

OBSERVATIONS ON ITCHING PRODUCED BY COWHAGE, AND ON THE PART PLAYED BY HISTAMINE AS A MEDIATOR OF THE ITCH SENSATION

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The concept of histamine as a chemical mediator of the itch sensation is not new. A substance indistinguishable from histamine exists in a combined form in the human skin and is known to be liberated when the skin is damaged in various ways (Lewis, 1927, 1942; Rosenthal, 1949). Lewis suggested that the itching of urticaria might be due to liberated "H" substance, and he showed that all the features of an urticarial lesion—*weal*, *flare*, and *itching* ("the triple response")—could be reproduced by pricking histamine into the skin.

With such an association between histamine and itching it is not surprising that antihistamine drugs should relieve both the rash and the pruritus of urticaria. But it is unexpected that orally administered antihistamine drugs should relieve the itching of many conditions which are apparently unassociated with histamine release (for references see the Discussion).

In order to investigate this apparent anomaly it was necessary to devise some method of producing itching in normal people by some means not involving histamine. For this purpose cowhage seemed to be suitable, it being generally accepted that this produces itching in a purely mechanical fashion. But it was soon apparent that the pruritus produced by cowhage is in fact due to the liberation of histamine in the skin. It is with the demonstration of this fact, and the consideration of various consequences deriving from it, that this paper is concerned.

MATERIALS AND METHODS

Cowhage is the name given to the trichomes which cover the pod of a tropical plant *Mucuna pruriens* DC. (*Dolichos pruriens* L.). At one time it gained a reputation as a therapeutic agent in the treatment of roundworm infection of the bowel (Chamberlaine, 1804). It is sometimes sold in novelty shops as "itching powder," and has been used previously for the

experimental production of itching (see Rothman, 1941). A sample of the cowhage used in these experiments is illustrated in Fig. 1.

Extracts of cowhage were prepared by boiling weighed amounts of cowhage in a known volume of normal saline solution for 30 minutes. At the end of this period the fluid loss was replaced by distilled water and the trichomes removed by filtration.

"*Extracted cowhage*" was prepared from the boiled trichomes by boiling again with fresh distilled water for 30 minutes and filtering. The trichomes were then washed with further distilled water, and allowed to dry at room temperature.

Experiments on the Human Skin.—Comparisons of the two samples of cowhage, for instance ordinary cowhage and extracted cowhage, were made in the following way. Each subject drew in ink two circles about the size of a shilling, one on either forearm, in similar situations. The two cowhage samples, labelled "A" and "B," were applied to the marked areas of skin, one sample on the right arm, the other on the left. The arms were kept as still as possible throughout the experiment. The subjects were asked to compare subsequent sensations in respect of type, duration, and exact location (i.e., if confined to the area of application). They were also required to note the presence or absence of erythema and *weal* formation.

Two people applied the cowhage: one dealt only with sample "A," and the other with sample "B." The quantity of cowhage was not measured accurately but was about 2 mg. of each sample. It was applied with a metal scoop, and gently rubbed into the skin for 2–3 seconds by the index finger of the operator. Care was taken to avoid cross-contamination, and the students were warned against scratching and other ways of disseminating the cowhage. Each subject had a partner who recorded the results.

In order to test the effect of mepyramine on the itching produced by cowhage half of a group of medical students received tablets of 100 mg. mepyramine maleate t.d.s. on the day preceding, and one tablet on the morning of the experiment. The other half had control tablets of ferrous sulphate at the

