

- and HLA-DR positivity in the dermis. *Arthritis Rheum* 1988;31:672-7.
60. Seibold JR, Giorno RC, Claman HN. Dermal mast cell degranulation in systemic sclerosis. *Arthritis Rheum* 1990;33:1702-9.
 61. Chanez P, Lacoste J-Y, Guillot B, et al. Mast cells' contribution to the fibrosing alveolitis of the scleroderma lung. *Am Rev Resp Dis* 1993;147:1497-502.
 62. de Paulis A, Valentini G, Spadaro G, Lupoli S, Tirri G, Marone G. Human basophil releasability. VIII. Increased basophil releasability in patients with scleroderma. *Arthritis Rheum* 1991;34:1289-96.
 63. Kaufman LD, Gruber BL, Marchese MJ, Seibold JR. Anti-IgE autoantibodies in systemic sclerosis (scleroderma). *Ann Rheum Dis* 1989;48:201-5.
 64. Valent P, Bettelheim P. Cell surface structures on human basophils and mast cells: biochemical and functional characterization. *Adv Immunol* 1992;52:333-423.
 65. Columbo M, Horowitz EM, Botana LM, et al. The human recombinant *c-kit* receptor ligand, rhSCF, induces mediator release from human cutaneous mast cells and enhances IgE-dependent mediator release from both skin mast cell and peripheral blood basophils. *J Immunol* 1992;149:599-608.
 66. de Paulis A, Ciccarelli A, Cirillo R, de Crescenzo G, Columbo M, Marone G. Modulation of human lung mast cell function by the *c-kit* receptor ligand. *Int Arch Allergy Immunol* 1992;99:326-9.
 67. MacGlashan DW Jr, Hubbard WC. IL-3 alters free arachidonic acid generation in C5a-stimulated human basophils. *J Immunol* 1993;151:6358-69.
 68. Cirillo R, Triggiani M, Siri L, et al. Cyclosporin A rapidly inhibits mediator release from human basophils presumably by interacting with cyclophilin. *J Immunol* 1990;144:3891-7.
 69. de Paulis A, Ciccarelli A, Cirillo R, de Crescenzo G, Columbo M, Marone G. Cytokine-induced modulation of human Fc ϵ RI⁺ inflammatory cells. In: Romagnani S, Mosmann TR, Abbas AK, eds. *New advances on cytokines*. New York: Raven Press, 1992:367-86.
 70. Merget RD, Maurer AB, Koch U, et al. Histamine release from basophils after in vivo application of recombinant human interleukin-3 in man. *Int Arch Allergy Appl Immunol* 1990;92:366-74.
 71. White MV, Igarashi Y, Emmerly BE, Lotze MT, Kaliner MA. Effects of in vivo administration of interleukin-2 (IL-2) and IL-4, alone and in combination, on ex vivo human basophil histamine release. *Blood* 1992;76:1491-5.

Basophils and eosinophils in allergic rhinitis

**Robert M. Naclerio, MD, Fuad M. Baroody, MD, Anne Kagey-Sobotka, PhD,
and Lawrence M. Lichtenstein, MD** *Baltimore, Md.*

Unequivocal data support the role of the mast cell in the immediate or early-phase anaphylactoid reaction to antigen. Although the contribution of the early reaction to the pathophysiology of allergic rhinitis should not be ignored, there is clear evidence that the early response cannot fully explain the extent of the disease. One of the more important observations that led investigators to this conclusion is that systemic corticosteroids do not inhibit the early response to antigen in the nose, despite having a profound effect on the clinical course of the disease.¹ This discrepancy in the effect of systemic corticosteroids between experimental and clinical disease led to multiple

Abbreviations used

ICAM-1: Intercellular adhesion molecule-1
IL: Interleukin
PGD₂: Prostaglandin D₂
VCAM-1: Vascular cell adhesion molecule-1

investigations into the inflammatory processes after the early reaction. The central hypothesis behind these efforts was that the infiltration of inflammatory cells into the site of an allergic reaction alters the reactivity of the end organ. In the nose, manifestations of altered reactivity include late-phase reactions, priming, and hyperresponsiveness to nonantigenic stimuli. We briefly describe here some of our observations on the characterization of the cellular changes that occur after nasal provocation with antigen. We will not only focus on changes in basophils and eosinophils in nasal secretions but also include some observations on cellular changes that occur within the nasal mucosa.

From the Departments of Medicine (Division of Clinical Immunology) and Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine.

