

THE JOURNAL OF
**Allergy AND Clinical
Immunology**

July 1994 • Volume 94 • Number 1

Assessment of eosinophil and neutrophil participation in atopic dermatitis: Comparison with the IgE-mediated late-phase reaction

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Abstract

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We hypothesized that repeated IgE-mediated late-phase reactions are critical in the pathogenesis of atopic dermatitis (AD). Prior studies have shown that extracellular deposition of eosinophil granule major basic protein (MBP) occurs in lesional AD skin, despite a paucity of infiltrating eosinophils, and that deposition of both neutrophil and eosinophil granule proteins occurs in the IgE-mediated late-phase reaction. We evaluated the participation of both eosinophil and neutrophil granule proteins in AD. Cutaneous biopsy specimens and serum and urine samples were obtained from 22 patients with AD. Lesional tissue was examined by means of immunofluorescence for neutrophil elastase and lactoferrin and for eosinophil granule MBP, eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP). Serum levels of elastase, MBP, EDN, and ECP and urine levels of MBP, EDN, and ECP were measured. Marked extracellular deposition of at least one of the eosinophil granule proteins was present in the dermis of 15 of the 22 AD skin specimens, but minimal or no extracellular neutrophil elastase or lactoferrin deposition was observed in any specimens. Serum and urine levels of MBP, EDN, and ECP in the patients were elevated when compared with those of normal controls, whereas serum levels of neutrophil elastase were not elevated. Serum MBP levels correlated with extent of body surface involvement. These results suggest that eosinophil degranulation occurs in AD but that neutrophil degranulation does not. Although eosinophil degranulation is prominent in both the late-phase reaction and in AD, the lack of neutrophil degranulation in AD demonstrates differences in the inflammatory reactions. (J ALLERGY CLIN IMMUNOL 1994;94:120-8.)

AD Atopic dermatitis
ECP Eosinophil cationic protein
EDN Eosinophil-derived neurotoxin
IL Interleukin
LPR Late-phase reaction
MBP Major basic protein

(Click on a term to search this journal for other articles containing that term.)

Key words: [Eosinophil](#), [neutrophil](#), [IgE-mediated late-phase reaction](#), [atopic dermatitis](#)

Atopic dermatitis (AD) is an intensely pruritic, eczematous skin disease that affects 1% to 4% of the population. Diagnosis is based on a cluster of signs and symptoms, as there are no specific skin changes, diagnostic histologic features, or characteristic laboratory markers.^{1, 2} AD is often

associated with a personal or a family history of atopy, elevated serum levels of IgE, and peripheral blood eosinophilia.^{1, 2} Foods and aeroallergens may provoke lesions and have been implicated as etiologic agents in some cases.^{3, 4} Extracellular eosinophil granule major basic protein (MBP) deposition has been found in the dermis of both spontaneously occurring and food allergen–provoked lesions.^{5, 6}

The late phase of the IgE-mediated reaction has been proposed as a model for chronic allergic inflammation, including that seen in AD.^{7, 8} Immediate hypersensitivity reactions in the skin are characterized by the development of a wheal and flare, which peaks in 10 to 20 minutes. This may be followed by a late inflammatory reaction at the same site. Pathologic examination of the cutaneous late-phase reaction (LPR) has shown infiltration with mononuclear cells, neutrophils, basophils, and eosinophils, and edema and mast cell degranulation.^{9, 11} Recent studies have shown extracellular deposition of eosinophil and neutrophil granule proteins in the LPR beginning 1 hour after antigen challenge and persisting for as many as 56 hours.¹² Electron microscopy has also shown evidence for eosinophil disruption in the LPR, with fragments of eosinophils and free granules in interstitial spaces.¹² Studies from allergen-induced pulmonary late-phase inflammation have shown increased interleukin (IL)-5 levels, in concert with increased levels of leukotriene C₄ and increased release of eosinophil granule proteins.¹³ IL-5 possesses eosinophilopoietic activity, enhances eosinophil survival, and is chemotactic for eosinophils.^{14, 15} Studies of the cutaneous LPR have shown increased messenger RNA expression of the cytokine gene cluster, IL-3, IL-4, IL-5, and granulocyte monocyte colony stimulating factor.¹⁶ IL-3 and granulocyte monocyte colony stimulating factor, in addition to IL-5, strikingly enhance eosinophil degranulation.¹⁷

To determine whether the pathologic changes in AD resemble those of the cutaneous LPR, we studied lesional AD specimens for evidence of neutrophil and eosinophil degranulation by indirect immunofluorescent localization of granule proteins. We also performed immunoassays of serum and urine for eosinophil granule MBP, eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP), and neutrophil elastase and correlated these with the extent of AD lesions.

