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THE METABOLISM OF HISTAMINE*

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A lecture on histamine published three years ago (Gaddum, 1948) showed that, in spite of much work, there were many gaps in our knowledge of this substance. Since that time some progress has been made, but there is still much that we do not know. We do not know whether histamine is to be regarded as an essential part of the normal machinery without which the body would not work, or whether it is a substance which appears only as part of the response to injury. We know that the body of a cat, for example, contains enough histamine to kill the cat, but we do not know why it does not normally do so. We imagine that the histamine must be stored in combination with something else which inactivates it, and suggestions have been made about how this is done, but no one has isolated the compound which we imagine to be formed. We do not know where the body histamine is formed or why some tissues contain much more than others. The pharmacological actions of histamine can be summed up by saying that it causes a contraction of most plain muscles, a dilatation of capillaries, and secretion of most glands, and particularly of the acid-secreting glands in the stomach. There is no need to say more about these pharmacological actions, except to acknowledge our debt to the guinea-pig, whose plain muscles are so very sensitive to histamine. Most of our knowledge about the metabolism of histamine depends upon pharmacological assays using guinea-pigs' plain muscle.

Antihistamines

The antihistamines, which have done so much to attract attention to histamine in recent years, antagonize all its effects except that on the gastric juice. They may be used in evidence for or against the theory that any particular phenomenon is due to the release of histamine, but if so used they must be used with care. In addition to their actions against histamine, many antihistamines have a local anaesthetic action, actions like atropine and quinidine, and a depressant action on the central nervous system. A phenomenon which is abolished by an antihistamine may thus, for example, be due to the release of acetylcholine. Some of the antihistamines are, of course, more specific than others. The one which was originally known as "neoantergan," and has now been officially christened mepyramine, is more specific in its action against histamine than atropine is in its action against acetylcholine. If any phenomenon is abolished by mepyramine, the possibility that

it is due to the release of histamine must be seriously considered, but should not be accepted without further evidence. It should also be abolished by other antihistamines more easily than by atropine, and, if possible, there should be direct evidence that abnormal amounts of histamine can be detected by suitable tests in fluids which have been in contact with stimulated tissues.

It might be thought that an effect which is not abolished by an antihistamine cannot be due to the release of histamine, and there is indeed some force in this argument. It is not, however, conclusive, as there are various nerves which are thought to act by liberating acetylcholine, although their effects are not abolished by atropine (Dale and Gaddum, 1930). This question has been discussed by Sir Henry Dale (1948), who comes to the conclusion that effects may be due to the release either of intrinsic histamine or of extrinsic histamine. The histamine is called intrinsic when it is released by the cells which give the response, as it presumably is when the plain muscle of a guinea-pig gives an anaphylactic response. The histamine is called extrinsic when it is released by one cell and acts upon another. In urticaria, for example, the histamine is thought to be released by the epithelial cells and to act upon the blood vessels. Dale suggests that effects due to extrinsic histamine are more easily abolished by antihistamines than effects due to intrinsic histamine. In the latter case, the histamine is perhaps released behind the barrier set up by the antihistamines. This theory explains some of the peculiarities of the actions of antihistamines.

With these facts in mind, it is safe to say that the antihistamines have lent strong support to the view that anaphylactic and allergic phenomena are many of them due to the release of histamine. They have also been used as evidence that various other effects are due to the release of histamine. An interesting example of this is the work of Erspamer and Paolini (1948), who have found that antihistamines inhibit the action of irritant purgatives, such as jalap and castor oil, and suggest that these substances produce their purgative effect by liberating histamine in the wall of the intestine.

