

Inflammatory response to histamine in atopic and nonatopic individuals

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The inflammatory response to histamine was studied in ten atopic and ten nonatopic control patients by a skin-window technique. All of the atopic individuals responded in 45 minutes with the exudation of large numbers of polymorphonuclear leukocytes and significant eosinophils. Only an occasional cell was exuded by the nonatopic individuals in the same time period, despite the fact that the whealing response in both groups was similar. This immediate inflammatory response to histamine is another evidence of the unique constitutional capacity of atopic individuals.

We have studied the inflammatory and whealing response to histamine in 10 atopic and 10 nonatopic individuals. Those who were atopic had clinical symptoms of allergic respiratory disease and gave positive intradermal reactions to house dust, ragweed pollen, grass pollen, or a combination of the three. Those who were nonatopic had no clinical symptoms suggestive of allergic respiratory disease and did not react when skin tested with a variety of allergens. The skin-window technique of Rebeck and Crowley¹ was used to study the cellular exudates resulting from the production of histamine wheals.

METHODS

We have used the skin of the back or the anterior surface of the thigh as the sites of our tests. The skin, if hairy, is shaved and cleansed with alcohol. With a sterile scalpel blade, the epithelium is scraped away from an area 3 to 5 ml. in diameter so as to expose the papillary layer of the corium. When removal of the epidermis is satisfactory, punctate bleeding points are seen. The denuded area is washed gently with saline, a drop of 1 to 1,000 dilution of histamine is

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placed on it or injected intradermally into it, and the area is covered with a clean sterile cover slip which in turn is covered by a slightly larger piece of cardboard. Adhesive is then applied to hold the material in place. The cover slip is removed at the appropriate time, dried in air, fixed in methyl alcohol, and stained with hematoxylin and eosin. The exuded cells form a single layer and are easily identified. There was no significant difference in the over-all response between histamine applied locally or injected intradermally into the skin-window site.

In this study a 45 minute time interval was used since Kline, Cohen, and Rudolph² reported that the maximal early response occurred in atopic individuals between 30 and 45 minutes after the intradermal injection of histamine. Furthermore, Rebuck and Crowley¹ demonstrated that there is a nonspecific response to a variety of substances which occurs later in man, a large number of neutrophils being present at three hours.

RESULTS

No significant leukocyte emigration occurred within 45 minutes in any of the ten nonatopic individuals. Search of the entire cover slip demonstrated only a very occasional area where one or two polymorphonuclear cells were seen. In the atopic patients, by contrast, large numbers of polymorphonuclear neutrophils were seen in many areas of the slide, and some eosinophils were present in almost every field. The differences were so obvious that differentiation between the two groups could be seen at a glance. Table I and Figs. 1 and 2 give the details of the patients studied and illustrate their reactions.

