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PHARMACOLOGICAL ACTION OF ANTIHISTAMINE COMPOUNDS*

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We owe the development of a specialized group of compounds known as "antihistamine compounds" to the Swiss pharmacologist Daniel Bovet, who worked in the Institut Pasteur in Paris. Although he recorded preliminary observations in 1937, his first full paper was published in 1944 (Bovet, 1944). There are three highly active substances present in the body—adrenaline, acetylcholine, and histamine—and antagonists to the first two of these have long been known. Some of the ergot alkaloids and synthetic compounds such as "priscol" are anti-adrenaline compounds, while atropine and synthetic compounds like "trasentin" are anti-acetylcholine compounds. Bovet's contribution was to devise tests by which antihistamine compounds could be recognized, and to foresee that the more highly active substances would have a clinical application in allergic states like hay-fever and urticaria.

The pharmacological work which has been carried out on antihistamine compounds in the last few years has shown that these are not highly specialized substances with unusual properties as has been commonly believed, but that they share properties with well-known drugs like atropine, procaine, quinidine, and pethidine, and that these substances in their turn can exert an antihistamine action. I propose to describe briefly how this work has developed and its practical consequences, and to suggest the basis which underlies the results.

In 1945 Dr. G. S. Dawes was working in my laboratory to find substitutes for quinidine, and made the important observation that several substances having a quinidine action on cardiac muscle were also local anaesthetics (Dawes, 1946). Thus cocaine, procaine, and amethocaine were among these substances. This observation recalled the fact that quinine and quinidine are both local anaesthetics, and thus it appeared there was a close relation between power to prolong the refractory period of cardiac muscle and local anaesthetic action. This was not all. Dawes then observed that various substances used as spasmolytics to relax smooth muscle, such as atropine, papaverine, trasentin, and "syntropan," also had a quinidine-like action on the heart. All these substances were also known to have local anaesthetic action. Finally, he examined the analgesic substance pethidine, and found that it exerted a quinidine-like action on the heart and possessed a local anaesthetic action. Thus Dawes's work suggested that the power of lengthening the refractory period, local anaesthetic action, spasmolytic action, and analgesic action were related to one another in many compounds.

*Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Liverpool, 1950.

Anthisan and Histostab

In 1946 we obtained a specimen of the antihistamine substance "neoantergan," as Bovet called it, or "anthisan," and it occurred to me that we should examine it to see if it fell in the category of these substances. Would it have a quinidine-like action, prolonging the refractory period of cardiac muscle? My colleagues Dews and Graham (1946) found that it did; indeed, they found that neoantergan was twice as active as quinidine. Would it have a local anaesthetic action like procaine? It was found that it had this action also, being three times as effective as procaine when injected into the skin of a guinea-pig. Would it have an analgesic action like pethidine? It was found that it possessed not only an analgesic action but a general narcotic action, though the dose required was as large as 100 mg./kg. Thus its analgesic action was weak, for pethidine produced analgesia in a dose of 5 mg./kg. We were thus able to demonstrate that neoantergan was not only an antihistamine substance, but that it possessed properties in common with quinidine, procaine, atropine, papaverine, and also pethidine.

An extension of this investigation to other antihistamine substances was later carried out by my colleague Dutta (1949b). He compared "histostab" (also known as "antistin") and "benadryl" with procaine as local anaesthetics, and found that histostab was 2.3 times and benadryl 3.2 times as potent as procaine. He compared the same substances with quinidine for power to prolong the refractory period of the auricle, and found that each was about twice as active as quinidine. He showed that, like procaine and quinidine, histostab and benadryl reduced the action of acetylcholine on the heart and on skeletal muscle, both in the frog and in the rat. He showed a similarity of action on the perfused superior cervical ganglion.

The observations thus made have greatly clarified one aspect of drug action, since they have shown that many substances used for quite different purposes in medicine and hitherto thought to have quite dissimilar modes of action have many common properties, and that among these substances are the antihistamine compounds.