Reprint requests: Robert M. Naclerio, MD, Department of Surgery MC 1035, University of Chicago Medical Center, Room E-114, 5841 S. Maryland Ave., Chicago, IL 60637. *J ALLERGY CLIN IMMUNOL* 1994;94:1303-9.

Copyright © 1994 by Mosby-Year Book, Inc.
0091-6749/94/\$3.00 + 0 1/0/59930

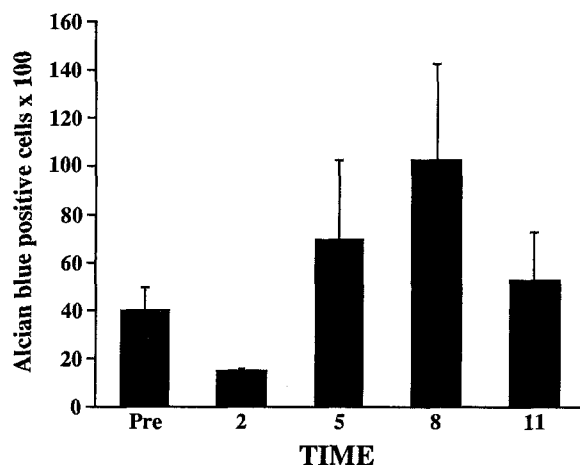


FIG. 1. Number of alcian blue-positive cells recovered by combining nasal lavages obtained at different time points before and after allergen provocation. Data are depicted as mean $\pm$ SEM of 10 allergic subjects. Abscissa represents different time points of collection: *Pre*, Cells recovered from three nasal washes performed at baseline before allergen challenge; 2, cells recovered from washes obtained 20 minutes, 1 hour, and 2 hours after allergen challenge; 5, cells recovered from washes obtained 3, 4, and 5 hours after allergen challenge; 8, cells recovered from washes obtained 6, 7 and 8 hours after allergen challenge; 11, cells recovered from washes obtained 9, 10 and 11 hours after allergen challenge.

BASOPHILS

In human nasal provocation studies levels of both histamine and prostaglandin D_2 (PGD_2) increased in nasal lavages during the early reaction to allergen challenge, but only histamine increased during the late reaction.² Because mast cells and basophils both contain histamine but only mast cells, not basophils, can generate PGD_2 ,³ we hypothesized that mast cells were the source of histamine during the early reaction whereas basophils were the source during the late reaction. To support this hypothesis we used light-microscopic criteria and alcian blue staining to identify basophils in nasal secretions during the late reaction (Fig. 1). We found a strong correlation between the influx of basophils during the late-phase reaction and the concurrent late increase in histamine ($r = 0.72$; $p < 0.001$).⁴ Because basophils made up approximately 1% of the cell influx, their numbers were too small to allow the use of electron microscopy for more definitive identification. Therefore we tried to study the functional characteristics of these cells *ex vivo* in an attempt to confirm our hypothesis.

We challenged allergic subjects with antigen and recovered cells from their nasal secretions 24 hours

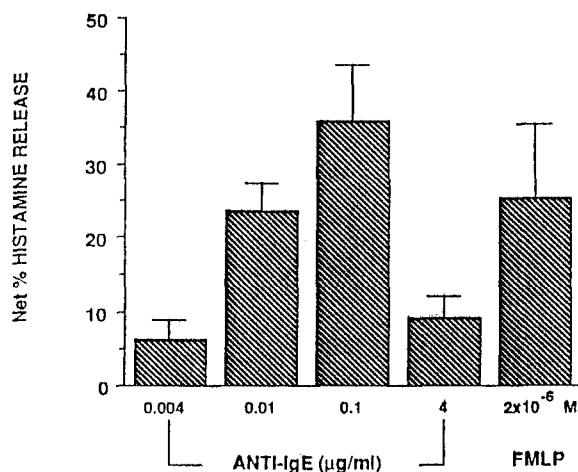


FIG. 2. Nasal leukocyte histamine release in response to different stimuli. Data are depicted as mean $\pm$ SEM of seven experiments. Nasal leukocytes released histamine in a dose-dependent fashion in response to anti-IgE and also responded to *N*-formyl-methionyl-leucyl-phenylalanine (*FMLP*). (From Iliopoulos O, Baroody F, Naclerio RM, Bochner BS, Kagey-Sobotka A, Lichtenstein LM, *J Immunol* 1992;148:2223-8. Copyright 1992, The Journal of Immunology.)