Histamine in Blood

Our knowledge of the physiological and pathological roles of histamine depends largely upon experiments in which it was detected and estimated by pharmacological methods. The concentration of histamine in blood may be estimated pharmacologically, but the results have on the whole been disappointing, mainly because blood is

*A lecture delivered at the invitation of the Swedish universities.

such a complicated fluid. When human blood is centrifuged most of the histamine is found in the leucocytes. It is probably in granulocyte cells, since when these are present in the blood in very large numbers in myelogenous leukaemia the blood histamine is very high (Marcou *et al.*, 1937; Code and Macdonald, 1937). It seemed probable at one time that most of the histamine was in the eosinophil cells. The theory has now been discredited, since Rose (1950) caused a complete disappearance of eosinophils from the circulating blood by injecting the adrenocorticotrophic hormone (A.C.T.H.) without any clear effect on the blood histamine. A comparatively low concentration is normally present in the plasma, but it is doubtful whether the methods as yet available give a reliable estimate of this. Histamine added to blood *in vitro* is partly taken up by the red cells, which do not part with it easily (Anrep *et al.*, 1939). Some of those who study the release of histamine in the body estimate its concentration in the blood coming from a tissue which is expected to release it, and their results may possibly be due to the squeezing of leucocytes out of the tissue. Others estimate the concentration in the plasma, and their results may possibly be due to the disintegration of leucocytes with the liberation of histamine from these leucocytes into the plasma. When large changes are observed such things do not matter, but when smaller changes are being studied they may become important.

The experiments of Rose (1941) on anaphylaxis in rabbits provide an example of the odd results which may be obtained by estimating histamine in the blood. It is known that histamine is liberated in anaphylactic shock. It might therefore be expected that during this kind of shock histamine would disappear from the lung and spleen and appear in the blood. Rose found, on the contrary, that histamine disappeared not only from the lung and spleen but also from the blood itself. The blood cells liberated their histamine in just the same way as the lung cells and spleen cells, and he never found where the histamine went to next. Care is evidently needed in the interpretation of the results of experiments on blood histamine.

Histamine in Urine

During recent years a number of conclusions have been reached by estimating the concentration of histamine in the urine. The first clear evidence about this appeared in an interesting paper from Cairo (Anrep *et al.*, 1944). In this paper, Anrep and his colleagues described a method for concentrating histamine by adsorbing it on charcoal and so separating it from the large amounts of potassium which would otherwise interfere with pharmacological assays. They found that the urine histamine was partly free and partly conjugated. The conjugated histamine had no pharmacological activity, but became active when hydrolysed with acid. They collected urines from various animals in the Cairo zoo, including elephants, camels, water-buffaloes, anthropoid apes, lions, tigers, and leopards. These experiments showed that a diet of meat leads to the excretion of large amounts of conjugated histamine in the urine. When pure histamine was given by the mouth to dogs some of it appeared in the conjugated form in the urine; when it was injected some of it appeared as free histamine in the urine.

These interesting results have been confirmed and extended in other laboratories. Urbach (1949) used

paper chromatography to separate the two forms of histamine from one another and from the other substances present in urine, and in this way he obtained evidence that conjugated histamine is acetylhistamine. There can be no doubt about this, since Tabor and Mosettig (1949) have actually isolated acetylhistamine from the urine of a dog which had been given histamine by the mouth.

Henry Adam, with various colleagues, has been studying the excretion of histamine by man, in my laboratory. At first he used Anrep's methods, adsorbing the histamine on charcoal and estimating the difference between hydrolysed and unhydrolysed samples. More recently, he has been using other absorbents and separating the two forms of histamine from one another. His results show clearly that free histamine is normally present in human urine as well as acetylhistamine.

When histamine was given by the mouth there was a large increase in the amount of conjugated histamine in the urine and a small but definite increase in the amount of free histamine. When histamine was given by slow intravenous injection there was a large increase in the amount of free histamine in the urine and no change at all in the amount of conjugated histamine (Adam, 1950; Roberts and Adam, 1950). These observations confirm those of Anrep *et al.* (1944) on dogs, and support the view that the conjugation of histamine occurs in the intestine or liver. The amount normally present in the urine depends on the diet, and varies widely. Estimations of conjugated histamine might perhaps be used as an indication of the amount of histamine in the diet, but it seems likely that care would be needed in the calculations. In the experiments on man the proportion of an oral dose of histamine recovered in the urine varied between 0.17 and 1.2%.

