BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 7 1948

ANTIHISTAMINE SUBSTANCES*

BY

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As one of those who took part in the recognition of histamine in nature and in the first detailed examination of its intense physiological activities, I shall try to avoid the temptation to be unduly reminiscent. I may just remind you that at that time, nearly 40 years ago, much interest in circles concerned with experimental pathology was centred on the syndrome of the anaphylactic reaction and on the curious differences which it presented in the different species. You can imagine that Laidlaw and I (Dale and Laidlaw, 1910, 1911) had to discipline our eagerness as we examined one by one the actions of histamine on the different organs and systems of the dog and the guinea-pig in particular, and found them fitting neatly, like units of a jigsaw puzzle, into the contrasting pictures of the anaphylactic reactions in those two species as others had then recently described them. Biedl and Kraus (1910) had already drawn attention to the close correspondence—even closer, in fact—between the contrasted reactions of the normal dog and guinea-pig to intravenous Witte's peptone and those of the anaphylactic dog and guinea-pig to the reinjection of the antigen. I well remember Biedl's account of this at the International Physiological Congress in Vienna in 1910; and my own description later in the same programme of the newly discovered and, except for a few points, identical effects of histamine on the same two species. There was, of course, an obvious probability that a correspondence at so many points would have some significance, but it was difficult to guess just what it might mean. It certainly did not mean, what some were too ready to assume, that histamine was the hypothetical "anaphylatoxin" of which there was then so much talk, as a poison supposed to be liberated in the blood by some kind of enzymatic cleavage of the reinjected antigen; for there were features of the anaphylactic and peptone shocks which were not represented in the actions of histamine, such as the gross swelling of the liver and the failure of the shed blood to clot, and Laidlaw and I thought, and said, that these gaps must be taken into account in any discussion of the meaning of the general correspondence.

That, of course, is ancient history, and a great deal has happened since to clarify what was then obscure. Fortunately there have been several most valuable reviews of the all too abundant literature. I may mention the monograph of Feldberg and Schilf in 1930, Gaddum's (1936) monograph on vasodilator substances, and quite recently a review-lecture by Gaddum (1948), full of suggestive thought, dealing chiefly with later and contemporary work. Let me just indicate what seem to me a few of the landmarks of progress on the way to the present position, and then mention certain outstanding problems which seem to be

worth further attention, if only to provide us with a more completely rational basis for the use of the so-called anti-histamines with which to-day's discussion is largely concerned.

Landmarks of Progress

First, as to the pharmacological action of histamine, I suppose that we shall now agree that it is a general stimulator of the tone and rhythm of plain muscle in most mammalian species, the *Muridae* presenting an exception; and then that the vasodilator-depressor action which it produces so conspicuously on intravenous injection into certain species, including the human, is due to a special inhibitor action on the tone of minute blood vessels, involving always the tone of the capillaries and extending in some species, man among them, but to different levels in the different species, on to the ultimate arteriolar branchings. The involvement of the capillaries, and the resulting permeability of their walls if the action is powerful, came to light when Laidlaw, Richards, and I resumed the study of the action of histamine in the middle of the first world war under the stimulus of the demand for any light which experimental work could throw, even obliquely, on the obscure problems of wound shock, a demand which was naturally revived in the second world war. Concerning our work (Dale and Richards, 1918; Dale and Laidlaw, 1918) in 1917-18, I should just like to note, in passing, the useful and stimulating coincidence with our conclusions at that juncture of those reached by others who were then working on similar reactions. Krogh (1929), as we learned a little later, was already engaged on his more general study of the variable tone of the capillary vessels; Lewis, Cotton, and Slade (1917) had already published a year earlier the initial stage of what became Lewis's classical studies of the "threefold reaction" of the small blood vessels of the human skin to various injuries; and, still more aptly for our immediate purpose, Sollmann and Pilcher (1917) had just shown that application of histamine itself in high dilutions to the human epidermis after microscopic breaches of its surface caused local capillary dilatation and weal formation. We ourselves, being impressed by the analogy, pointed out that a not too destructive local injury, such as a blow from a whip or cane, would produce a closely similar local vascular effect, just as the generalized effects of histamine on the blood vessels which we were describing resembled those of a generalized tissue injury.