later.⁵ We examined the ability of these cells to release histamine in response to a number of stimuli. Before any stimulation, the cells had a high degree of spontaneous histamine release. However, they responded to *N*-formyl-methionyl-leucyl-phenylalanine, a secretagogue that preferentially stimulates basophils but not mast cells (Fig. 2). They also responded to anti-IgE in a dose-dependent fashion, and the highest histamine release occurred at 0.1 $\mu\text{g/ml}$ of anti-IgE, a dose that also leads to maximal release from blood basophils⁶ (Fig. 2). On the other hand, maximal histamine release from lung mast cells occurs at anti-IgE concentrations between 1 and 3 $\mu\text{g/ml}$.⁷ Nasal cells also released histamine in response to ragweed *Amba* I.⁵ These studies demonstrated that the functional characteristics of nasal leukocytes were those of basophils, not mast cells.

We further attempted to characterize these histamine-secreting cells by evaluating them for surface markers with indirect immunofluorescence and flow cytometry. Cells obtained 24 hours after antigen provocation were double stained for IgE and CD18, a surface marker present on basophils but not on mast cells.⁸⁻¹⁰ More than 90% of IgE-bearing cells were also found to coexpress CD18 (Fig. 3), further evidence that cells entering the nasal secretions during the late reaction were basophils.⁵

The different pattern of mediator release be-

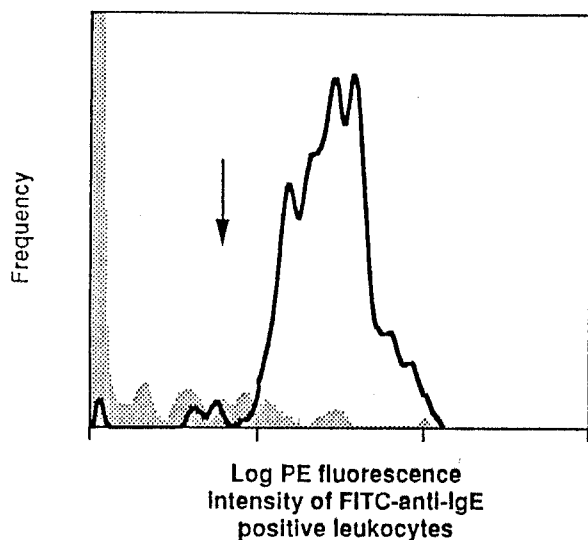


FIG. 3. Coexpression of CD18 on IgE-bearing nasal leukocytes recovered by nasal lavages of allergic volunteers 24 hours after allergen provocation. Coexpression of CD18 was analyzed after initial gating with scatter, and green fluorescence was done to identify uniform population of IgE-bearing cells. Shaded and solid lines delineate areas that represent staining with control and CD18 antibodies, respectively. Region to left of arrow represents 95% of all control events. Data from one experiment are representative of three others. (From Iliopoulos O, Baroody F, Naclerio RM, Bcohrer BS, Kagey-Sobotka A, Lichtenstein LM. *J Immunol* 1992;148:2223-8. Copyright 1992, The Journal of Immunology.)

tween the early and late reaction suggested that mast cells did not participate in the late reaction. We tested this hypothesis further by evaluating nasal secretions for tryptase and $9\alpha, 11\beta$ PGF₂. The former is a specific marker for mast cells and not basophils, whereas the latter is the major metabolite of PGD₂ and can thus provide information on whether PGD₂ is synthesized but then rapidly metabolized, resulting in our inability to detect it during late-phase reactions. We studied seven subjects who had a late histamine response to nasal provocation with antigen. In these experiments striking increases in tryptase, PGD₂ and $9\alpha, 11\beta$ PGF₂ were associated with the release of histamine during the early but not the late reaction (Fig. 4).¹¹ This study supports the role of the basophil in the late reaction and suggests that mast cells are not activated during the late reaction. This latter observation could have been determined only by lavage studies because biopsies would not distinguish the time at which mast cells were degranulated.