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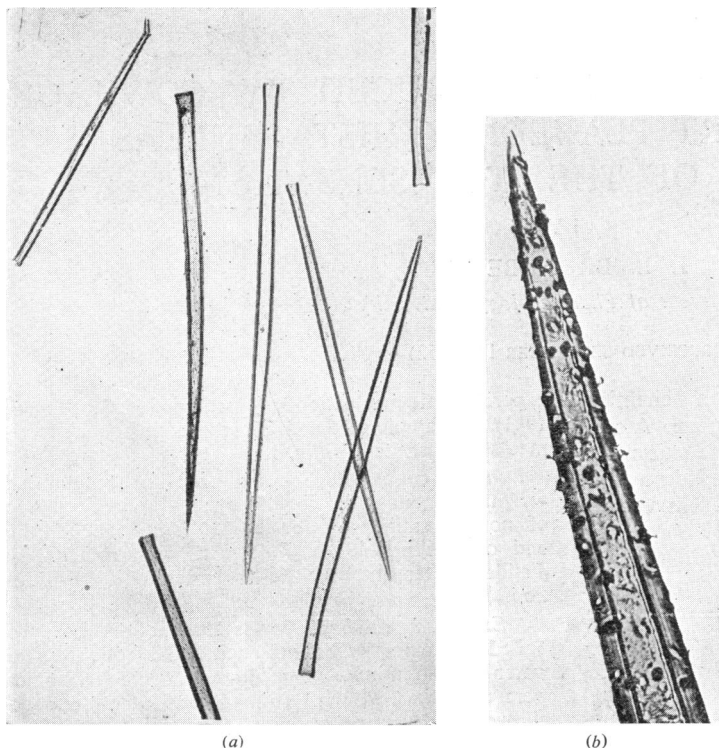


FIG. 1.—Photomicrographs of cowhage. (a) Shows a number of hairs (trichomes) which constitute cowhage ($\times 46$). The trichomes are pointed at one end and are between 1.5 and 2.5 mm. in length. There are approximately 450 trichomes in 1 mg. of cowhage. (b) A high-power view ($\times 300$) of one trichome. The small lateral barbs, which are about $2\ \mu$ in length, are shown.

same times. The students were unaware of the nature of the tablets.

Approximately 3 hours after the ingestion of the last tablet, a cowhage-containing ointment (3.7% in paraffin) was applied to a marked area, the size of a shilling, on the forearm. This particular strength of ointment was chosen after a trial with a number of dilutions. The use of ointment is an improvement on the previous method, as it is easier to localize the cowhage. Each student was required to note the latent period between the application of the ointment and the start of the itch, the duration of the itch, and whether the itch was intense, moderate, or slight.

One week later the experiment was repeated with the two groups interchanged, so that the persons previously in the control group now had the antihistamine drug.

Throughout the paper histamine acid phosphate and morphine sulphate have been calculated as base.

RESULTS

Histamine Content of Cowhage

It has usually been assumed that both the itching and the anthelmintic properties of cowhage are mechanical effects, and that the barbs are

important factors in this mechanical stimulation. While itching may certainly be produced without any evident skin reaction, many subjects show minute weals when the hairs are rubbed into the skin with a fair degree of pressure. As it is known that the nettle sting owes its properties to the presence of histamine and acetylcholine (Emmeline and Feldberg, 1947), it seemed possible that cowhage might also contain histamine. An extract obtained by boiling 1.0 g. of cowhage in 100 ml. of normal saline solution was tested for histamine (1) on the human skin, (2) on the arterial blood pressure of a cat, (3) on the isolated guinea-pig ileum, and (4) by a chemical method.

(1) 1 ml. of the extract was diluted with 9 ml. of sterile normal saline solution and 0.05 ml. of the diluted extract injected intradermally into the ventral aspect of the forearm. This resulted in the appearance of a weal and flare. The response was maximal in about 10 minutes. The weal was outlined with ink, and a permanent record obtained by a tracing on transparent paper.

In this person the weal area, 1.08 sq. cm., was the approximate equivalent of a weal produced by $1\ \mu\text{g.}$ of histamine base.

A slight burning pain was noticed during the period of the injection, but there was no itching. In appearance the reaction was indistinguishable from that produced by the intradermal injection of histamine. Flushing, asthenia, and nausea were also observed, so that experiments involving the injection of extracts have been limited in number.

(2) The same afternoon samples of the extract were injected intravenously into an atropinized cat under chloralose anaesthesia (Fig. 2). No effect was produced by 0.5 ml. of the undiluted extract, but the blood pressure fell on injection of $2.5\ \mu\text{g.}$ histamine. Some depression was noticed with 1.0 and 2.0 ml. of the undiluted extract and this was more prolonged than that produced by histamine.