Methods

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Identification of patients and collection of specimens

Twenty-two patients whose skin disease satisfied the diagnostic criteria for AD as defined by Hanifin and Rajka were studied.² This study was approved by our Institutional Review Board, and all participating patients gave informed consent. Body surface involvement was estimated by the “rule of nines.”¹⁸ Four millimeter punch biopsy specimens from lesional skin were obtained, fixed in 10% neutral buffered formaldehyde, and embedded in paraffin. Serum and urine were collected the same day as the skin specimens from 19 and 14 patients, respectively. Eosinophil

counts on the blood were calculated by multiplying the total white blood cell count by the percentage of eosinophils.

Immunofluorescent localization of granule proteins

An indirect immunofluorescent method was used to detect the presence of eosinophil MBP, EDN, and ECP and neutrophil elastase and lactoferrin in the formaldehyde-fixed, paraffin-embedded skin biopsy specimens, as described previously.^{12 19 21} Briefly, tissue sections were cut and affixed to glass slides with fast resin glue (LePage's Ltd., Bramalea, Ontario, Canada). The sections were deparaffinized in xylene, rehydrated, and digested with trypsin. After the trypsin treatment, sections were washed thoroughly and incubated overnight in 10% normal serum at 4° C (10% normal goat serum for detection of eosinophil granule proteins, MBP, EDN, ECP, and lactoferrin; 10% normal rabbit serum for detection of neutrophil elastase). After the washing, serial sections were overlaid with either control sera or antibody (affinity chromatography-purified rabbit antihuman MBP, affinity chromatography-purified rabbit antihuman EDN, rabbit antihuman ECP, rabbit antihuman lactoferrin [Sigma, St. Louis, Mo.], sheep antihuman neutrophil elastase [Serotec, Oxford, U.K.]) and incubated for 30 minutes at 37° C. Subsequently, the slides were washed and stained with 1% chromotrope 2R (Index No. 15670, Harleco, Gibbstown, N.J.) for 30 minutes at room temperature to eliminate nonspecific staining of eosinophils.²² After they were washed, the slides were overlaid with fluorescein isothiocyanate-conjugated antiimmunoglobulin (either goat antirabbit IgG or rabbit antisheep IgG); slides were incubated at 37° C for 30 minutes and washed again. Finally, the slides were mounted in glycerol solution containing paraphenylenediamine,²³ and they were examined with a Zeiss standard microscope (Carl Zeiss, Oberkochen, F.R.G.) equipped with a Zeiss IV FL vertical illumination for epi-fluorescence and fluorescein filter system (Zeiss No. 487710). Representative photomicrographs were taken. Formaldehyde-fixed nasal polyp tissue with both eosinophil and neutrophil infiltration was included in each assay as a positive control.²⁴

Stained biopsy specimens were evaluated microscopically and assigned a score from 0 to +3 for extracellular protein deposition, on the basis of the intensity and extent of the fluorescence, as follows: 0, no extracellular protein deposition; +1, focal areas of extracellular protein deposition; +2, focal but dense areas of extracellular protein deposition; +3, extensively distributed areas of extracellular protein deposition.

Immunoassays for serum and urine MBP, EDN, ECP, and elastase

MBP, EDN, and ECP were measured in serum and urine by immunoassay as previously described.^{25 27} Neutrophil elastase was measured in serum with a two-site immunoradiometric assay. A panel of 19 mouse monoclonal anti-elastase antibodies were generated from mice injected with neutrophil elastase (Elastin Products, Inc., Owensville, Mo.); supernatants were tested for their ability to bind ¹²⁵I-labeled elastase (98% pure elastase, Biodesign, Inc., Kennebunkport, Maine). The five antibodies that bound the highest quantities of elastase were used in 25 different combinations in a two-site immunoradiometric assay to determine the best pair, on the basis of the maximum counts of the second antibody bound. Two antibodies were selected for the assay on the basis of the combination trials, the slope and range of the titration curve, and the degree of nonspecific binding. Briefly, wells (Immunolon 4; Dynatech Laboratories, Inc., Chantilly, Va.) were coated for 3 hours with affinity-purified rabbit antimouse IgG antibody (Cappel Laboratories, West Chester, Pa.), diluted 1:100 with phosphate-buffered saline solution. After a