In addition to relating basophils to histamine release during the late reaction, we also investi-

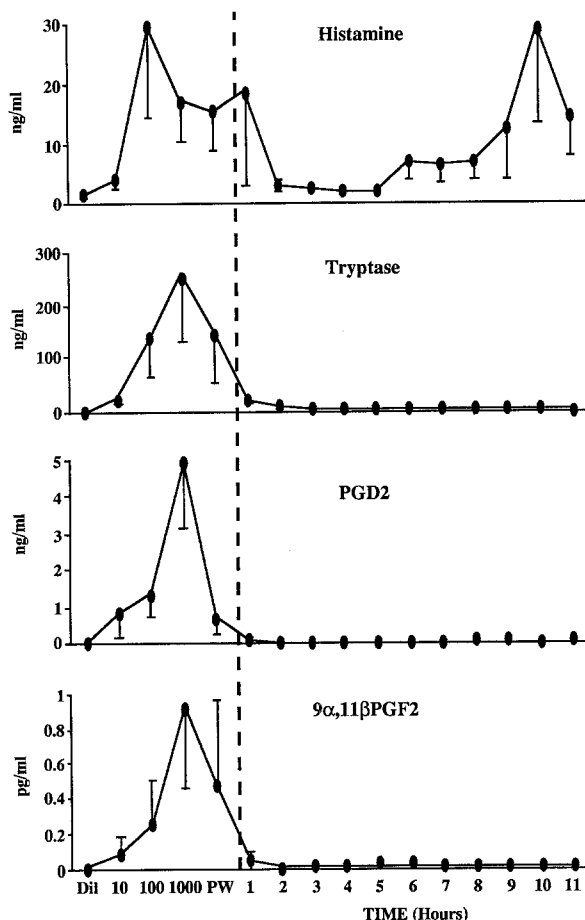


FIG. 4. Mediator release after nasal allergen challenge of allergic subjects. Data are depicted as mean $\pm$ SEM of seven subjects. Challenge protocol is shown on abscissa. Dil, diluent; 10, 100, and 1000; doses of antigen in protein nitrogen units; PW, wash 20 minutes after challenge with highest antigen dose. Dashed line separates early and late reactions.

gated their relationship to hyperresponsiveness. In a study of nasal priming (defined as the increased reactivity to antigen subsequent to prior antigen stimulation) we found that the number of basophils increased on the days when priming occurred.¹² Because our ex vivo studies showed that basophils obtained from nasal secretions released histamine in a dose-dependent manner in response to *Amba* I, it is reasonable to speculate that these cells may be a target for repeated antigen exposure in the nasal mucosa. Supporting this notion is the observation that rechallenge of the nasal mucosa 11 hours after an initial challenge leads to augmented histamine release without an augmentation in the release of PGD₂.¹ This study suggests that the histamine obtained during the rechallenge response originates not

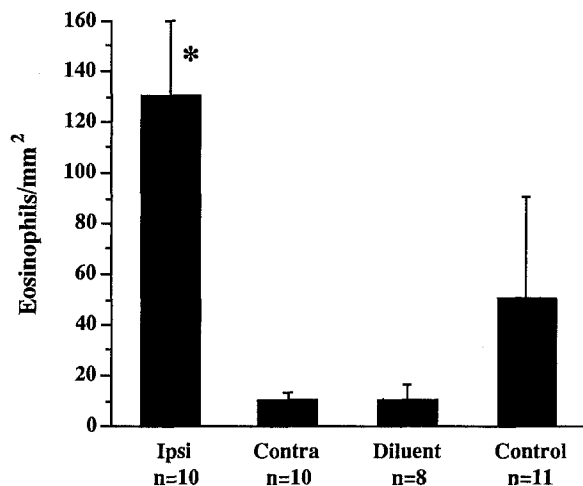


FIG. 5. Eosinophil count in nasal biopsy specimens from allergic and nonallergic subjects. Data are depicted as mean $\pm$ SEM. *Ipsi*, Specimens obtained at ipsilateral (same) site of allergen challenge in allergic subjects out of season; *Contra*, specimens obtained from contralateral unchallenged site in same allergic subjects; *Diluent*, specimens obtained from seasonal allergic subjects out of season, 24 hours after challenge with diluent for allergen extract; *Control*, specimens from nonallergic subjects 24 hours after ragweed allergen challenge. Asterisk, $p < 0.05$ versus all other groups.

only from the acute degranulation of mast cells but also from basophils that have been recruited during the late-phase reaction. Interestingly this increase in histamine on rechallenge with antigen is reduced by treatment with systemic steroids.¹ Basophil numbers also increase when the nose becomes hyperresponsive to histamine, an example of increased nonspecific reactivity.¹³