If the weal response in the skin had been due to histamine, 1.0 ml. of the undiluted extract would have contained about $200\ \mu\text{g.}$ of histamine. The effect on the blood pressure of the cat did not support this hypothesis.

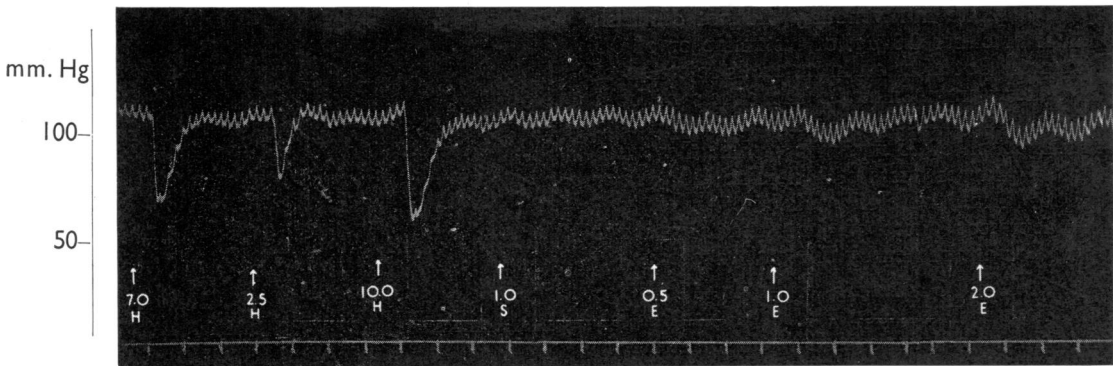


FIG. 2.—Record of arterial blood pressure of atropinized cat (2.3 kg.) under chloralose anaesthesia. Effects of intravenous injections of cowhage extract (E) in ml. and of histamine acid phosphate (H) expressed in μ g. (S) 1 ml. saline solution intravenously. Time in 30 seconds.

(3) The extract caused contraction of the isolated guinea-pig ileum suspended in atropinized Tyrode solution. This contraction was compared with that produced by histamine, and it appeared that 1 ml. of extract might contain about 4 μ g. of histamine, as against the expected 200 μ g. per ml. suggested by the experiment on the human skin.

Thus when assayed on the human skin, the isolated ileum of the guinea-pig, and the blood pressure of a cat, the extract produced effects rather similar to histamine, but quantitatively there was no agreement.

(4) An improved colorimetric method for the chemical identification of histamine has been described by Rosenthal and Tabor (1948). Fresh extracts of cowhage were examined by this method and no histamine appeared to be present. The interpretation of the results was, however, complicated by the colour of the extracts; initially brown, they became yellow in the final solutions. An appreciable darkening of this colour could be obtained by adding 1.0 μ g. of histamine base to each ml. of extract; and following the addition of

20 μ g. per ml., the pink colour of histamine was unmistakable and not masked by the yellow of the cowhage.

This was taken as confirmatory evidence that histamine is not normally present in the extracts, but the observed effects might be due to the liberation of histamine from the tissues with which the extract came into contact.

Pharmacological Actions of Cowhage Extracts

Experiments on a Cat under Chloralose Anaesthesia.—Fig. 3 shows the effect on the blood pressure of an intravenous injection of an extract prepared by boiling 2 g. of cowhage in 50 ml. of normal saline solution. Both 0.5 ml. of the extract and 0.3 μ g. of histamine produced a fall in the blood pressure. The latent period between the injection and the depression was about equal, but the depression due to the extract was more prolonged. Whilst the response to repeated injections of histamine remained constant, the effect of the extract increased with each dose, both in the degree and the duration of the depression. One mg. of