Side-actions of Antihistamine Compounds

The first practical consequence of this conclusion so far as antihistamine compounds are concerned is that it is clear that they will all cause side-actions. Since benadryl, for example, has properties in common with atropine, we must expect that benadryl will cause some dryness of the mouth. Since benadryl has properties in common with the analgesic pethidine, we must expect that benadryl will cause some degree of central depression and mental confusion.

What applies to benadryl must apply to a greater or less extent to all the other antihistamine compounds, and none will be free from side-effects in sensitive persons.

The second practical consequence of this conclusion is that antihistamine compounds will have many other actions than those in which they obviously antagonize histamine.

I have pointed out that they resemble atropine, but since they combine a power to dry up secretions with central depression it would be more correct to say they resemble atropine's near relation hyoscine. It can therefore be said at once that antihistamine compounds should be of value in sea-sickness, as during the war hyoscine was demonstrated to be the best available remedy for that condition. The substance of which benadryl is the hydrochloride when united to chlorotheophylline is known as " dramamine," and that has been shown to be effective in all forms of travel sickness, sickness due to pregnancy, sickness following irradiation, and sickness after operation on the labyrinth. What we do not know at the present time is whether dramamine is better than hyoscine, and whether its side-effects, when taken over a period of days, are more or less severe. The point is important, because dramamine is very much more expensive than hyoscine. The only comparison so far made is that by Chinn and Oberst (1950), which indicates that hyoscine is more effective in controlling air-sickness. Another consequence of the resemblance of antihistamine compounds to atropine and hyoscine is that they are useful in Parkinsonism, in which they relax the spasm of skeletal muscles.

The action of antihistamine substances in aborting the common cold if given early enough has been believed to indicate that the initial phase of the cold is an allergic reaction due to histamine. It is, however, possible that this is also an atropine-like action, for atropine appears to abort some cases of common cold when given early.

I have pointed out that the antihistamine compounds resemble quinidine and quinine in their action in prolonging the refractory period of heart muscle. There is no doubt that benadryl, anthisan, antistin, and other compounds could be used to restore a normal rhythm in patients with auricular fibrillation. So far as I am aware this has not been tried, but it is a reasonable deduction from the pharmacological evidence that the trial would be successful. They have, however, been used in a condition which can be regarded as similar, which arises in skeletal muscle. That is to say, they have been used in myotonia, a disease in which the contraction of the muscle is prolonged, so that in shaking hands, for example, there is much delay in releasing the grasp. There is an abnormal stream of impulses from the motor end-plate which maintains the contraction unduly. The usual treatment is to give quinine, which is thought to act as it acts in auricular fibrillation, by prolonging the refractory period, and so renders the stream of impulses ineffective. My former colleague Dr. Lawrence Bussell (1949) has described the relief of the symptoms of myotonia with benadryl and also with anthisan, thus providing clinical evidence of their similarity to quinine.

If the antihistamine compounds resemble in their properties substances like atropine, pethidine, procaine, and quinine, then, conversely, these latter substances should exert an antihistaminic action. My colleague Dutta (1949a) has shown that they have such an action when tested on the guinea-pig for their power to depress the bronchoconstrictor action of histamine. He found that atropine and pethidine had more than one-tenth the activity of histostab or benadryl; procaine and quinidine were much less active, having only 1/100 and 1/400 of the potency of histostab. The observations bring to mind the recent use of intravenous procaine for the release of bronchial spasm in man. They suggest that intravenous pethidine would be much more effective than intravenous procaine. Procaine is, however, a safe substance for intravenous use, since it is rapidly destroyed in the body, *p*-aminobenzoic acid and diethylaminoethanol being formed by cleavage; larger amounts are, however, required than would be required of a substance like pethidine.

The Properties of Acetylcholine

What is the explanation of the similarity of the properties of so many medicaments? Dawes furnished a hint to explain the similarity between quinidine, procaine, and quinine, for he pointed out that in all forms of muscle—skeletal, cardiac, and smooth—they were antagonists of acetylcholine, and their common properties might depend on this antagonism. Elio then examined a series of other substances which had a quinidine-like action, and found that they too antagonized the action of acetylcholine on different forms of muscle, including the muscle of the blood vessels. Stephenson (1948) added to the list the alkaloid conessine and its isomers; they acted like quinidine on the heart, were local anaesthetics, and antagonized the action of acetylcholine in all forms of muscle. Dutta and I (1948) then showed that a selection of these substances which included atropine, benadryl, pethidine, procaine, and quinidine, when examined on the blood vessels of the rabbit ear, inhibited the action not only of acetylcholine but of adrenaline and of histamine as well.