What was known of the pharmacological actions of histamine was thus already sufficient to arouse a suspicion that its release in response to injury of tissue cells *might* account for a substantial part at least of the resulting vascular and other reactions, whether the injury was produced by mechanical trauma, by corrosive or precipitant

*Read in opening a discussion in the Section of Pharmacology at the Annual Meeting of the British Medical Association, Cambridge, 1948.

chemicals, or, in an anaphylactic subject, by the specific antigen. For by that time I think it was generally agreed that the anaphylactic condition was due, at least in the main, to the predominant attachment of a precipitating immune substance to the tissue cells, and that the different symptomatology of the shock in different species was due to the way in which this sensitizing antibody was allocated among the cells of the different organs—being mainly attached to those of the liver of the dog, and mainly to those of plain muscle in the guinea-pig. We were not yet entitled, however, to indulge in any definite theories about such a release of histamine, since we had no real evidence so far that it was a constituent of normal tissue cells; we had only the early finding of it by Barger and myself (1911) as a constituent of intestinal mucosa, which we could hardly regard as a typical tissue for this purpose. Most of a further decade was required, then, before the evidence from different sources once again converged to a new point of advance. We had the resumption of the brilliant series of experiments, chiefly on human skin, by Lewis and his team, producing cumulative evidence of the release by the various kinds of mild injury of something having all the observable properties of histamine, but always by them called "H-substance" with a truly scientific caution. I think there can be little reason to doubt that they were dealing with histamine itself, either free or in loose association with some more complex vector.

I suppose that everybody working with this group of phenomena had in mind the possibility that the effect of the specific antigen on the cells of the anaphylactic animal might be to cause histamine to appear. I, rather perversely perhaps, had myself been inclined (Dale, 1919) for a time to discount it, pointing out that for aught we knew the action of histamine itself might be to produce an aggregating effect comparable to that which we had reason to impute to the reaction between anaphylactic antigen and cell-fixed antibody. Abel and Kubota (1919) had favoured the idea that histamine was somehow concerned, but I believe that it was Lewis (1927) who, having seen a dermal allergic reaction and recognized the characteristic "threefold response," first definitely attributed the effect to the appearance of histamine, or, more strictly, "H-substance." It was at this point, however, that there was once again such a convergence of researches; for at that same period an irrelevant side issue had led me to organize with Best, Dudley, and Thorpe (1927) an effort to obtain unequivocal evidence regarding the nature of the substances with histamine-like actions extractable from different fresh tissues—liver first, then lung, then muscle, then spleen. In all cases it was histamine itself, detachable without any drastic treatment from more complex materials, its tendency to cling to which had apparently misled earlier workers. So that it did not seem necessary to suppose, as Abel and even Lewis had been inclined to do, that histamine was *formed* in response to injurious stimuli, including that of the anaphylactic antigen, or allergic haptene; it was there already, held inside the cell in inactive association, and we had only to postulate its release. And then that chapter seemed to be rounded off and completed when Dragstedt and his associates found histamine in the lymph flowing from the dog's liver in the anaphylactic shock (Gebauer-Fuelnegg, Dragstedt, and Mullenix, 1932), and Feldberg with his team found it appearing in the effluent from the perfused lungs of an anaphylactic guinea-pig (Bartosch, Feldberg, and Nagel, 1932) when the antigen was added to the inflowing saline solution and evoked the bronchial constriction.