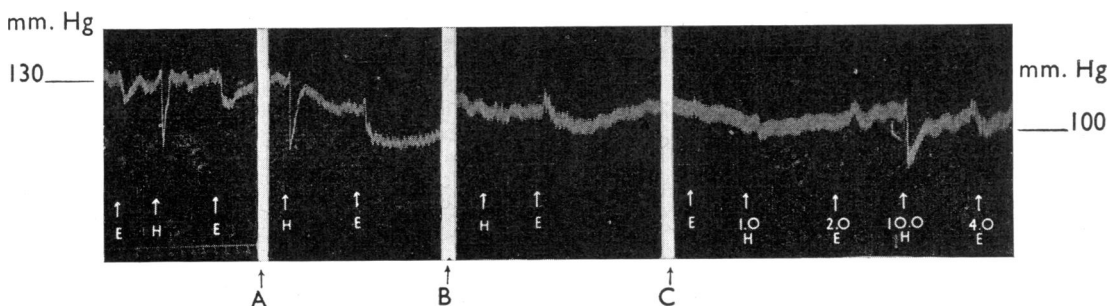


FIG. 3.—Record of arterial blood pressure of a cat under chloralose anaesthesia. Effects of intravenous injection of 0.5 ml. (E) and 4 ml. (4E) cowhage extract, and of histamine (0.3 μ g., H; 1 μ g., 1H; 10 μ g., 10H). At A atropine 1 mg. was injected intravenously, at B and C 10 and 25 mg. mepyramine maleate respectively.

atropine sulphate intravenously did not diminish the effect of either 0.3 μ g. of histamine or of 0.5 ml. extract. But after an intravenous injection of 10 mg. mepyramine maleate the effects of both histamine and extract were reduced, and after a further injection of 25 mg. mepyramine they were abolished. Larger doses of histamine (10 μ g.) or of extract (4 ml.) were still active.

The depressor effect of the extracts was not abolished or diminished by bilateral vagotomy.

The Isolated Guinea-pig Intestine.—Cowhage extracts have a pH of about 4; but the contraction of the guinea-pig ileum caused by these extracts is not a pH effect because neutralization with sodium hydroxide, using neutral red as an indicator, did not reduce their spasmogenic properties. The addition of 1 mg. of atropine sulphate per l. of Tyrode solution likewise had no effect.

Graded doses of extract may at first produce graded responses, but repeated additions of extract to the intestine bath tend to produce less and less effect, although the sensitivity to histamine remains unaltered. Fig. 4 illustrates this point;

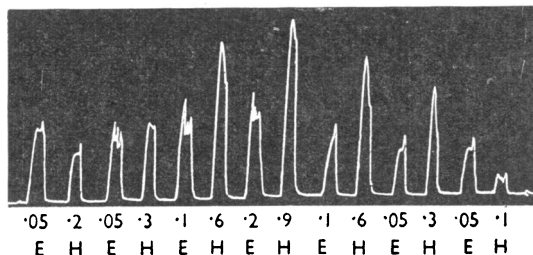


FIG. 4.—Guinea-pig ileum in 3 ml. of Tyrode at 31° C. Cowhage extract (ml. E) and histamine (μ g. H) were added to the bath alternately.

whilst graded doses of histamine produce graded responses the contractions due to the cowhage extracts become gradually less.

The contraction produced by the extract is prevented or diminished by antihistamine drugs. Fig. 5 demonstrates that mepyramine maleate blocks the effect of both histamine and extract, but not that of acetylcholine. The cowhage contraction seems to be less reduced than the histamine response. The intestine still responds to 2.0 mg. of barium chloride.

The effects on guinea-pig ileum and cat blood pressure are strikingly similar to those produced by certain snake venoms and shown by Feldberg and Kellaway (1937a and b) to be due to liberation of histamine. This and the specific antagonism by mepyramine maleate suggest that the effects of cowhage extracts may also be due to histamine liberation.

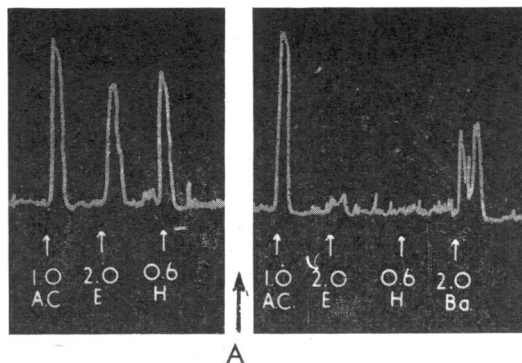


FIG. 5.—Guinea-pig ileum in 50 ml. Tyrode at 31° C. To show the effect of 1 μ g. acetylcholine (A.C.), 2 ml. cowhage extract (E), 0.6 μ g. histamine (H), and 2 mg. barium chloride (Ba). At A the Tyrode solution was replaced with one containing mepyramine maleate 1 mg./l.