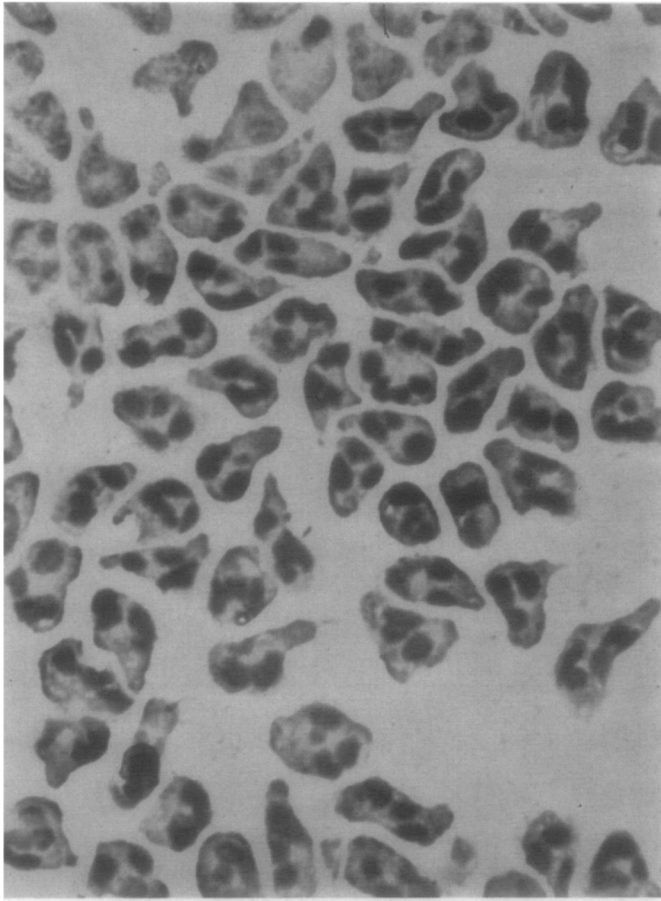
DISCUSSION

It has long been recognized that atopy is a familial immunologic disease and that one of the capacities of atopic individuals is to develop reagin to a wide variety of allergens making contact with either the respiratory or the alimentary mucosa.

Table I.

<i>Case No.</i>	<i>Sensitivity</i>	<i>Reaction</i>	<i>Case No.</i>	<i>Sensitivity</i>	<i>Reaction</i>
1	Dust	+++	11	Not sensitive	±
2	Dust	++	12	Not sensitive	0
3	Dust	+	13	Not sensitive	0
4	Dust and ragweed	++++	14	Not sensitive	0
5	Dust	+++	15	Not sensitive	0
6	Dust	++++	16	Not sensitive	0
7	Dust and ragweed	++++	17	Not sensitive	±
8	Dust	+++	18	Not sensitive	0
9	Dust	+++	19	Not sensitive	0
10	Dust	+++	20	Not sensitive	0

0, 1 or 2 cells on entire cover slip.
±, 1 or 2 cells in not more than 2 fields.
+, 10 to 30 cells in several fields.
++, 30 to 60 cells in several fields.
+++, 60 to 100 cells in many fields.
++++, More than 100 cells in most fields.

**Fig. 1**

Typical polymorphonuclear response.

Studies of the threshold of the whealing response to histamine indicate no significant difference between atopic and nonatopic persons. However, Kline, Cohen, and Rudolph² reported that there were marked differences in the cellular inflammation in the dermis involved in the wheal. They compared specific allergen and histamine wheals in human skin removed from 5 minutes to 22 hours after induction of the wheals. They stated “. . . that whereas intracutaneous injection of histamine produces but a slight tissue reaction in nonallergic individuals, its effect thirty-five minutes, three, six and twenty-two hours after injection in allergic individuals is almost indistinguishable from that produced by allergen.” The characteristic lesion resulting from either specific allergen or histamine consisted of edema and emigration of polymorphonuclear leukocytes distinguishable from ordinary inflammation in the speed of emigration and in the large numbers of eosinophils in the specimens removed at 30 minutes after induction of the wheals. At 3 hours eosinophils had disappeared, and neutrophilic polymorphonuclear cells alone were present.