Basophils might have roles other than generation of histamine during the late-phase response, and among these could be the release of proinflammatory cytokines. Recent *in vitro* experiments with peripheral blood basophils have shown that these cells are capable of producing interleukin (IL)-4 in response to an IgE-mediated stimulus such as anti-IgE. The importance of this observation is evident because IL-4 is a mast cell growth factor¹⁴ and also promotes the switching of B cells to the production of IgE.¹⁵

EOSINOPHILS

The presence of basophils in nasal secretions has been a focus of our studies. We recognize, however, that the cells entering the nasal lumen in greatest numbers are neutrophils and eosinophils.¹⁶ The eosinophil not only enters the nasal cavity hours after nasal provocation but also degranulates, as evidenced by the recovery of major

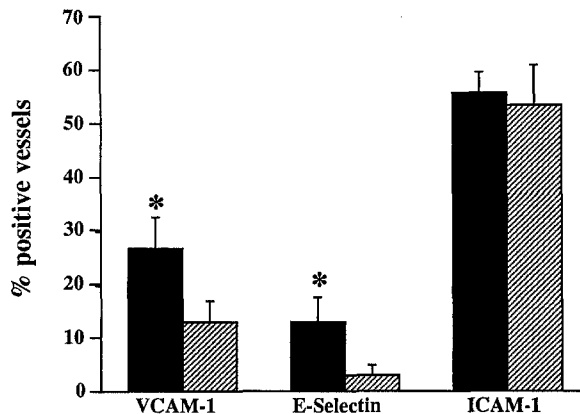


FIG. 6. Expression of adhesion molecules on nasal vascular endothelium. Data represent percentage of total vessels (identified by staining with von Willebrand factor) that stained positive with each of adhesion molecules studied: VCAM-1, E-selectin, and ICAM-1. Data are depicted as mean $\pm$ SEM of 10 allergic subjects (dark bars) and 13 nonallergic control subjects (striped bars). Biopsies were performed 24 hours after allergen provocation in both groups. Asterisk, $p < 0.05$ when allergic subjects were compared with nonallergic control subjects.

basic protein in nasal lavage fluids.¹⁷ Multiple other lines of evidence support the eosinophil's functional role in allergic inflammation, but these are beyond the scope of this review. Instead, studies relating to the eosinophil in the nasal mucosa are discussed.

We developed a localized nasal challenge system that allows us to perform biopsies at the site of challenge and at distant sites. To understand better the relationship between changes in cell number in nasal secretions and in the nasal mucosa after antigen challenge, we obtained nasal lavage and biopsy specimens from 18 allergic and 11 nonallergic subjects.¹⁸ We assessed biopsy specimens 24 hours after antigen challenge for mucosal thickening, intraepithelial migration of inflammatory cells, density of goblet cells and mucoserous glands, and thickness of basement membrane and subepithelial collagen deposition, and compared allergic and nonallergic subjects. The numbers of eosinophils, mononuclear cells, and neutrophils in lavages were also quantified. In 10 subjects we also obtained biopsy specimens 24 hours after allergen provocation from the challenged inferior turbinate (ipsilateral) and from the opposite unchallenged turbinate (contralateral).

No significant differences were found in the numbers of goblet cells and glands or in basement membrane thickness and subepithelial collagen between the groups. Allergic subjects had significantly thicker epithelium than did nonallergic

subjects (0.04 ± 0.004 mm vs 0.07 ± 0.01 mm; $p < 0.01$). Counts of intraepithelial mononuclear cells were significantly higher in allergic versus nonallergic subjects (56 ± 4 cells/mm² vs 39 ± 7 cells/mm²; $p < 0.05$). These differences between the allergic and nonallergic subjects were observed on examination of both the ipsilateral and contralateral biopsy specimens of the allergic subjects, suggesting that the increases in intraepithelial mononuclear cells and the thickening of the basement membrane are preexisting conditions in allergic subjects. When compared with nonallergic subjects, allergic subjects had significantly more eosinophils and neutrophils in lavage and more eosinophils and mononuclear cells in the nasal mucosa (Fig. 5). A significant increase in tissue eosinophils and mononuclear cells occurred only at the site of challenge. The increase in eosinophil count did not affect the histologic appearance of the epithelium, because the epithelial thickness was similar at the site of challenge and in the opposite nostril. This finding contrasts with the idea that eosinophil influx leads to epithelial desquamation during the late-phase reaction.