Experiments on the Human Skin

Effect of Ordinary and Extracted Cowhage.—Table I shows that rubbing about 2 mg. ordinary cowhage into the skin produced weals in only 18 out of 26 subjects; 3 subjects observed neither weal nor erythema, although definite itching was experienced in everyone. Wealing is uncommon with smaller quantities of cowhage, and after con-

TABLE I
A COMPARISON OF THE ITCHING PROPERTIES OF COWHAGE AND EXTRACTED COWHAGE ON 26 SUBJECTS

| | Cowhage | Extracted Cowhage |
|--|-------------|-------------------|
| Definite itching | 26 | 3 |
| Slight itching | 0 | 5 |
| No sensation | 0 | 18 |
| Mean duration of itching sensation | 9.6 min. | 1.4 min. |
| S.E. of the mean | ± 0.95 | ± 0.69 |
| | $P < 0.001$ | |
| Erythema | 23 | 19 |
| Weals | 18 | 5 |

tamination with only a few cowhage hairs itching with only slight erythema, or no visible change in the skin, is usual.

Preliminary experiments with dried cowhage from which extracts had been obtained suggested that its itching properties had been considerably reduced. An experiment was designed to compare the itching properties of the boiled extracted cowhage with that of ordinary cowhage. Twenty-six medical students acted as experimental subjects. The results are summarized in Table I.

With both samples a pricking sensation was reported when the hairs were being rubbed into the skin, but this is not recorded in the Table. Most subjects then experienced a latent period of

about 10 seconds, after which an itching type of sensation was noticed where the ordinary cowhage had been applied. This was usually described as an "itching sensation," but also as a "burning itch," and more rarely as a "burning pain." Other descriptions are "stinging like a nettle sting," "intense pricking," "sensation like a gnat bite," and "like prickly heat" (from a student who had lived in the tropics). The desire to scratch seemed to be universal.

At the site of application of boiled extracted cowhage the sensations described above were either absent or greatly diminished. Several subjects described an ill-defined mild itch or tickle sensation, and this is shown in the Table as "slight itching." In part, at least, this seemed to be due to movements of the arms driving the cowhage hairs further into the epidermis. Even if this sensation is not differentiated from the more intense reaction of the cowhage, it is seen that there is a significant difference between the mean durations of sensation for the two samples.

Microscopic examination showed that boiling had no appreciable effect on the morphology of the cowhage hairs, and in particular that the pointed ends of the trichomes and the small barbs were not broken by this treatment. It thus appears that the itching property is not due to the mechanical peculiarities of the cowhage hairs, but to some contained chemical substance. It is tempting to assume that this same substance is responsible for the histamine-liberating properties of the cowhage extracts.

Restoration of Itching Properties to Extracted Cowhage.—Two experiments were performed to see if it was possible to restore the itching property to the extracted cowhage by histamine and morphine. The latter was chosen because itching is a relatively common complication of morphine therapy and morphine salts are known to liberate histamine from animal tissues and also from the human skin (Nasmyth and Stewart, 1950; Feldberg and Paton, 1950).

Approximately equal quantities of extracted cowhage were rubbed into a marked area of the skin of each forearm for 3 to 4 seconds. Then 0.1 ml. saline solution was added to the cowhage on one arm and 0.1 ml. saline solution, containing either histamine acid phosphate 1 in 3,000, or morphine sulphate 1 in 500, to the cowhage on the other arm. The results are summarized in Tables II and III, and show that both histamine and morphine restore the itching property of the hairs.