Free histamine is more interesting than conjugated histamine. The average amount found in 30 urines from five normal young men was 21.6 μg . per 24 hours, and the extreme values were 12 and 41 μg . The concentration in the urine is less than that in whole blood, but much greater than that in plasma. When histamine was given by slow intravenous injection there was a definite increase in the amount of free histamine in the urine, even when the rate of injection was so slow that no effects could be detected except a small secretion of acid in the stomach. By conventional methods estimates were made of the concentration of histamine in the plasma in these experiments, and no definite change was detected. The estimation of free histamine in the urine is thus the most sensitive way we know of detecting the liberation of histamine in the body. It is, of course, necessary to collect all the urine secreted during a given time; a simple estimate of concentration is likely to be too much affected by drinks.

The increase in the amount of free histamine in the urine was about 1% of the amount injected. Most of the histamine must be destroyed elsewhere in the body, and the amount escaping in the urine makes no practical difference to the rate of disappearance of histamine. It does, however, provide an indirect measure of one aspect of histamine metabolism. The percentage appearing in the urine seemed to be independent of the dose (which was never very large), so it is reasonable to assume that the amount normally present in the urine was 1% of the amount of histamine normally liberated into the blood by physiological processes. This leads to the conclusion

that free histamine was appearing in the blood stream of these young men at the rate of 2 to 3 mg. per 24 hours.

It might be suggested that this histamine came directly from the gut and represented the small amount which had escaped acetylation. This is unlikely for the following reasons. The excretion of conjugated histamine showed wide fluctuations presumably associated with the diet, but the excretion of free histamine was much more constant, and showed no tendency to increase when the excretion of conjugated histamine increased. It seems more likely that this 2 to 3 mg. of histamine is liberated into the blood from the tissues every 24 hours. It may, of course, represent only a small fraction of a much larger amount most of which is immediately destroyed by histaminase before absorption in the blood, but it does provide something to think about. The total amount of histamine liberated must be at least as much as this.

It is too soon to say much yet about the excretion of histamine in disease, but Adam *et al.* (1950) did find that the rate of excretion of free histamine was higher in patients suffering from urticaria than in other patients or in normal persons.

Little is definitely known about where the histamine in the body comes from. One theory is that it is all absorbed from the gut like a vitamin. Adam and his colleagues did, in fact, find some increases of free histamine in the urine when histamine was given by the mouth. It is, however, doubtful whether this is the main source of body histamine. We know very little about the histamine content of diets and cannot calculate with confidence how much histamine may come from this source.

The other theory is that the histamine in the body has mostly been formed from histidine by the enzyme histidine decarboxylase. This enzyme was discovered and has been studied by Holtz (1937) and his colleagues. Blaschko (1945) has thrown doubt on its importance, since it appears to be absent in many species of animal, but the matter should be reinvestigated.

The excretion of histamine in the urine represents a very small proportion of the total histamine metabolism in man. When the body is flooded with histamine, however, the proportion may be larger, as is illustrated by some experiments by Alexander (1946), who injected 3 mg. of histamine intravenously in each of a group of mice and followed its fate by making an extract of the whole animal and estimating the total amount of histamine contained in it. The mouse is particularly adapted to such experiments, not only because of its small size, but also because of its great resistance to histamine. In these experiments about 1 mg. of histamine appeared in the urine, and the other 2 mg. was destroyed by the mouse within 24 hours.