To identify the mononuclear cells in the nasal mucosa after allergen provocation, we challenged with ragweed extract 13 subjects with allergic rhinitis out of season.¹⁹ Antigen was applied to one inferior turbinate, and biopsy specimens of both turbinates were obtained 24 hours later. Results of the ipsilateral biopsies were compared with those of the contralateral side and with biopsy results of the inferior turbinates of eight allergic subjects with rhinitis out of season without previous challenge. Immunostaining with the modified alkaline phosphatase/anti-alkaline phosphatase method was then performed. Monoclonal antibodies against CD3 (total T lymphocytes), CD4 (helper T cells), CD8 (suppressor T cells), CD25 (IL-2 receptor-bearing cells), CD19 (B cells), CD14 (monocytes), CD45 (leukocytes), and HLA-DR were used for staining. There were significant increases in the numbers of CD45⁺, CD3⁺, CD4⁺, and CD25⁺ cells in the allergic subjects at the site of challenge when compared with the contralateral side and with biopsy specimens obtained from allergic subjects without prior provocation. No significant differences were noted in the numbers of CD8⁺, CD19⁺, CD14⁺, or HLA-DR⁺ cells. From these studies we concluded that the majority of leukocytes infiltrating the submucosa were lymphocytes of the helper subset, a portion of which are activated as evidenced by IL-2-receptor expression (CD25).

In contrast to the results obtained from nasal

provocation studies, biopsy specimens obtained only from subjects preseasonally and postseasonally showed changes in tryptase-positive mast cells and activated eosinophils, whereas changes in lymphocyte numbers were not identified. We found a similar difference between provocation and natural exposure when we compared changes in the number of lymphocytes 24 hours after challenge with those of lymphocytes in biopsy specimens obtained from symptomatic unchallenged perennial allergic subjects.¹⁹ The differences between provocation experiments and natural exposure may reflect dose and duration of antigen stimulation and the ability of provocation experiments to concentrate antigen placement at the site of biopsy. We need to extend our observations to other time points to determine better the kinetics of the lymphocytic response. Changes found at 24 hours may reflect changes early in the season, whereas changes days later may better mimic seasonal changes.

Because we hypothesize that cellular infiltration is important in the events that occur hours after allergen provocation, such as hyperresponsiveness to antigen and histamine, we must understand how these cells arrive at the site of inflammation. An early step in the movement of cells from the peripheral blood involves adhesion between circulating leukocytes and the vascular endothelium. The recent availability of monoclonal antibodies directed toward adhesion molecules permits the investigation of eosinophil recruitment in vivo. In vitro evidence suggests that vascular cell adhesion molecule-1 (VCAM-1) may be responsible in part for the selective adherence of eosinophils to the endothelium²⁰ whereas intercellular adhesion molecule-1 (ICAM-1) is more important in transmigration.²¹ VCAM-1 upregulation on nasal vascular endothelium has been reported in perennial allergic subjects.²² Further support arises from subjects with leukocyte adhesion molecule deficiency (absence of CD18/CD11 glycoprotein on circulating leukocytes), who cannot recruit neutrophils to areas of inflammation but who can recruit eosinophils and lymphocytes to these sites via VCAM-1.²³ In biopsy specimens obtained 24 hours after antigen challenge, VCAM-1 expression on the vascular endothelium increased significantly in allergic subjects ($n = 10$) when compared with normal control subjects ($n = 13$) ($26.7\% \pm 5.6\%$ vs $12.9\% \pm 3.8\%$; $p < 0.05$) whereas ICAM-1 was constitutively expressed and E-selectin was increased only slightly²⁴ (Fig. 6). Together with endothelial adhesion molecule upregulation, significantly more

eosinophils were found in the nasal mucosa of the allergic subjects as compared with the nonallergic control subjects. Because the counterligand for VCAM-1, very late antigen-4, is present on eosinophils and lymphocytes but not on neutrophils, VCAM-1 upregulation may contribute to the selective recruitment of eosinophils to the nasal mucosa after allergen provocation. The modest upregulation of E-selectin after allergen provocation can be explained by *in vitro* studies with human umbilical vein endothelial cells, which showed that E-selectin expression in response to tumor necrosis factor- α and IL-1 began 1 to 2 hours after exposure was maximal at 4 to 6 hours, and decreased markedly by 24 hours.^{25, 26} Although the upregulation of VCAM-1 may play a role in the recruitment of eosinophils, chemoattractants and growth factors undoubtedly also contribute to the selective recruitment of eosinophils.