As the application of histamine or morphine solutions to the unbroken skin produced no irri-

TABLE II

A COMPARISON OF THE ITCHING PROPERTIES OF EXTRACTED COWHAGE WITH NORMAL SALINE, AND WITH NORMAL SALINE CONTAINING HISTAMINE, ON 24 SUBJECTS

| | 0.1 ml. Normal Saline | 0.1 ml. Normal Saline with 30 μ g. Histamine |
|--|-------------------------|--|
| Definite itching | 8 | 22 |
| Slight itching | 7 | 0 |
| No sensation | 9 | 2 |
| Mean duration of itching sensation | 3.3 min. | 10.7 min. |
| S.E. of the mean | ± 0.86 P < 0.001 | ± 1.76 |
| Erythema | 17 | 24 |
| Weals | 2 | 23 |

TABLE III

A COMPARISON OF THE ITCHING PROPERTIES OF EXTRACTED COWHAGE WITH NORMAL SALINE, AND WITH NORMAL SALINE CONTAINING MORPHINE, ON 18 SUBJECTS

| | 0.1 ml. Normal Saline | 0.1 ml. Normal Saline with 200 μ g. Morphine |
|--|-----------------------|--|
| Definite itching | 7 | 17 |
| Slight itching | 6 | 1 |
| No sensation | 5 | 0 |
| Mean duration of itching sensation | 4.5 min. | 9.6 min. |
| S.E. of the mean | ± 1.2 P < 0.01 | ± 1.3 |
| Erythema | 16 | 18 |
| Weals | 3 | 17 |

tation, it seems that the cowhage hairs abrade the skin surface, and enable the solutions to enter the epidermis; superficial nerve endings between the cells are then stimulated by histamine to give rise to the sensation of itching. This hypothesis is supported by the observation that the substitution of fine glass wool for extracted cowhage yields similar results.

There is considerable variation, from one experiment to another, in the duration of itching produced by the "control." This might be due to a number of factors: for example, a very severe itch on one arm might completely mask a mild sensation which would be observed were the two sensations more nearly equal in intensity.

*The Effect of Orally Administered Mepyramine Maleate on the Itch Produced by Cowhage.**—From the above observations it might be expected that an orally administered antihistamine drug would reduce the itching produced by cowhage.

A "cross-over" test was carried out in which the anti-pruritic effect of mepyramine maleate was

*This experiment was performed at University College, Ibadan, Nigeria.

compared with that of control tablets. The results are summarized in Table IV.

It is seen that the mepyramine maleate significantly prolongs the latent period before the start of the itching and decreases the duration of the itch.

TABLE IV
THE REDUCTION IN ITCHING OF A COWHAGE-CONTAINING OINTMENT BY MEPYRAMINE MALEATE, IN 13 SUBJECTS

| | Control | Mepyramine Maleate 100 mg. t.d.s. by Mouth |
|---|------------|--|
| Intense itching | 13 | 9 |
| Moderate itching | 0 | 2 |
| Slight itching | 0 | 2 |
| Mean latent period (in seconds) between application of ointment and start of itching .. | 7.16 | 12.16 |
| S.E. of mean | ± 1.05 | ± 1.93 |
| | $P < 0.05$ | |
| Mean duration of itching (in minutes) | 6.04 | 4.11 |
| S.E. of mean | ± 0.84 | ± 0.32 |
| | $P < 0.05$ | |

Experiments with Histamine.—In the course of work on the relative potencies and durations of action of antihistamine drugs (Bain, Hellier, and Warin, 1948; Bain, Broadbent, and Warin, 1949; and Bain, 1949) it was necessary to make many hundreds of intradermal injections of small amounts of histamine. Whilst pain was common, even before the exhibition of a histamine antagonist, the subjects complained only very rarely of itching, and then usually with high doses, or when an injection was exceedingly superficial. The volume of the injection was 0.1 ml. or 0.05 ml., and histamine acid phosphate was present in amounts equivalent to 0.01–30.0 $\mu\text{g.}$ of base, dissolved in normal saline.

Similar observations were made by Rosenthal and Sonnenschein (1946). However, Melton and Shelley (1950) describe itching following intradermal injections of histamine when, instead of being dissolved in normal saline or in distilled water, it was dissolved in the following specially buffered medium:

| | |
|-----------------------------------|----------|
| Sodium chloride | 8.5 g. |
| Sodium acid phosphate | 0.576 g. |
| Disodium hydrogen phosphate | 2.5 g. |
| Distilled water to 1 litre. | |

We have repeated these experiments by comparing the itching properties of histamine in normal saline and in the buffered medium of Melton and Shelley.