Histaminase

Most of the histamine is presumably destroyed by the enzyme histaminase, which was discovered by Best (1929) and has recently been studied extensively in Sweden. Our knowledge of its distribution in the body is fragmentary. According to Best and McHenry (1930), particularly high concentrations are found in the kidneys and intestines of dogs. In Carlsten's (1950) interesting experiments on cats in Lund, lymph from the kidneys and intestines also appeared to be particularly rich in histaminase, but the enzyme was not found in the kidneys of rats or guinea-pigs (McHenry and Gavin, 1931)

or rabbits (Anrep *et al.*, 1936). In rats it is found in the lungs, and the amount present is not increased by the repeated administration of histamine (Rose *et al.*, 1940). The distribution of the enzyme seems to be different in different species. The fact that it is found in the lymph suggests that it may move about from one part of the body to another. The fact that adrenalectomy increases the amount in the lymph suggests that the distribution of this enzyme in the body may depend upon the state of the adrenal glands and, possibly, upon other experimental conditions.

Estimates of histaminase are being made by several different methods, and it is difficult to compare the results because the conditions are not always the same. This may be illustrated by comparing three curves showing estimates of the histaminase in blood throughout

Estimates of histaminase in serum or plasma during pregnancy. Different methods give different results.

pregnancy. In each case the result is expressed in the Chart as the amount of histamine destroyed per hour. The middle curve represents the results of Ahlmark (1944). The lower curve shows earlier results obtained by a similar method in Egypt. It might be thought that these results showed that Egyptian bloods contained less enzyme than Swedish bloods. Actually, the difference is probably due to the fact that less histamine was used in the Egyptian experiments, in which the maximum possible rate corresponding to complete destruction of all the histamine was 2.2 µg. per ml. per hour.

The upper curve shows results obtained by a method recently developed in my laboratory by Mrs. Kapeller-Adler (1951a). In this method the enzyme is incubated with histamine and indigo carmine for 24 hours in the presence of chloroform. The indigo carmine is partly decolorized by H_2O_2 liberated by the action of the enzyme on the histamine, and the result depends on measuring the amount of permanganate necessary to decolorize the rest of the dye. This method is not so sensitive as the biological methods, but is accurate and sensitive enough to estimate the histaminase in blood after the eighth week of pregnancy. It has the advantage that it avoids the use of bioassay. It is no more

difficult than the estimation of phosphatase, and is likely to be popular for this reason. The results in terms of histamine destroyed tend to be higher than those obtained by other methods.

There is danger of confusion in the estimation of histamine. Consider the effect of the concentration of histamine during incubation, which varies between 0.17 and 150 $\mu\text{g. per ml.}$ in different methods, and may even vary as much as fivefold in different experiments with the same method. With most enzymes the effect of changing the concentration of the substrate may be expressed approximately by the equation of Michaelis. At a certain critical concentration, defined by the Michaelis constant, the rate is half the maximal rate. At concentrations much higher than this the rate is independent of the concentration of the substrate, while at lower concentrations it is proportional to the concentration of the substrate. For consistent results, either the concentration must be well above the critical figure or it must be very rigidly standardized. The published figures for the Michaelis constant of histaminase correspond to concentrations of between 50 and 90 mg. per litre. These figures are probably higher than the real figure, but the concentrations actually used are almost certainly below the critical concentration. This can be seen clearly from the results of Best and McHenry (1930). The concentration of histamine should be more rigidly standardized than it is.

According to Mrs. Kapeller-Adler, the rate of destruction of histamine is increased by oxygen, by flavine-adenine dinucleotide, and by oestrogens. Such factors will have to be taken into account before we have a perfect method of estimating histaminase. Her results for the concentration of histaminase in the serum throughout pregnancy seem to show, in the first place, that the concentration of histaminase, as measured by her method, tends to be low in pre-eclamptic toxæmia. Other workers, using other methods, do not agree about this. She also found that the concentration was high when there were twins. All her results are consistent with the view that the amount of histaminase in the plasma is directly proportional to the amount of living placental tissue in the uterus. Since it is generally agreed that the histaminase comes from the placenta (Swanberg, 1950), this is not a surprising conclusion.