We have shown that the predominant cells in nasal lavage 24 hours after challenge are eosinophils and neutrophils whereas simultaneous biopsy specimens have shown that the predominant cell in the mucosa is the CD4⁺ lymphocyte. Therefore we wanted to know which compartment, the nasal secretions or the mucosa, was more important in the allergic process. We thus studied the effect of intranasal steroids on the early symptomatic response and on the cellular infiltration that occurs 24 hours after allergen provocation.²⁷ Previous studies indicated that intranasal steroids did not prevent the increase in eosinophil numbers in the nasal mucosa after allergen provocation but did affect their level of activation.²⁸ These results are in contrast to other reports showing that eosinophil levels in lavage are decreased.^{4, 16} These disparities may reflect changes in compartmentalization of cells between the mucosa and secretions. For example, eosinophils expressing very late antigen-4 can bind to fibronectin in the extracellular matrix, and steroids might not affect this process. Alternatively the levels of cytokines that promote eosinophil survival may be altered. Preliminary results from our study showed that sneezing and secretion weights were significantly suppressed by intranasal steroids, suggesting an effect on the immediate response to allergen provocation.²⁷ In nasal secretions the number of eosinophils that appeared was significantly lower when the subjects were treated with intranasal steroids. In contrast to the secretions, there was no difference in the number of eosinophils in the nasal mucosa between the

placebo-treated and steroid-treated groups. These results suggest an effect of steroids on the superficial compartment without an effect on the deeper tissues. Therefore many potential explanations exist for these results and further studies are needed to better understand our findings.

In conclusion, both the eosinophil and the basophil participate in the response to nasal challenge with allergen. However, as we learn more about the pathophysiologic mechanisms of allergic inflammation, the role of these two cell types seems to become more, rather than less, complex. They are being found to secrete more and more mediators, and the location of release of these mediators may differ (e.g., nasal mucosa vs nasal secretions). Furthermore, it is clear from the literature that other inflammatory cells also contribute to the pathophysiology of allergic inflammation, and the consideration of all the possible interactions of these cells with the basophil and the eosinophil make the process even more complex. Unraveling the contribution of each cell type and the effects of the mediators it secretes will help to improve our understanding of how deposition of allergen molecules on the nasal mucosal surface of a sensitized person leads to the clinical manifestations of allergic rhinitis.

REFERENCES

1. Pipkorn U, Proud D, Lichtenstein LM, et al. Effect of short-term systemic glucocorticoid treatment on human nasal mediator release after antigen challenge. *J Clin Invest* 1987;80:957-61.
2. Naclerio RM, Proud D, Togias AG, et al. Inflammatory mediators in late antigen-induced rhinitis. *N Engl J Med* 1985;313:65-70.
3. MacGlashan DW Jr, Schleimer RP, Peters SP, et al. Comparative studies of basophils and mast cells. *Fed Proc* 1983;42:2504.
4. Bascom R, Wachs M, Naclerio RM, Pipkorn U, Galli SJ, Lichtenstein LM. Basophil influx occurs after nasal antigen challenge: effects of topical corticosteroid pretreatment. *J ALLERGY CLIN IMMUNOL* 1988;81:580-9.
5. Iliopoulos O, Baroody F, Naclerio RM, Bochner BS, Kagey-Sobotka A, Lichtenstein LM. Histamine-containing cells obtained from the nose hours after antigen challenge have functional and phenotypic characteristics of basophils. *J Immunol* 1992;148:2223-8.
6. Marone G, Kagey-Sobotka A, Lichtenstein LM. IgE-mediated histamine release from human basophils: differences between antigen E and anti-IgE-induced secretion. *Int Arch Allergy Appl Immunol* 1981;65:339-43.
7. Schulman ES, MacGlashan DW Jr, Peters SP, Schleimer RP, Newball HH, Lichtenstein LM. Human lung mast cells: purification and characterization. *J Immunol* 1982;129:2662-7.
8. Valent P, Ashman LK, Hinterberger W, et al. Mast cell typing: demonstration of a distinct hematopoietic cell type