The volume of fluid injected was 0.1 ml., and this contained histamine acid phosphate equivalent to

2 $\mu\text{g.}$ of base. These solutions were compared on 6 normal volunteers. One person experienced itching with both solutions, two with the buffered solution only. In all experiments, pain was the predominant sensation, and the itching, when present, was not intense and was of short duration (2 min., 2 min., and 1 min.) for the buffered saline solution. It therefore seems possible that when using buffered saline as the vehicle itching is more common than with normal saline. Even so itching seems to be inconstant and of short duration.

DISCUSSION

The results described above indicate that the itching properties of cowhage are not due to mechanical stimulation by the hairs, but to a chemically unidentified substance, which appears to have the property of liberating histamine from the human epidermis and dermis.

This hypothesis is supported by the following observations: (a) Cowhage extracts produce a triple response when injected intradermally, (b) the itching properties of extracted cowhage are greatly reduced, (c) both histamine, and morphine, which is known to liberate histamine in the skin, can restore pruritic properties to the extracted cowhage, (d) an orally administered antihistamine drug reduces cowhage itching.

The extracts have pharmacological effects on the cat blood pressure and isolated guinea-pig ileum resembling certain snake venoms and a substance present in bee venom (Feldberg and Kellaway, 1937a and 1937b), both of which were shown to liberate histamine from isolated animal lung, and so produced a fall in blood pressure when injected intravenously. The latent period between the intravenous injection of these venoms and the depression of blood pressure was similar to the latent period following the injection of histamine. This is also true of cowhage extracts. These three therefore differ from the histamine liberating substances described by Macintosh and Paton (1949) which have a much longer latent period.

A further difference is that the latter have no effect, except in massive doses, on the isolated guinea-pig ileum, whereas bee venom, the snake venoms, and cowhage extracts all cause a contraction. Feldberg and Kellaway believed this to be due to the liberation of histamine from the gut. With cowhage extracts the diminishing effect on repeated application, and the antagonism by mepyramine maleate, support the view that histamine liberation may be responsible. A feature common to cowhage extracts and to the organic bases of Macintosh and Paton is that progressively

larger responses, as measured on the blood pressure of the cat, follow repeated doses.

A superficial situation in the skin of the nerve endings subserving the itch sensation is suggested by the relative infrequency of itching when histamine is injected intradermally; though when applied to the epidermis—by pricking into the skin (Lewis, 1942), or by applying to scarified skin (Sollman and Pilcher, 1917), or to skin abraded by exhausted cowhage hairs—itching is usual and prominent. It is concluded that pain is the predominant sensation produced by histamine in the dermis, and that unless massive doses of histamine are injected itching is usually absent. But itching is the most prominent sensation when histamine is introduced into the epidermal layers of the skin.

In some itching conditions changes are seen mainly in the epidermis. Scabies and eczema are examples. In the lesions of prickly heat itching occurs with the early superficial retention cysts, but not with the later and more deeply situated cysts (O'Brien, 1947). In papular urticaria where the lesions are small and raised, scratching regularly provides early relief, probably by damaging the nerve endings in the papules which transmit the itch sensation.

In anaphylactic responses itching may occur as the first or only symptom (Klinkert, 1923): and either generalized pruritus (Nomland, 1944) or a generalized pruritic urticaria may result from the injection of acetyl- β -methyl choline into people who respond in this way to effects of heat, exertion, or emotion (Grant, Comeau, and Pearson, 1936). Further evidence is provided by the present experiments with cowhage, which unless rubbed hard into the skin does not produce bleeding points. Itching, however, is always observed and is practically the sole effect when small quantities come in contact with the skin. It seems, therefore, that the trichomes remain in the epidermis. Moreover, as cowhage produces little or no itching where the keratinized layer of the epidermis is thick, as in the palm of the hand, the nerve endings are probably situated in the basal layers of the epidermis. All these observations agree with those of Torok (1907) and Kenedy (1936), who noted that itching cannot be elicited from areas of skin denuded of epidermis.