We are so accustomed to look upon acetylcholine and adrenaline as antagonists and of histamine and adrenaline as antagonists that it is difficult to think of these three as related substances linked to one another in their actions. But as long ago as 1930 Dale and Gaddum (1930) showed that in denervated skeletal muscle the action of acetylcholine could be either potentiated or inhibited by the action of adrenaline. It is this kind of relation which now appears to exist in many tissues of the body.

There is evidence that in the heart, in the intestine and other smooth muscle organs, and in the central nervous system the synthesis of acetylcholine proceeds continually and may be responsible for the activity of the organ. Thus in the auricles of the heart the synthesis seems to be responsible for maintaining the rhythmic contractions. There is evidence of a similar synthesis in blood vessels, where it may be responsible for vascular tone. We commonly think of vascular tone as due to nervous impulses, forgetting that, though tone is lost when the nerves are cut, it is rapidly regained in a few days, although the nerves degenerate. It may be that the acetylcholine synthesis is the basis of the normal function in all these tissues, and that the effect of the acetylcholine so produced is modified, being either potentiated or inhibited, by histamine and adrenaline, which may also be synthesized, or possibly are liberated by the nerves.

Thus the conception forms in our minds of acetylcholine, adrenaline, and histamine acting as local hormones and governing tissue activity in many organs. We then begin to see why substances such as anthisan, which inhibit one of them, in some degree inhibit all of them, and why such substances have many properties. They may prolong the refractory period of the heart muscle, neutralize the action of histamine in the nasal mucous membrane and in the skin, and exert a depressant action on the vestibular apparatus in the central nervous system. For in all these

and other functions substances like anthisan, procaine, and quinidine are inhibiting the effect of the local hormones.

Summary

Many substances used medicinally as local anaesthetics, as analgesics, and as spasmolytics have common properties, among which is included the ability to act like quinidine on the heart. Antihistamine compounds also belong to this large group of drugs. The side-effects they produce are therefore to be expected. They can also be used for other purposes—as local anaesthetics, as quinidine substitutes for fibrillation, as quinine substitutes for myotonia, for travel sickness, and to relieve pain. Similarly, local anaesthetics such as procaine, or analgesics such as pethidine, have an antihistamine action which is considerable.

The basis of these common properties is that the substances which possess them depress the effects of acetylcholine, histamine, and adrenaline; these substances control activity locally in many tissues.

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CONGENITAL HEART DISEASE*

A REVIEW OF ITS CLINICAL ASPECTS IN THE LIGHT OF EXPERIENCE GAINED BY MEANS OF MODERN TECHNIQUES

BY

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[WITH SPECIAL PLATE]

PART II

Atrial Septal Defect

There were 35 cases of A.S.D.—12 male and 23 female. Their ages ranged from 5 to 61, eight being under 14, six being adolescent, and 21 adult. There were no symptoms in 20, and only slight breathlessness or difficulty in keeping up with others in 10. Of the remaining five, two had Lutembacher's syndrome and were in congestive failure; one had severe hypertension resulting from polycystic kidneys, and two had considerable limitation of cardiac reserve. Only one had haemoptysis.

The physical signs included a small or normal pulse, a normal or high normal jugular venous pressure without exaggeration of the *a* wave, a tapping cardiac impulse, a lifting right ventricular outflow tract, visible or palpable pulsation of the pulmonary artery, a pulmonary systolic murmur with or without thrill, a pulmonary diastolic murmur, and wide splitting of the second heart sound at the pulmonary area without accentuation of the pulmonary element.