- and evidence for immunophenotypic relationship to mononuclear phagocytes. *Blood* 1989;73:1778-85.
9. Valent P, Majdic O, Maurer D, Bodger M, Muhm M, Bettelheim P. Further characterization of surface membrane structures expressed on human basophils and mast cells. *Int Arch Allergy Appl Immunol* 1990;91:198-203.
10. Rimmer EF, Horton MA. Mast cells form a unique hemopoietic lineage. In: McMichael AJ, ed. *Leukocyte typing III: white cell differentiation antigens*. Oxford: Oxford University Press, 1988:729-31.
11. Naclerio RM, Hubbard W, Lichtenstein LM, Kagey-Sobotka A, Proud D. Histamine released during the nasal late phase reaction does not originate from mast cells. *J ALLERGY CLIN IMMUNOL* (in press).
12. Wachs M, Proud D, Lichtenstein LM, Kagey-Sobotka A, Norman PS, Naclerio RM. Observations on the pathogenesis of nasal priming. *J ALLERGY CLIN IMMUNOL* 1989;84:492-501.
13. Walden SM, Proud D, Lichtenstein LM, Kagey-Sobotka A, Naclerio RM. Antigen-provoked increase in histamine reactivity: observations on mechanisms. *Am Rev Respir Dis* 1991;143:642-8.
14. Saito H, Hatake K, Dvorak AM, et al. Selective differentiation and proliferation of hematopoietic cells induced by recombinant human interleukins. *Proc Natl Acad Sci USA* 1988;85:2288-92.
15. Del Prete G, Maggi E, Parronchi P, et al. IL-4 is an essential co-factor for the IgE synthesis induced in vitro by human T cell clones and their supernatants. *J Immunol* 1988;140:4193-8.
16. Bascom R, Pipkorn U, Lichtenstein LM, Naclerio RM. The influx of inflammatory cells into nasal washings during the late response to antigen challenge: effect of systemic steroid pretreatment. *Am Rev Respir Dis* 1988;138:406-12.
17. Bascom R, Pipkorn U, Proud D, et al. Major basic protein and eosinophil-derived neurotoxin concentrations in nasal lavage fluid after antigen challenge: effect of systemic corticosteroids and relationship to eosinophil influx. *J ALLERGY CLIN IMMUNOL* 1989;84:338-46.
18. Lim MC, Taylor RM, Naclerio RM. The histology of allergic rhinitis and its comparison to nasal lavage. *Am J Respir Crit Care Med* (in press).
19. Lim M, Baroody FM, Lee BJ, Naclerio RM, Taylor RM. Nasal mucosa cellular changes after allergen challenge [Abstract]. *J ALLERGY CLIN IMMUNOL* 1993;91:181.
20. Bochner BS, Luscinskas FW, Gimbrone MA, Lichtenstein LM, Schleimer RP. Adhesion of human basophils, eosinophils and neutrophils to IL-1-activated human vascular endothelial cells: contributions of endothelial cell adhesion molecules. *J Exp Med* 1991;173:1553-7.
21. Ebisawa M, Bochner BS, Georas SN, Schleimer RP. Eosinophil transendothelial migration induced by cytokines. *J Immunol* 1992;149:4021-8.
22. Montefort A, Feather IH, Wilson SJ, et al. The expression of leukocyte-endothelial adhesion molecules is increased in perennial allergic rhinitis. *Am J Respir Cell Mol Biol* 1992;7:393-8.
23. Williams TJ, Hellewell PG. Adhesion cell molecules involved in the microvascular inflammatory response. *Am Rev Respir Dis* 1992;146:S45-S50.
24. Lee BJ, Naclerio RM, Bochner BS, Baroody FM. Upregulation of vascular cell adhesion molecule-1 (VCAM-1) after nasal allergen (Ag) challenge [Abstract]. *J ALLERGY CLIN IMMUNOL* 1994;93:183.
25. Bevilacqua MP, Stengelin S, Gimbrone MA Jr, Seed B. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 1989;243:1160-5.
26. Pober JS, Bevilacqua MP, Mendrick DL, Lapierre LA, Fiers W, Gimbrone MA. Two distinct monokines, interleukin 1 and tumor necrosis factor, each independently induce biosynthesis and transient expression of the same antigen on the surface of cultured human vascular endothelial cells. *J Immunol* 1986;136:1680-7.
27. Driscoll PV, Naclerio RM, Baroody FM. Intranasal corticosteroids (IC) reduce eosinophil (EOS) in nasal secretions but not in the submucosa after allergen (Ag) challenge [Abstract]. *J ALLERGY CLIN IMMUNOL* 1994;93:216.
28. Lozewicz S, Wang J, Duddle J, et al. Topical glucocorticoids inhibit activation by allergen in the upper respiratory tract. *J ALLERGY CLIN IMMUNOL* 1992;89:951-7.