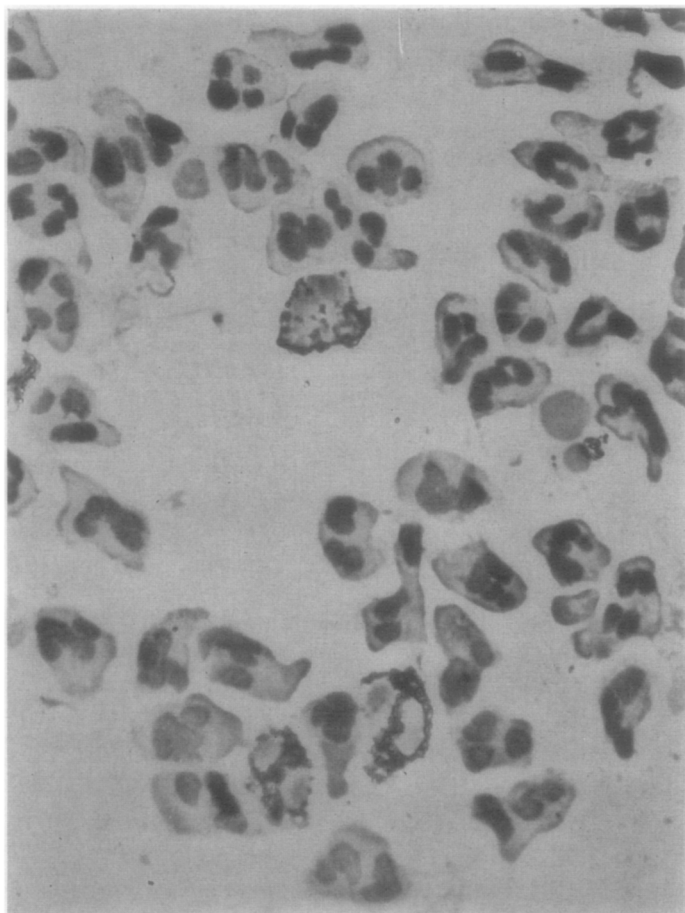


Fig. 2

Typical polymorphonuclear and eosinophil response.

Eidinger, Wilkinson, and Rose,³ utilizing the skin-window technique in humans, studied the cellular response to allergen and histamine with particular reference to eosinophilia. In the one allergic subject whose response was charted, the cover slip removed 2 hours after the application of allergen revealed a marked polymorphonuclear response as compared with that of the control non-allergic subject. Their study was concerned largely with the response at 24 hours and with the percentage of eosinophils. They do state, however: "The cellular response began earlier with appreciable numbers of polymorphonuclear leukocytes noted at 1 hour in contrast to the relative absence of cells in the control site."

Unpublished studies of one of us (M. B. C.) indicate that the peak of the eosinophilia in the nasal secretion of hay fever patients after local application of ragweed pollen occurs between 60 and 90 minutes. Since Hurley,⁴ working with rats, has noted that histamine and various other substances induced a polymorphonuclear response coming on several hours after injection and in view of the findings of Kline and co-workers,² and Eidinger and associates,³ we used an

interval of 45 minutes in our experimental system. It is probable that the variation in the cellular response, especially the eosinophilia reported by Kline, Cohen, and Rudolph, and that of Eidinger, Wilkinson, and Rose is due to differences in the techniques used (biopsy and skin window), the degree of sensitivity, and the strength of the stimulating agents. They are in agreement, however, with each other and with us that the inflammatory response begins earlier in the atopic than in the nonatopic person. If the view of Hurley, that normal rats show an inflammatory response beginning in 3 hours, can be accepted for man, it seems likely that studies should be made before the normal response could be expected to begin, if a significant difference in the inflammatory response between atopic and nonatopic individuals is to be measured. The time interval is therefore important, and probably explains the sharp differences obtained by us in this study. Hurley stated, "In addition, experiments are described showing that in certain circumstances leucocytic emigration and vascular permeability are separate phenomenon. . . ." The observation and the findings reported here refute the opinion held by some that an allergic or histamine wheal consists only of edema.

CONCLUSIONS

1. The skin-window technique is a simple and accurate method of studying the inflammatory response in man.
2. Nonatopic individuals show little or no cellular emigration 45 minutes after challenge with histamine.
3. Atopic individuals regularly produce large numbers of polymorphonuclear cells at the same time interval after challenge.
4. Eosinophilia varying from 3 to 15 per cent were present in all atopic subjects.
5. The skin-window technique may be found to be an additional method of determining the atopic constitution.

Studies are in progress to determine:

1. Whether the response described is specific for histamine or may be induced by other pharmacodynamic agents associated with the allergic response, or by less specific agents.
2. Whether parents or siblings with negative histories of allergy in whom no reaction can be demonstrated will react similarly to histamine, or
3. Whether the presence of reagin is essential for the reaction.

REFERENCES

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