In urticaria the main changes are seen in the dermis, but itching, which is usually marked, precedes the appearance of the weal. In this respect it differs from the lesions of dermatographism in which itching is usually, but not always, absent. Both are believed to be due to abnormal histamine release,

as they resemble in appearance the triple response to histamine, and they are both controlled by anti-histamine drugs (Bain, Hellier, and Warin, 1948). The lesions of urticaria can be mimicked by applying histamine to the abraded epidermis. It is tempting to postulate that in urticaria some, at least, of the histamine is liberated amongst the basal epidermal cells, whereas in dermatographism mechanical stimulation of the skin causes liberation only in the dermis.

The precise relationship between histamine release and itching requires further consideration. It is well known that the systemic administration of histamine-liberating drugs, such as morphine and stilbamidine (Macintosh and Paton, 1949), produces itching in a proportion of patients, and that morphine will exacerbate an existing itch. Also, drug rashes which follow the administration of a drug to a sensitive patient are frequently pruritic. However, the intravenous injection of histamine in man does not cause pruritus (Weiss, Robb, and Ellis, 1932). It is therefore likely that the itching in drug hypersensitivity reactions, or after the systemic use of a histamine liberator, is due to histamine liberation in the basal epidermal layers of the skin. It is not to be expected that histamine liberated from other body tissues will cause itching.

The objection that all itching drug hypersensitivity reactions are not associated with a triple response can be met, as it seems that the release of sufficient histamine in the epidermis to cause severe itching may not be accompanied by a triple response, which is a dermal reaction. This view, which is in opposition to the contention of Rothman (1941) that itching without visible changes in the skin cannot be due to histamine, is strengthened by many reports that orally administered anti-histamine drugs have some effect in relieving the pruritus of such conditions as eczema, prickly heat, chickenpox rashes, mosquito bites, the dermatitis of poison ivy, pruritus ani and vulvae (of uncertain aetiology), and pruritus associated with Hodgkin's disease, and obstructive jaundice (Baer and Sulzberger, 1946; Blumenthal and Rosenberg, 1947; Davis, 1950; Feinberg, 1950; Friedlaender and Feinberg, 1946; Gordon and Crewe, 1948; Hunter and Dunlop, 1948; Kuhn, 1949; Lynch, 1947; Silverman, 1949; Waldbott, 1946; and Waldriff, Davis, and Lewis, 1950). In many instances improvement in the pruritus leaves the rash unchanged.

In many itching conditions there is evidence that antigen-antibody mechanisms are involved, and in these circumstances one might expect the liberation of histamine. Drug rashes have already

been mentioned. In scabies the itching starts only when the patients become sensitive to some product of the causal mite (Mellanby, 1943); similar considerations apply to the itching of mosquito bites (Mellanby, 1946; Gordon and Crewe, 1948; Heilesen, 1949) and possibly to the itching lesions associated with other types of "insect" bite.

An antigen-antibody reaction is also well established in contact dermatitis. But it must be admitted that in many itching rashes the precise mechanism of cellular damage, sufficient to liberate histamine, but not so severe as to destroy the superficial nerve endings, remains unknown. Moreover, in the generalized pruritus of toxic conditions such as chronic nephritis, diabetes, and obstructive jaundice, there is no direct evidence to implicate histamine. But in all these conditions there are gross disturbances of the blood chemistry, and it may be that some metabolite has either histamine-liberating properties or may itself act as an antigen. In any event it seems certain that the liberation of histamine in the epidermis causes itching, and the fact that such itching may occur without any visible vascular or other effect in the skin makes it impossible to argue that when itching is not associated with vascular effects it cannot be due to histamine.

SUMMARY

1. The itching produced by cowhage is not a mechanical effect, but is due to a chemically unidentified substance which liberates histamine in the human epidermis.

2. In its pharmacological effects this substance resembles others present in some snake venoms, and also in bee venom, which have been shown to liberate histamine from animal tissues.

3. The nerve endings which subserve itching are located in the basal layers of the epidermis, and are probably absent from the dermis.

4. Histamine liberation in the epidermis can produce marked itching unassociated with a triple response.

5. It is probable that histamine release is involved in many more itching conditions than has been hitherto supposed.

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