There is no general agreement about the specificity of histaminase. Preparations of this enzyme oxidize the diamines putrescine and cadaverine as well as histamine, and their rates of action on the three substrates are similarly affected by drugs and by changes of pH. The effect of serum on all three substrates is increased during pregnancy. The presence of cadaverine inhibits the rate of inactivation of histamine (Kapeller-Adler, 1949). These facts all support the theory of Zeller according to which the enzyme which inactivates histamine also acts on diamines in general and should be called diaminoxidase.

On the other hand, there is evidence that this theory is too simple :

1. When the purified enzyme is dialysed its action on histamine decreases, while that on cadaverine, etc., increases. Both these changes seem to be due to the loss of flavine-adenine dinucleotide (F.A.D.), which reverses them (Kapeller-Adler, 1949). Oestrogens appear to act like F.A.D. (Kapeller-Adler, 1951b).

2. The ratio of the effect on histamine to that on cadaverine is high for purified enzyme from hog's kidney and

low for the serum of pregnant women, especially if they are suffering from pre-eclamptic toxæmia (Kapeller-Adler, 1951a).

3. The enzyme has no effect on diamines in which the two amino groups are separated by a straight chain of more than eight carbon atoms (Blaschko, 1949).

The moral of all this is that the term diaminoxidase should be avoided for the present.

It is clear that much remains to be done with histaminase. Its general importance is emphasized by some experiments by Mongar and Schild (1951), who found that various substances which poison histaminase produced an increase in the effect of histamine on a piece of plain muscle isolated from the body and suspended in a bath. These observations suggest that the enzyme is present at the site where the histamine acts in sufficient concentration to destroy histamine more rapidly than it can diffuse in from outside, and that histaminase controls the action of histamine in the same sort of way that cholinesterase controls the actions of acetylcholine. Our methods of detecting and estimating histaminase are not very sensitive, and it seems likely that it is much more widely distributed in the tissues than our present evidence would suggest. It does not act very rapidly, and it is possible that it is normally in action all the time, and that the histamine content of tissues represents a balance between production and destruction.

Allergy

Consider now the phenomena of anaphylaxis and allergy. It is agreed by most people that anaphylaxis is due to the combination of antigen with antibody inside cells, which damages the cells and may lead to the release not only of histamine but also of various other toxic substances. It is also generally agreed that allergy is very similar to anaphylaxis, and that allergic urticaria, for example, is due to the release of histamine. There was little doubt about this even before the introduction of antihistamines. The successful use of these drugs in the treatment of urticaria has settled the question. The allergic response is primarily due to the mechanism which produces anaphylaxis, but this does not explain why some people are allergic and some are not. There must be some biochemical peculiarity which distinguishes allergic people from normal people. Their condition might be due either to the liberation of abnormally large amounts of histamine or to an abnormal sensitivity to histamine. It is perhaps surprising to find that there is evidence in favour of both these theories.

Evidence of an abnormal release of histamine was obtained by Katz and Cohen (1941), who incubated blood from allergic patients with various allergens and showed that the allergen to which the patient was susceptible released histamine from the blood cells into the plasma. Hawkins *et al.* (1951) have recently obtained similar results with fragments of lung removed from allergic patients. Serafini (1948) observed a brief rise of blood histamine when horse dander was injected intradermally in 54 places at once in a sensitive patient. The finding of abnormal quantities of histamine in the urine of allergic patients by Adam *et al.* has already been mentioned. All these results show that allergic patients release abnormal amounts of histamine.

It seems to be generally agreed also that allergic patients are abnormally sensitive to histamine. When given by intravenous injection this substance causes flushing of the face and neck in everyone, but allergic

manifestations such as asthma, urticaria and changes in the nasal mucous membrane occur only in persons who are liable to suffer from such complaints (Weiss *et al.*, 1932; Rose, 1947).

