

SKIN HISTAMINE LEVELS IN CHRONIC ATOPIC DERMATITIS*

HERBERT H. JOHNSON, JR., M.D., GERARD A. DeOREO, M.D.,
WILLIAM P. LASCHIED, M.D. AND FRANK MITCHELL, D.D.S.

Since the discovery that histamine is a normal constituent of mammalian tissue, numerous experiments have been performed in an effort to clarify the role of this substance in normal as well as abnormal states.

It has been repeatedly demonstrated that histamine is released from various tissues including the skin as a result of antigen-antibody reactions in sensitized skin (1, 2, 3).

The influence of the work of Lewis has directed interest to the role of histamine in allergic reactions of the skin. A direct causal relationship between histamine content in the skin and the degree of allergic response of the skin has not been established. As Perry (4) has pointed out, the mouse, rat, and cat (animals with high skin histamine levels) do not show skin reactions of either the immediate or delayed type, whereas the guinea pig, rabbit and man (animals with relatively low skin histamine levels) are the species showing striking skin reactivity.

Since chronic atopic dermatitis may approximate the clinical prototype of chronic cutaneous allergy, the skin histamine levels in this condition were investigated. Specimens were obtained from:

1. Eczematous skin from sixteen (16) adults with chronic atopic dermatitis. None of these patients had received steroid or x-ray therapy within one month.

2. Normal skin from fifteen (15) adults without cutaneous disease. Because of the considerable regional variations in skin histamine (5, 6, 7) all specimens were obtained from the antecubital area. In each case elliptical biopsy specimens measuring approximately 5 x 10 mm. were removed for study. After the subcutaneous fat was removed the specimens were homogenized in a mortar with 5% trichloroacetic acid (redistilled) and 20 mesh acid washed sand. This was centrifuged and the histamine content of an aliquot of

the clear supernatant fluid was determined by the microchemical method of Lowry, Graham, and associates (8) as adapted to the skin (9).

The histamine content of the 15 control specimens from normal skin varied from 4.2 to 14.3 micrograms of histamine base per gram of skin, wet weight, with an average of 9.2 micrograms per gram (Table 1).

The histamine content of the 16 specimens taken from areas of chronic atopic dermatitis varied from 9.7 to 24.8 micrograms of histamine base per gram of skin, wet weight, with an average of 16.0 micrograms per gram (Table 2).

DISCUSSION

The difference in the average skin histamine levels in normal skin and that of chronic atopic dermatitis is significant. When this difference is re-evaluated, however, in the light of individual variations found in normal skin from the same regions and the considerable regional variations seen in human skin (7) one would not be justified

TABLE 1

*Histamine levels in normal antecubital skin**

Case	Age	Color	Sex	Histamine
R. F.	25	W	M	4.2
B. B.	22	C	F	6.4
R. D.	25	W	M	6.8
M. P.	25	C	M	6.8
E. H.	24	W	F	7.2
J. K.	25	W	M	7.4
D. A.	26	W	M	8.2
H. B.	26	W	M	8.8
A. S.	29	W	M	8.9
J. N.	26	W	M	9.5
W. S.	26	W	M	11.1
G. M.	20	W	M	12.0
P. F.	28	W	F	12.5
E. M.	26	W	M	13.8
Q. K.	28	W	M	14.3
Average				9.2

* Values expressed in micrograms of histamine base per gram of skin, wet weight.

* From the Division of Dermatology, Department of Medicine, Western Reserve University, School of Medicine, Cleveland, Ohio.

(Aided by grant from Research and Development Division, Department of the Army, Contract #DA-49-007-MD-573)

Received for publication May 23, 1959.

TABLE 2

*Histamine levels in eczematous antecubital skin**

Case	Age	Color	Sex	Histamine
C. F.	20	W	F	9.7
D. S.	16	W	F	10.0
W. W.	42	C	M	11.0
S. W.	15	W	F	11.8
M. G.	68	W	M	13.7
J. M.	13	W	M	14.0
C. P.	25	C	F	14.4
J. R.	13	C	F	15.8
P. C.	15	W	F	15.9
R. G.	19	W	M	16.3
J. S.	28	W	F	16.7
C. S.	17	W	M	19.0
I. K.	24	W	F	19.8
V. S.	16	W	F	21.5
V. O.	46	W	F	22.2
R. O.	16	W	M	24.8
Average				16.0

* Values expressed in micrograms of histamine base per gram of skin, wet weight.

in concluding that the increase in histamine content in skin from individuals with atopic dermatitis was a significant factor in the production of this disease.