washing, the wells were coated again with one of the mouse monoclonal antibodies, protein A purified, at a concentration of 5 µg/ml, overnight at 4° C. Test samples at 100 µl dilutions or neutrophil elastase standard (Biodesign, Inc.) were incubated for 2 hours at 22° C, washed, and blocked with 1% normal mouse serum for 1 hour at 22° C. The wells were washed and incubated with 50 ng/ml of the other monoclonal antibody labeled with ¹²⁵I, washed again, and counted in a multichannel gamma counter (RIASTAR; Packard Instrument Co., Inc., Downers Grove, Ill.). All assays had an internal control, and the interassay variability was less than 15%. The lower detection limit of the assay was 0.25 ng elastase/ml. The specificity of the assay was also verified (Sur S, Kita H, Leiferman KM, et al. Localization of eosinophil-derived neurotoxin and eosinophil cationic protein in neutrophilic leukocytes. Submitted). Normal serum levels were established in a control group consisting of 50 blood bank donors with no history of smoking, asthma, or allergies. Normal urine levels were established in a control group of 20 normal individuals. Serum IgE levels were measured by using an IgE radioimmunoassay (Quanticlone assay; Kallestad Diagnostics, Chaska, Minn.).

Statistics

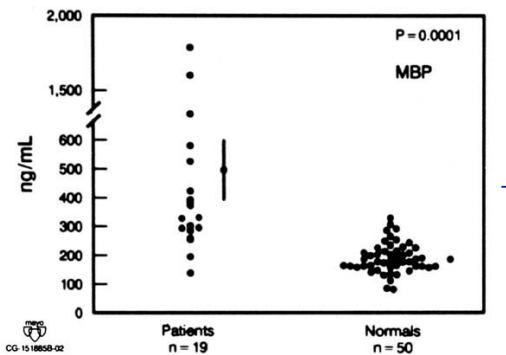
Spearman's rank correlation (Abacus Concepts, StatView II; Abacus Concepts, Inc., Berkeley, Calif.) was performed to analyze relationships among the test variables, including tissue deposition of MBP, EDN, and ECP, serum levels and urine levels of MBP, EDN, and ECP, tissue deposition and serum levels of neutrophil elastase, tissue deposition of lactoferrin, serum IgE levels, calculated blood eosinophils, and percent body surface involvement.

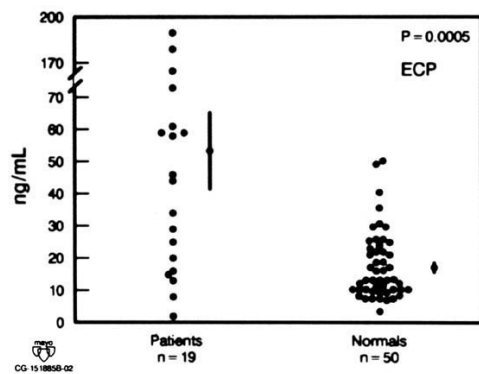
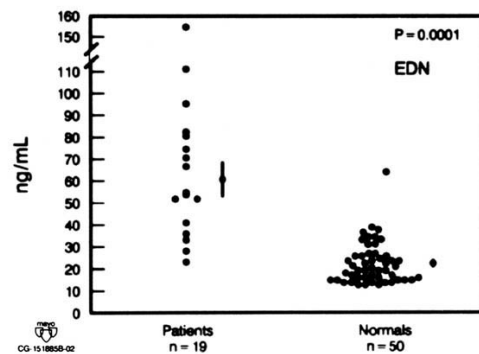
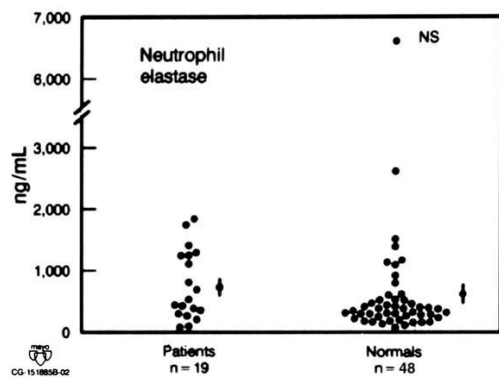
Results