All this evidence, of course, left it not only possible but practically certain that active and normally intracellular

constituents other than histamine would also be liberated with it. We know now, for example, that heparin is liberated from the liver by peptone or the anaphylactic reaction to make the blood incoagulable. Histamine, however, is by a long way the most potent in pharmacological action of any such cell constituents as are known, and it is the one which particularly concerns the present discussion. Let us consider, then, some points concerning the manner of its release which bear on our problem, and others on which more evidence would be of value.

Mode of Histamine Release

1. Consider the relationship between the cells from which histamine is released—the sensitized cells on which the antigen or haptene acts in the case of the allergic reactions—and those which react to the released histamine, producing the familiar syndrome. The cells which release histamine and those which respond to it may be identical, as they probably are when sensitized plain muscle encounters the antigen, and we may plausibly picture this as a reaction to histamine internally liberated and speak of it as a response to *intrinsic* histamine. On the other hand, when histamine is released in the liver it is obviously carried widely by the circulation to other histamine-sensitive tissues, causing a general vasomotor collapse and stimulating the plain muscle of remote organs. Even when the injury releases histamine from epidermis or nasopharyngeal epithelium it is not the epithelial cells which respond to it but the subjacent vascular plexus, which thus reacts to *extrinsic* histamine. It will be clear that the antagonism of an antihistamine, whatever the precise mechanism of its action, may be widely different against histamine from within and histamine from without. There might obviously be analogies with the action of atropine in suppressing readily certain effects of acetylcholine applied from without while leaving practically unchanged corresponding effects of its release from nerve endings. There is an even closer analogy in Schild's observation that the guinea-pig's sensitized plain muscle can be made tolerant of excess of histamine in the surrounding fluid so that it gives no response to further additions of histamine to the bath but still responds to the specific antigen—presumably, therefore, to *intrinsic* histamine. Such considerations may throw light on the relative effectiveness of antihistamines in urticaria and vasomotor rhinitis on the one hand and in spasmodic asthma on the other. The point is at least worth discussion in the light of clinical experience of the relative values of these drugs in different types of allergic reaction.

2. I think that we need more evidence yet concerning the manner of the release of histamine which might furnish more details to show whether, when so liberated, it is in free solution or associated with larger molecules as an "H-substance." Even if we accept the view that disturbance of the colloidal dispersion of the protoplasm liberates the histamine we still need more evidence whether it does so directly or by setting in action some enzyme system to which the actual liberation of histamine is due. Rocha e Silva's evidence that pure trypsin has this action is highly suggestive (Rocha e Silva and Andrade, 1945; Rocha e Silva, 1946), as are the earlier observations of Feldberg and Kellaway (1938) on the special factors concerned in the generally similar effects of cobra and bee venom. Kellaway's recent lecture (1947) gives a valuable review. We ought to know more, too, about the apparent new formation of "histamine" in scalded mice as recorded by Dekanski (1945).

3. We need still more information about the form in which histamine circulates in the blood. Estimates of histamine extracted from whole blood must, I think, be difficult

to interpret physiologically. The blood is a tissue, and histamine held inactive in its cells need have no different functional significance from that locked up in the cells of solid tissues. Code's (1937) work in my laboratory seemed, at the stage which it reached, to be pointing to the eosinophil cells as the source of most at least of the histamine extractable from normal blood; and, though it is also true that the abundant layer of platelets obtainable from citrated rabbit's blood seems to be the rich source in that species, I venture to suggest that a more critical haematology might throw light on the still rather curious anomaly that rabbit's whole blood yields so much more histamine than that of other common species. Another point which would, I suspect, repay further investigation is that of the possibility of the formation of histamine from proteins by hydrolysis, whether by enzymes or by heating with acids (cf. Abel and Kubota, 1919). I believe that it would be useful to have more definite evidence on the extent to which solutions containing "incoagulable" protein products can be heated with acid with a certainty that the histamine found in the product will be only that which was preformed in the original blood or other material.

