Missouri Section.

Washington University School of Medicine, February 12, 1930.

4815

Observations on the Formation of Wheals. II. Comparison of Wheals Induced by Allergens and by Histamin.

H. L. ALEXANDER, J. O. HARTER AND F. S. MC CONNELL.

From the Department of Medicine, Washington University Medical School, and The Barnard Free Skin and Cancer Hospital, St. Louis, Missouri.

The lesion of allergy (used in the sense of atopy) is essentially a localized edema, whether or not smooth muscle spasm occurs also. The edema of the bronchi in asthma, the swelling of the nasal mucosa in hay fever, the wheal of urticaria and the positive skin reaction in an allergic individual all show the same histological picture. With the hope of throwing some light on tissue participation in allergy, a study of wheal formation was undertaken.

In a previous publication,[1] it was shown that when intradermal tests were done with an offending allergen at different sites in an allergic individual, the resulting wheal varied greatly in size. This occurred despite the fact that the dose of the injected allergen was constant (0.02 ccm.). Wheals laid down on the back and abdomen were uniformly much larger than those on the extremities, and those on the upper outer thigh were intermediate in size.

The wheal of a positive skin test results presumably from a reaction between the injected allergen, and antibody in the skin tissues, with the consequent formation of some substance having a resemblance to histamin. This, in turn, acts directly upon the walls of the surrounding capillaries. These dilate and become permeable to their contained plasma which comes out into the tissues and forms the wheal.

In order to analyze which of these factors may be responsible for the discrepancy in the size of wheals in different sites on the skin in response to a constant amount of allergen, the following experiment was performed:

[1] Alexander, H. L., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 800.

Normal individuals were injected intradermally with 0.02 ccm. of a 1 to 2500 dilution of histamin phosphate in the interscapular region, the flexor surface of the left forearm and in the upper outer aspect of the right thigh. Two wheals were laid down on each site. Unless each pair of wheals were approximately of the same size, the subject was not used. A blue-barrel tuberculin syringe with a special attachment calibrated in 0.01 ccm. was used. The wheals were allowed to increase in size for 15 minutes and were then traced in ink.

In the 25 subjects tested, it was found that the largest wheals occurred on the back, the smallest on the forearm and those on the thigh were intermediate in size. Since this result is similar to that found with allergens, the experiment was repeated in allergic subjects who then received both histamin and allergens at the above 3 sites. If the dose of histamin happened to correspond to the dilution of allergens used, wheals of similar size and character were obtained at each site.

The outlines of wheals obtained at the 3 sites in 18 allergic subjects with allergens and in 14 normals with histamin were measured with a planimeter. The average sizes of these wheals were as follows:

	Back	Forearm	Thigh
Allergen	2.04 sq. cm.	1.14 sq. cm.	1.55 sq. cm.
Histamin	2.00 " "	1.35 " "	1.78 " "

In a recent publication by Gröbel,[2] similar results were obtained by producing wheals with morphine in normal subjects. He found a larger response on the trunk than on the extremities. Apparently, the cause of this discrepancy in allergic individuals is the same as that in normal subjects. Consequently, one may rule out immunological factors, such as irregular antibody distribution and failure of allergen and antibody to form a capillary dilating substance.

A final possibility, according to present conception, is a variability in response of skin capillaries at different sites. This was examined by experiments in dogs. In these animals there is a similar discrepancy in size of wheals to histamin, the skin of the thigh giving larger reactions than that of the leg to a 1 to 5000 dilution. This dilution was injected into the femoral artery and a diffuse redness appeared in the skin of the entire extremity, showing an apparently uniform capillary reaction. Although such an experiment is open to criticism, it at least throws doubt on the highly conjectural supposition that there is a great difference in response to histamin inherent in capillaries of the skin of the trunk compared to that of

[2] Gröbel, F., *Z. f. d. ges. Exp. Med.*, 1929, lxv, 352.

the extremities. Some other factor seems necessary to account for this discrepancy of skin response. This is dealt with in the paper following.

4816

Observations on the Formation of Wheals. III. The Participation of an Unidentified Tissue Substance.

H. L. ALEXANDER, W. K. WEAVER AND F. S. MC CONNELL.

From the Department of Medicine, Washington University Medical School, and The Barnard Free Skin and Cancer Hospital, St. Louis, Missouri.

In previous publications[1, 2] it was shown that if in an allergic individual, intradermal tests be done with an offending allergen, the resulting wheal will vary in size depending upon the site of the skin injected. Larger responses occur on the trunk than on the extremities. The same discrepancy occurs in normal subjects with histamin, morphine and atropin, all of which produce wheals in normal skin. The cause of this variability in response is apparently not due to immunological factors and probably not to inherent lack of response in the capillaries. Consequently, there seems to be some other participating factor and this was sought in the skin tissue itself.

Advantage was taken of the fact that a histamin wheal in a dog's skin is similar in time of formation, shape and histological picture as that in human skin. Moreover, the same discrepancy in size of wheal formation at various sites, to an intradermal injection of a constant amount of a given strength of histamin occurs in a dog just as it does in humans.

Dogs were anesthetized with amytal and a portion of the shaved skin of the abdomen dissected off. This was washed in 0.85% sodium chloride solution until free from blood. The subcutaneous fat was dissected off and the skin cut into fine pieces. Ten grams of washed chopped skin were placed in 90 cc. of 0.85% saline solution to which sufficient histamin phosphate had been added to make a final dilution of this drug 1 to 10,000. The mixture was thoroughly shaken at intervals for 2 hours and filtered. For a control, proportionate amounts of skin and saline solutions without histamin were prepared in the same way. These mixtures were tested

[1] Alexander, H. L., PROC. SOC. EXP. BIOL. AND MED., 1928, xxv, 800.

[2] Alexander, H. L., Harter, J. O., and McConnell, F. S., *Ibid.*, 1930, xxvii, 484.