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Characteristics of the 22 patients with atopic dermatitis are summarized in ■Table I. The patients ranged in age from 3 to 52 years (mean age, 25 years); nine were male, and 13 were female. Extent of body surface involvement with AD lesions ranged from 21% to 95% (mean, 58%). Four of 19 patients in whom blood differential counts were available exhibited peripheral-blood eosinophilia (greater than 760 cells/µl), and 18 of 19 patients demonstrated elevated levels of serum IgE (range, 76 to 38, 178 units/ml; mean, 9350 ± 2510 standard error of the mean; normal, 20 to 367 units/ml). Serum levels of MBP, EDN, and ECP were elevated in 15 of 19, 14 of 19, and 10 of 19 specimens, respectively; serum neutrophil elastase was not elevated in any of the 19 specimens (■Table I, ■Fig. 1). Urine levels of MBP, EDN, and ECP were elevated in 3 of 14, 7 of 14, and 0 of 14, respectively. Fifteen of the 22 patients demonstrated +2 or greater extracellular deposition of at least one eosinophil granule protein in lesional skin specimens, whereas no patient demonstrated greater than +1 neutrophil elastase or lactoferrin deposition (■Fig. 2). Representative photomicrographs of the immunofluorescence staining for MBP, EDN, ECP, neutrophil elastase, and lactoferrin are shown in ■Fig. 3.

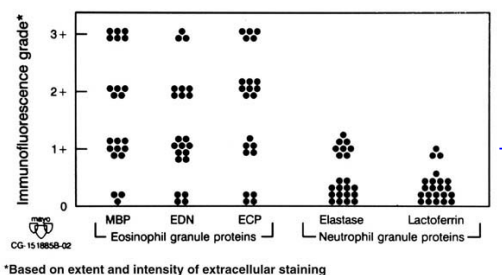
FIG. 1. Eosinophil and neutrophil granule protein levels in serum from atopic dermatitis (AD) patients and controls measured by radiometric assay and compared by Mann-Whitney U testing. Standard error of the mean (SEM). *Upper left:* Serum MBP levels in 19 AD patients and 50 controls; mean $499.4 \text{ ng/ml} \pm 100.3 \text{ (SEM)}$ and $184.7 \text{ ng/ml} \pm 6.5 \text{ (SEM)}$, respectively; $p = 0.0001$. *Upper right,* Serum neutrophil elastase levels in 19 AD patients and 48 controls; mean $755.7 \text{ ng/ml} \pm 132.9 \text{ (SEM)}$ and $612.9 \text{ ng/ml} \pm 143.8 \text{ (SEM)}$; not significant. *Lower left,* Serum EDN levels in 19 AD patients and 50 controls; mean $61.1 \text{ ng/ml} \pm 7.6 \text{ (SEM)}$ and $20 \text{ ng/ml} \pm 1.2 \text{ (SEM)}$, respectively; $p = 0.0001$. *Lower right,* Serum ECP levels in 19 AD patients and 50 controls; mean $53.1 \text{ ng/ml} \pm 12 \text{ (SEM)}$ and $17.4 \text{ ng/ml} \pm 1.5 \text{ (SEM)}$, respectively; $p = 0.0005$.





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FIG. 2. Extracellular eosinophil and neutrophil granule protein deposition in lesions of atopic dermatitis. Biopsy specimens from 22 AD patients were studied for three eosinophil granule proteins and two neutrophil granule proteins; extracellular protein deposition was graded from 0 to 3 +, as described in the text. Normal skin from normal subjects and patients with respiratory allergies showed no eosinophil or neutrophil granule protein deposition.



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FIG. 3. Localization of eosinophil and neutrophil granule proteins by indirect immunofluorescence in serial sections of atopic dermatitis lesion. **A**, Photomicrograph of lesional tissue stained for MBP (original magnification = $\times 160$); extracellular fibrillar deposition (+2) is present, with few intact eosinophils. **B**, Photomicrograph of **(A)** after counterstaining with hematoxylin and eosin (original magnification = $\times 160$). **C**, Photomicrograph of a section from the same tissue specimen as in **(A)** stained for EDN (original magnification = $\times 160$), showing (+2) extracellular fibrillar deposition with small numbers of intact eosinophils. **D**, Photomicrograph of a section from

the same tissue specimen as in **(A)** stained for ECP (original magnification = $\times 160$), showing (+3) extracellular fibrillar deposition with few intact eosinophils. **E**, Photomicrograph of a section from the same tissue specimen as in **(A)** stained for neutrophil elastase (original magnification = $\times 160$), showing cellular localization with no extracellular deposition. **F**, Photomicrograph of a section from the same tissue specimen as in **(A)** stained for neutrophil lactoferrin (original magnification = $\times 160$), showing cellular localization with no extracellular deposition.