4. Lastly, it seems to me that it might have an important bearing on our conception of the proper and safe use of the antihistamines if the evidence for the concern of histamine in the vasodilatation of normal functional activity were clearer and more consistent. I raised the question of this as a possibility in a lecture in 1919, pointing out how the relaxation of capillary tone by histamine would make it the ideal agent of a fine adjustment of the circulation to local metabolic needs if we had evidence that it existed in the tissue cells and that it was liberated by their normal activity. We have evidence of its presence now, but the evidence produced by Anrep and his colleagues for its liberation from active muscle still lacks confirmation. I need hardly point out that failure to detect an increase of it in the venous blood does not of necessity exclude the possibility of its local liberation and local action. It might, however, suggest the possibility that in relation to antihistamines it would behave more like "intrinsic" than "extrinsic" histamine. In any case, I suggest that further attempts to settle the matter, perhaps by experiments under conditions not so close to those of natural circulation, might provide useful information, and that clear evidence on this point might give valuable warning or reassurance concerning the use of the antihistamines in practice.

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CAFFEINE AND GASTRIC SECRETION

BY

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The effects of caffeine on gastric secretion have recently been investigated in animals and in man by Roth and Ivy (1944a, 1944b, 1944c) and by Merendino *et al.* (1945). It has been shown that, although there is a wide variation in sensitivity between species, caffeine stimulates gastric secretion in man, cat, guinea-pig, and dog. Man is relatively sensitive to this action of caffeine, while the dog is rather resistant. The effect is probably exerted directly on the parietal cells.

Roth and Ivy (1944a) showed that the intravenous injection of 65–125 mg. of caffeine into cats anaesthetized with chloroform provokes a secretion of acid gastric juice for about 45 minutes. Later they reported (Roth and Ivy, 1944c) that caffeine and histamine act synergistically in stimulating gastric secretion in the cat. The effect was considerable, and in one animal a previously ineffective dose of histamine stimulated secretion of highly acid juice after injection of caffeine. The doses of caffeine used were themselves large enough to cause a secretion of acid gastric juice, and it was desirable to determine whether the effect of histamine was potentiated by smaller doses of caffeine which did not stimulate gastric secretion. This was particularly necessary, since doses of 125 mg. of caffeine are bordering on the toxic for the cat, and attempts to repeat the experiments of Roth and Ivy often resulted in early death of the animal. At the same time theobromine and theophylline have been compared with caffeine in respect of this relation to histamine.

Methods

The cat, anaesthetized with sodium pentobarbitone intraperitoneally, was prepared for continuous drainage of gastric juice by Roth and Ivy's (1944a) modification of Lim's (1923) method. Ligatures were tied around the cardia and duodenum and a cannula was inserted into the stomach through the pylorus (see Wood, 1948). Juice was collected in graduated centrifuge tubes, and the free and total acid was estimated by titration with N/50 sodium hydroxide, using thymol blue as indicator for both end-points.

One hour after the completion of the preparation, secretion being basal (less than 0.05 ml. in 10 minutes), histamine acid phosphate was injected subcutaneously in a dose equivalent to 0.27–0.65 mg. of histamine (about 0.18 mg. per kg. of body weight). The resultant secretion of juice was measured at intervals of 10 minutes until the basal level of secretion returned.

The particular xanthine compound was then slowly injected intravenously over a period of two to five minutes. Solutions (1 or 2%) of caffeine sodium benzoate, theobromine sodium salicylate, and theophylline sodium acetate were used containing respectively about 1/2, 1/2, and 5/9 of caffeine, theobromine, and theophylline (w/w). Doses of caffeine were 10–20 mg. per kg. (20–75 mg. total dose), of theobromine 20 mg. per kg. (34–54 mg.), and of theophylline 20 mg. per kg. (42–62 mg.).

Two groups of experiments were done with caffeine. In one group of seven cats the second dose of histamine, the same as the first in any one cat, was injected 40–60 minutes after caffeine. This interval allowed enough time for any possible stimulant action of caffeine to pass off. Caffeine itself caused a significant increase in secretion in only three