As a result of experimental studies in allergic skin responses in the rat and guinea pig skin, Perry (4) has concluded that antigen-antibody combination leads to histamine release, but that the skin reaction is not due to the release of histamine. His experiments lead him to the theory that the antigen-antibody reaction causes the skin reaction which then leads to the histamine release, or that possibly the antigen-antibody reaction releases an enzyme causing both the skin reaction and the histamine release.

Also, the nature of the inflammatory leukocytic infiltrate is capable of influencing the histamine content in acute and chronically inflamed skin, and this has been emphasized by Craps and Inderbitzen (10, 11). Graham and associates (12) have shown that polymorphonuclear leukocytes contain about 7 micrograms histamine per gram, eosinophile leukocytes about 360 micrograms per gram and basophile leukocytes 2,400 micrograms per gram. Hence, a significant elevation of skin histamine may be possible by an inflammatory infiltrate of eosinophile or basophile leukocytes.

CONCLUSIONS

1. Skin from the antecubital fossae of fifteen (15) normal adults had an average histamine level of 9.2 micrograms per gram, with a range from 4.2 to 14.3 micrograms.

2. Involved skin from the antecubital fossae of sixteen (16) cases of adult chronic atopic dermatitis had an average skin histamine level of 16.0 micrograms per gram with a range from 9.7 to 24.8 micrograms.

3. Although the increased skin histamine levels in atopic dermatitis is of statistical significance, this does not justify the conclusion that the increased histamine is either responsible for or of major significance in the cutaneous alterations seen in atopic dermatitis.

REFERENCES

1. FELDBERG, W. AND PATON, W. D. M.: Release of histamine from skin and muscle in cat by opium alkaloids and other histamine liberators. *J. Physiol.*, **114**: 490-509, 1951.
2. FELDBERG, W. AND SCHACHTER, M.: Histamine release by horse serum from skin of the sensitized dog and non-sensitized cat. *J. Physiol.*, **118**: 124-134, 1952.
3. SILVA, M. ROCHA E.: Histamine, Its Role in Anaphylaxis and Allergy. Springfield, Ill. Charles C Thomas, 1955.
4. PERRY, W. L. M.: Skin Histamine, Ciba Symposium on Histamine, 242-247. Boston, Little, Brown, 1956.
5. FELDBERG, W. AND MILES, A. A.: Regional variations of increased permeability of skin capillaries induced by a histamine liberator and their relation to the histamine content of the skin. *J. Physiol.*, **120**: 205-213, 1953.
6. JOHNSON, H. H., JR.: Variations in histamine levels in guinea pig skin related to skin region: age (or weight) and time after death of the animal. *J. Invest. Dermat.*, **27**: 159-163, 1956.
7. JOHNSON, H. H., JR.: Histamine levels in human skin. *Arch. Dermat. & Syph.*, **76**: 726-730, 1957.
8. LOWRY, O. H., GRAHAM, H. T., HARRIS, F. B., PRIEBAT, M. K., MARKS, A. R. AND BREGMAN, R. U.: The chemical measurement of histamine in blood plasma and cells. *J. Pharmacol. & Exper. Therap.*, **112**: 116-126, 1954.
9. JOHNSON, H. H., JR.: A microchemical method for the determination of histamine; its application to skin biopsies. *Arch. Dermat. & Syph.*, **72**: 307-312, 1955.
10. CRAPS, L. AND INDERBITZEN, T.: Histamine Cutanee et Reactions Inflammatoires. *Arch. belges de Dermat et de Syph.*, **13**: 1-19, 1957.
11. CRAPS, L. AND INDERBITZEN, T.: L'Histamine Dans de peau Humaine normale et Pathologique. *Arch belges de Dermat et de Syph.*, **13**: 113-138, 1957.
12. GRAHAM, H. T., LOWRY, O. H., WHEELWRIGHT, F., LENZ, M. A. AND HAVNER, H. P., JR.: Distribution of histamine among leukocytes and platelets. *Blood*, **10**: 467-481, 1955.