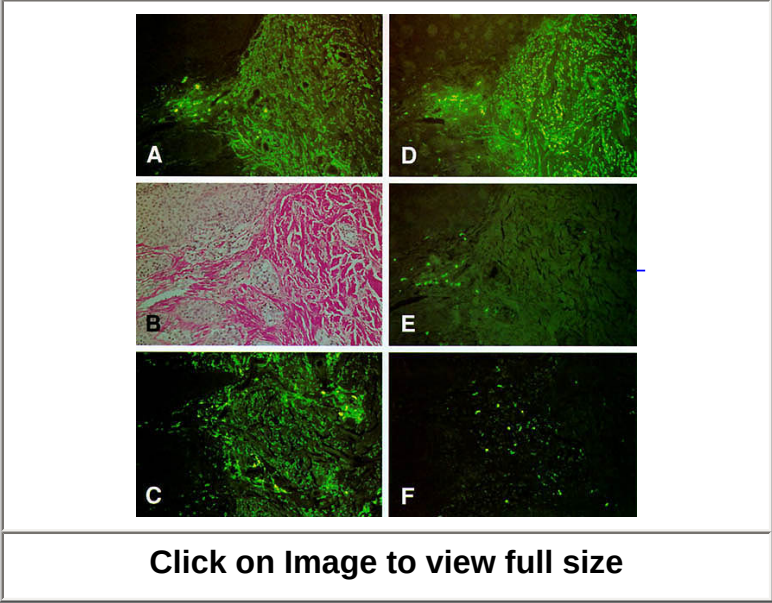


TABLE I. Characteristics of atopic dermatitis patients and investigative results

Case	Age/ gender	Serum IgE (20- 367 U/ ml)	% Body surface involvement	Serum MBP (87- 287 ng/ml)	Serum EDN (2.4- 37.6 ng/ml)	Serum ECP (0-39 ng/ml)	Serum elastase (0-2606 ng/ml)	Tissue MBP (0)	Tissue EDN (0)	Tissue ECP (0)	Tissue elastase (0)	Tissue lactoferrin (0)	Urine MBP (0- 24.2 ng/ ml)	Urine EDN (9- 593 ng/ ml)	Urine ECP (0-8 ng/ ml)
1	3/F	38,178	95	1775	80.4	33	450	1	0	0	1	1	NA	NA	NA
2	39/F	2348	50	226	26.7	1	138	3	3	2	0	0	NA	NA	NA
3	31/F	1522	79	428	35.1	15	858	1	2	1	0	0	11.5	496	1
4	9/M	1257	33	389	52.9	24	1462	1	1	0	1	0	18.9	895	1
5	36/M	2596	32	261	26.2	19	115	2	2	3	0	0	12.2	364	1
6	11/F	76	51	292	74.4	57	273	0	1	1	0	0	23.1	431	5
7	50/M	9557	46	300	38.8	12	285	1	1	1	0	0	10.0	1393	1
8	21/F	29,348	90	378	51.0	45	740	2	2	3	0	0	6.0	941	3
9	16/M	4685	27	583	94.6	178	1301	2	1	1	0	0	12.3	458	1
10	25/F	1395	84	1596	66.0	72	1159	1	1	2	1	1	91.0	346	1
11	39/M	8400	61	337	69.9	60	1457	1	0	2	0	0	7.3	676	1
12	31/F	27,002	46	334	22.2	7	581	3	3	3	1	0	5.0	425	1
13	52/M	8095	42	147	50.8	58	472	0	0	0	1	0	9.0	149	1
14	15/F	781	63	529	110.7	14	344	1	0	0	0	0	18.3	2121	7
15	15/M	25,667	64	309	53.5	28	432	0	1	2	0	0	26.0	2250	1
16	10/F	459	77	398	153.8	188	469	2	1	2	1	0	47.4	665	1
17	44/M	842	21	203	31.8	43	130	1	1	1	0	0	NA	NA	NA
18	23/F	10,221	56	302	40.0	58	1894	3	2	3	1	1	NA	NA	NA
19	14/F	27,193	60	662	82.0	97	1798	3	2	2	0	0	NA	NA	NA
20	25/M	2708	60	NA	NA	NA	NA	3	3	2	0	0	NA	NA	NA
21	25/F	1118	59	NA	NA	NA	NA	3	2	3	0	0	NA	NA	NA
22	22/F	2245	71	NA	NA	NA	NA	2	1	2	1	0	NA	NA	NA

NA, Not available for testing.

