following is a summary of the results. It is to be noted that the results are given for only 28 of the 30 cases since in two cases, treatment was discontinued because of intolerance to the drug at an early date so that the treatment could not be evaluated.

<table>
<thead>
<tr>
<th></th>
<th>X-ray</th>
<th>Sputum Volume</th>
<th>Sedimentation Rate</th>
<th>Weight</th>
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<tbody>
<tr>
<td>Slightly Improved</td>
<td>8</td>
<td>5</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>No change</td>
<td>20</td>
<td>18</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Worse</td>
<td>5</td>
<td>8</td>
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During the course of treatment 12 patients received streptomycin just prior to or simultaneously with the antihistaminics in a dose of one gram daily for 28 days. It should be noted that in general the most suggestive radiologic improvement occurred in this group. Another two patients who did not receive streptomycin also showed significant improvement. The first was a case of diffuse acute pleurisy complicating pneumothorax where the sputum had been negative for approximately four months, and in whom the antihistaminics quickly reduced the temperature and fluid formation in less than six days. The second patient had exudative lesions in both upper lobes which showed only slight retrogression following a course of streptomycin in March 1949. When the antihistaminics were begun, the sputum became converted in one month, the most recent x-rays showing an almost complete clearing. It should be noted that this individual was an almost perfect bed rest case during this period.

CONCLUSIONS

While a large number of our patients may be said to have shown some degree of improvement it is difficult to evaluate these findings. All of us are familiar with the psychosedative effects of any new drug in tuberculosis in which the patient goes through periods of hope and despair. The volumetric decrease in the sputum can well be due to the atropine-like effect of the antihistaminic drugs. On the other hand the excellent soporific effect of phenergan may also play a certain role. It is necessary for us to conclude then that in our limited experience the antihistaminics whether alone or associated with streptomycin have not produced striking results in a trial of treatment of pulmonary tuberculosis. In this opinion we join the previous conclusions of the French investigators. An attempt will be made to choose a more select series for future investigation.

SUMMARY

1) The present knowledge of antihistaminics, particularly the pharmacologic considerations are presented.

2) Tuberculous allergy and tuberculous anaphylaxis are presented as widely different mechanisms and carefully differentiated.

3) Neo-Antergan and phenergan (RP3277) were given for several months in a series of thirty patients with tuberculosis. Although small changes in symptoms with slight improvement were noted in some cases, no definitive x-ray changes could be attributed to the use of these antihistaminics.

4) A further study using mainly cases with exudative lesions is planned.
REFERENCES


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