A thrusting hyperdynamic cardiac impulse, as described by Roesler (1934), simulating the left ventricular thrust of patent ductus or V.S.D., was felt in five cases and was attributed to a grossly overfilled right ventricle forming the apex beat of the heart. A lifting right ventricular outflow tract or palpable right ventricular conus could be appreciated in the third and fourth intercostal spaces to the left of the sternum in most cases, and explained the precordial bulge of the chest wall that might be seen in this situation. Visible or palpable pulsation of the pulmonary artery in the second left space was also common; but neither this nor the palpable conus was well documented. Precise figures for their incidence are therefore not given.

Although the systolic murmur was classed as pulmonary, being usually best heard in the second space, it was maximal in the third space in six instances. It was accompanied by a thrill, usually rather faint, in nine. In four cases there was a loud mitral systolic murmur and in eight a mitral diastolic murmur; but only two of these had other evidence of Lutembacher's syndrome. Nevertheless, all mitral murmurs in A.S.D. were attributed to mitral valve disease, presumably rheumatic.

Functional pulmonary incompetence occurred in half the cases. In respect of the size of the shunt there was no difference between those with a Graham Steell murmur and those without.

Noticeable splitting of the second heart sound was characteristic and was heard in practically all cases. The split was usually distinctly wider in A.S.D. than in normal controls, but there was some overlap between the two. The intensity of the pulmonary element was commonly normal, not accentuated. The wide split was attributed to right bundle-branch block or to delay in the emptying-time of a grossly overfilled right ventricle.

The electrocardiogram showed the pattern of partial or well-developed right bundle-branch block in all but two cases, and the S wave in Lead V_1 was never conspicuous (under 5 mm.). The secondary R wave in Leads V_1 or V_2 was rarely very tall. The only case that showed a really high R wave had a considerable degree of pulmonary hypertension.

Skiagrams revealed right ventricular enlargement, dilatation of the pulmonary artery, and pulmonary plethora in varying degree in all cases, as described by Roesler (1934) and by Bedford, Papp, and Parkinson (1941). Skiagrams in the antero-posterior view were often difficult to distinguish from those of V.S.D. or patent ductus; but in the second oblique position the chamber responsible for the enlargement could usually be recognized.

Cardiac catheterization was undertaken in 25 cases (Table IV). The mean pulmonary artery pressure was

TABLE IV.—*Atrial Septal Defect*

Case No.	Age	Mean Pul. Art. Pressure (mm. Hg)	O_2 Saturation			Ratio of Pul. to Systemic Flow	Pul. Resistance $\left(\frac{\text{P.A. Pressure}}{\text{Pul. Flow}}\right)$
			S.V.C.	R.A.	P.A. R.V.		
1 H	16	13	70	83	85	2·5:1	1·1d
3 1	24	18	68	80	81	2·5:1	1·4
4 9	36	12	58	80	81	2·7:1	0·9d
5 11	16	8	63	82	81	2·5:1	0·6d
6 24	51	16	59	81	82	3:1	1·0d
8 44	14	13	62	—	76	1·8:1	1·5
10 47	6	10	64	78	83	2·5:1	0·8d
11 63	12	17	67	76	78	1·6:1	2·0
12 78	35	6	71	81	82	1·8:1	0·7d
13 79	12	64	52	70	68	1·6:1	8·0*
14 95	18	13	62	85	85	3·2:1	0·9d
15 97	16	14	68	86	90	4:1	0·7d
16 109	14	7	71	81	89	3·5:1	0·4d
17 111	5	10	69	85	85	3:1	0·7d
18 118	29	6	65	88	90	4·5:1	0·3d
19 148	53	12	67	82	82	2·3:1	1·0d
20 149	5	13	69	86	87	4:1	0·7d
21 150	30	6	71	88	88	3·2:1	0·4d
23 159	21	18	63	81	84	3·3:1	1·4
25 162	18	13	73	82	85	2:1	1·3

* Increased pulmonary resistance. d = Diminished pulmonary resistance.
(No attempt to enter the pulmonary artery was made in 5 cases; these have been omitted from the Table).

*Conclusion of the St. Cyres Lecture delivered on June 13 at the Royal Society of Medicine under the auspices of the National Heart Hospital. Part I appeared in last week's issue.