Normal values indicated in parentheses beneath column headings; tissues were graded 0 to 3 as described in text.

Thirteen significant correlations emerged from the statistical testing and are shown in ■ Table II. Positive correlations were found between serum levels of eosinophil granule proteins and tissue deposition of eosinophil granule proteins and between extent of body surface involvement and serum MBP ($p < 0.02$). Tissue deposition of neutrophil elastase and lactoferrin was also correlated ($p < 0.02$), but both proteins were minimally deposited. A negative correlation was found comparing serum EDN to EDN tissue deposition. A negative correlation was also found comparing urinary MBP and serum IgE.

TABLE II. Significant correlations by Spearman's rank test*

Parameters compared†		<i>n</i>	<i>r_s</i>	<i>p</i> Value
Serum MBP	Serum EDN	19	0.64	<0.007
Serum EDN	Serum ECP	19	0.63	<0.008
Serum ECP	Serum elastase	19	0.50	<0.04
Serum MBP	Serum elastase	19	0.53	<0.03
Serum EDN	EDN Deposition	19	-0.58	<0.02
MBP Deposition	EDN Deposition	22	0.76	<0.0005
MBP Deposition	ECP Deposition	22	0.67	<0.003
EDN Deposition	ECP Deposition	22	0.68	<0.002
Elastase deposition	Lactoferrin deposition	22	0.53	<0.02
Urine MBP	Serum EDN	14	0.60	<0.04
Urine MBP	Serum IgE	14	-0.70	<0.02
Body surface involvement (%)	Serum MBP	19	0.59	<0.02
Calculated eosinophils	MBP Deposition	19	0.49	<0.04

*Abacus Concepts, StatView II (Abacus Concepts, Inc., Berkeley, Calif., 1987).

†Statistical comparisons were performed on all the following parameters in all possible combinations: serum MBP levels, serum EDN levels, serum ECP levels, serum elastase levels, tissue MBP deposition, tissue EDN deposition, tissue ECP deposition, tissue elastase deposition, tissue lactoferrin deposition, urine MBP levels, urine ECP levels, urine EDN levels, serum IgE, calculated eosinophil counts and percent body surface involvement (105 total). Only significant correlations are indicated.

Discussion

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The finding of prominent dermal extracellular eosinophil granule protein deposition in the absence of dermal neutrophil granule protein deposition suggests that eosinophil degranulation is important in AD but that neutrophil degranulation is not. This is in contrast to the IgE-mediated LPR, in which both eosinophil granule protein and neutrophil elastase deposition are prominent in the dermis,^{[12](#)} and also suggests that AD cannot be explained simply as a reaction to single antigen exposure. Moreover, we studied the deposition of two neutrophil proteins from both azurophilic and specific granules to detect possible differential deposition,^{[28](#) [29](#)} and we found minimal or no deposition of either protein; the lactoferrin and elastase that were deposited were correlated ($r_s = 0.53$; $p < 0.02$). The prominent extracellular deposition of eosinophil granule proteins in the dermis was out of proportion to the few infiltrating intact eosinophils in the tissue. This pattern of eosinophil granule protein staining and the lack of neutrophil granule protein staining in the dermis have been observed in other disorders with similar clinical findings, namely prurigo nodularis and chronic lesions of onchocerciasis,^{[5](#) [30](#)} suggesting pathophysiologic similarities. In contrast, the staining pattern observed in the LPR more closely resembles that seen in physical urticarias and some cases of chronic urticaria,^{[31](#)} in which dermal deposition of eosinophil granule proteins parallels dermal deposition of neutrophil granule proteins as lesions evolve.

