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

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

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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.

in a second dog under amytal anesthesia. Three intradermal injections of 0.02 cc. each into the shaved skin of the abdomen were made as follows: (1) Histamin phosphate 1 to 10,000 dilution, (2) Saline extract of skin (1 part in 10) containing histamin phosphate in 1 to 10,000 dilution, (3) Saline extract of skin without histamin.

Planimeter measurements were made of both the initial and the enlarged wheal. The difference between the 2 measurements represents the increase in size in sq. cm. This is recorded in Table I.

TABLE I.

H	*S*	*H*	*S*
0.2	0.8	0.5	1.0
0.2	0.7	0.2	0.6
0.3	0.9	0.3	0.9
0.4	0.9	0.2	0.8
0.3	0.8		

H = Histamine 10,000. S = Skin Extract + Histamine 10,000.
Each pair of figures represents one experiment—0.02 cc. of fluid injected. Figures record in sq. cm. increase of size of wheals after 15 minutes.

Several hundred such wheals were measured. It is apparent that there is something in skin tissue which augments histamin inasmuch as wheals induced with histamin and skin extract were uniformly larger than those made by histamin alone.

That the tissue factor is not histamin is evident from the skin extract control and also because the same increase is obtained with atropin and codein. This tissue factor is contained in organs other than skin, notably lung and liver.

Although further investigations are being carried on, it appears possible that wheal formation is dependent on this tissue substance. This may explain the discrepancy in the size of wheals induced in various parts of the skin by assuming that more of the substance is contained in the skin of the trunk than in that of the extremities. Further study of this phenomenon may throw some light on tissue response in allergy in which the wheal is the essential lesion. Chemical studies on the identification of this tissue factor are being conducted.