Both sets of facts can be explained on the theory that allergic patients are deficient in histaminase. This would mean that any histamine released on injury would be more likely to escape into the circulation and be detected by the experimenter. It might mean that the tissues contained more histamine than those of normal persons, and so had more histamine to release when injured. A deficiency of histaminase would also be expected to make the tissues more sensitive to histamine, as it did when Mongar and Schild poisoned the enzyme with suitable drugs. This deficiency might be localized in the skin in urticaria and in the nasal mucous membrane in hay-fever. A deficiency of histaminase and an excess of histamine in the tissues might be expected to diminish the rate of disappearance of histamine in the body.

Serafini and his colleagues in Rome (Serafini, 1948; Frugoni and Serafini, 1950) have obtained some evidence of this by constructing what they call histamine-tolerance curves. Histamine is injected subcutaneously in a dose of 1 mg. and its concentration is estimated in eight samples of blood collected during the next 20 minutes. In normal persons no changes are detected in the blood histamine, but in asthmatics it is found to rise to a maximum value in three minutes and to remain high for about 15 minutes. On the other hand, Jiménez Díaz *et al.* (1950) failed to confirm these results, and Adam *et al.* (1950) found no clear difference between allergic patients and normal persons when they estimated the percentage of an intravenous dose which appeared in the urine.

It is clear that some of the evidence is conflicting, but the theory that a deficiency of histaminase in the tissues plays a part in the causation of allergy appears to deserve serious consideration. This theory may perhaps have been in the minds of those who sought to treat allergy by the injection of histaminase (see Feinberg, 1946). The failure of this treatment does not disprove the theory.

Summary

Work on antihistamines has emphasized the importance of histamine itself and drawn attention to many gaps in our knowledge. Changes in the total blood histamine are difficult to interpret, as histamine is normally present in the leucocytes, and the available methods do not give a reliable estimate of plasma histamine unless this is much increased above the normal value.

The urine normally contains free histamine and the inactive substance acetylhistamine. The amount of free histamine excreted by man is normally about 20 μ g. per 24 hours. This is increased after intravenous injections of histamine and may be increased during allergic attacks. The amount of acetylhistamine can be increased by giving histamine orally. Estimates of this substance are of comparatively little interest at present.

The normal fate of most of the histamine in the body is to be destroyed by the enzyme histaminase, which should retain its original name and not be called diaminoxidase. The discovery that substances which poison histaminase may sensitize tissues to histamine suggests that this enzyme plays a part in the body similar to that of cholinesterase.

In allergy the tissues not only release abnormal amounts of histamine but are also abnormally sensitive to this substance. Both these facts can be explained on the theory that those tissues which give an allergic response are deficient in histaminase.

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The Report of Proceedings of the Scottish Society of the History of Medicine has just been published; membership now exceeds the hundred mark, and three meetings were held during the year—at Edinburgh, Glasgow, and Aberdeen. At the annual general meeting the president talked about Maya and Inca medicine. When the Spaniards invaded Southern and Central America they found that the Incas had a firmly established socialist state in Peru and Bolivia at a time when the Aztecs were committing genocide by mass sacrifices in Mexico; the Mayas, or Greeks of the New World as they have been called, were living in a remarkable state of civilization, sculptural remains of which may still be seen at Chichen Itza and elsewhere. Little is known of their system of medicine, though they made use of a wide range of medicinal plants, a practice which is now dying out as synthetic drugs become cheaper and easier to obtain; an interesting feature of the modern Maya is his low pulse rate—averaging 52 per minute. The main sources of the early medical history of the Incas are to be found in earthenware jars, some of which are decorated with designs representing diseases. The results of mutilation of the lips and nose, sacrificial and punitive, are also depicted, and also the operation of trephining—practised with the idea of allowing the demon of disease to escape from the victim's head. This operation was one of the early practices of the people of ancient Peru, and the spade-shaped knife used has been adopted as the emblem of the Peruvian Academy of Surgery. Another interesting practice prevalent among the Incas was the embalming of the dead. The corpse was flexed at all the joints in the foetal position, set in a basket, and treated with varnishes and resins; it was then wrapped in many layers of cloth and the resulting pear-shaped bundle placed in an artificial tomb.