Faint epidermal staining, coating cell surfaces of keratinocytes with elastase and lactoferrin, was observed in several AD specimens. Although neutrophils were not prominent in the dermal infiltrates, it is possible that neutrophils were present early in the inflammatory reaction. If so, the presence of neutrophil granule proteins would be minimal because the biopsy specimens were obtained from well-established lesions. Wiedow et al.^{[32](#)} found increases in elastase activity in lesional epidermis of patients with AD. They speculated that the elastase activity was important in the epidermal spongiosis observed in atopic dermatitis, but they did not identify a specific cellular source for it. Our studies do not point to neutrophil participation in mature lesions, but they suggest faint persistence of elastase and lactoferrin in intercellular areas of epidermal cells.

Evidence for MBP and ECP elevations in sera from AD patients has been previously reported.^{[33](#) [36](#)} Our study indicates that eosinophil granule MBP, EDN, and ECP are elevated in AD sera but that serum levels of neutrophil elastase are not elevated. Although neutrophils also contain EDN and ECP, they possess much less than do eosinophils,^{[37](#)} and in the absence of elastase or lactoferrin in tissue or serum, it is unlikely that the EDN or ECP in the tissue or serum is from a neutrophil source. A recent study demonstrated EG-2 (antibody to ECP) positive eosinophils in

close contact to OKT6-positive cells (Langerhans cells) in the epidermis and dermis of AD lesions. EG-2 staining was also extracellularly distributed.³⁸ It is most likely that eosinophil granule proteins are released locally in affected areas of tissue and leak into the circulation, but we cannot exclude a release of proteins directly into the systemic circulation by activated blood eosinophils.

Serum levels of MBP and EDN were correlated ($r_s = 0.64$; $p < 0.007$) and serum levels of EDN and ECP were correlated ($r_s = 0.63$; $p < 0.008$; ■ Table II). Tissue deposition of the eosinophil granule proteins was prominent and out of proportion to the few infiltrating cells. Tissue deposition of MBP and EDN was correlated ($r_s = 0.76$; $p < 0.0005$), as was tissue deposition of MBP and ECP ($r_s = 0.67$; $p < 0.003$) and tissue deposition of EDN and ECP ($r_s = 0.68$; $p < 0.002$). The negative correlation between serum EDN levels and tissue EDN deposition ($r_s = -0.58$; $p < 0.02$) may reflect reduced ability of EDN (compared with MBP) to adhere to tissue.³⁹ Tissue deposition of the neutrophil granule proteins was minimal or absent in the specimens. One of the most interesting correlations to emerge from the studies was a relationship between body surface involvement and serum MBP levels ($r_s = 0.59$; $p < 0.02$). Previous studies have shown a correlation between serum IgE levels and extent of skin involvement.⁴⁰ Recently, studies have reported a correlation between serum ECP and disease activity in atopic dermatitis,^{36 41 42} and another report demonstrated that serum levels of ECP decreased with clinical improvement after high-dose UVA therapy.⁴³ Taken together, these studies suggest that eosinophil granule protein levels are indicators of disease activity.

These results indicate that eosinophils actively participate in the pathogenesis of AD. Unlike the IgE-mediated LPR, neutrophils do not appear to play a role in established lesions of AD. Although the immunohistochemical findings are different in AD and the IgE-mediated LPR, we cannot exclude the possibility that they are part of the same mechanism. Repeated antigen exposure may alter inflammatory reactivity to strengthen eosinophil participation while neutrophil involvement diminishes, as has been seen in a monkey model of antigen challenge in the lung.⁴⁴ Furthermore, in AD exposure to allergen may be through a transepidermal route with Langerhans cell involvement; this is clearly different from the intradermally administered allergen in the LPR. Therefore disease expression may be modified, depending on antigen presentation, by different immunocompetent cells in the various skin compartments. These studies demonstrate that the inflammatory reaction in AD is different than in the IgE-mediated LPR.

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Publishing and Reprint Information

TOP

- *From the Department of Pediatric and Adolescent Medicine, Immunology, and Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minn.*
- *Supported, in part, by National Institutes of Health Grants AR36008 and AI 15231, The Mayo Foundation, and the Kieckhefer Foundation (Prescott, Ariz.).*
- *Received for publication April 14, 1993.*
- *Revised Oct. 7, 1993;*
- *Accepted for publication Jan. 21, 1994.*
- *Reprint requests: Kristin M. Leiferman, Mayo Clinic, 2200 First Street S.W., Rochester, MN 55905.*
- *Copyright © 1994 by Mosby—Year Book, Inc.*
- *0091-6749/94 \$3.00 + 0 1/1/54734*

Articles with References to this Article

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