

Levels of circulating CD8⁺ T lymphocytes, natural killer cells, and eosinophils increase upon acute psychosocial stress in patients with atopic dermatitis

Gerhard Schmid-Ott, MD,^a Burkard Jaeger, PhD,^a Christiane Adamek,^a Heidrun Koch,^a Friedhelm Lamprecht, MD,^a Alexander Kapp, MD,^b and Thomas Werfel, MD,^b
Hannover, Germany

Background: Different exogenous and endogenous provocation factors such as mental stress are hypothesized as being relevant in the pathophysiology of atopic dermatitis (AD).

Objective: The purpose of this study was to examine the effects of acute psychological stress on illness-specific immunologic parameters in AD. Patients with psoriasis and healthy volunteers were investigated in parallel.

Methods: Patients with AD (n = 15), patients with psoriasis (n = 15), and control subjects (n = 15) were exposed to mental stress lasting 10 minutes (public speaking, mental arithmetic). In vitro analyses were done 1 hour before, immediately after, and 1 hour after stress exposure. Vital parameters (blood pressure, heart rate) and plasma noradrenaline concentrations were determined to prove the effects of mental stress on the individuals. Lymphocytes were phenotypically analyzed by flow cytometry.

Results: The results indicate a higher ability of CD8⁺ T lymphocytes to react to stress, including the subpopulations of CD8⁺/CD11b⁺ T lymphocytes and eosinophils in patients with AD compared with healthy volunteers. The increases in the subpopulation of CD8⁺/CD11b⁺ T lymphocytes on psychological stress were higher in the patients with AD and psoriasis than in healthy control subjects. Significant stress-induced changes of natural killer cells were revealed for all 3 groups. **Conclusion:** The results suggest that psychological stress has different immunologic effects in patients with AD than in patients with psoriasis and healthy men. (*J Allergy Clin Immunol* 2001;107:171-7.)

Key words: Atopic dermatitis, psoriasis, T lymphocytes, eosinophils, noradrenaline, stress, coping

Abbreviations used

- 1*3-ANOVA: Assessment of 1 group with 3 repeated measures
2*3-ANOVA: Assessment of 2 groups (patients and controls) with 3 repeated measures
AD: Atopic dermatitis
NK: Natural killer

Atopic dermatitis (AD) is a chronic pruritic skin disease affecting about 10% to 15% of the population.¹ Different provocation factors are hypothesized as being relevant in the pathophysiology of the extrinsic and intrinsic variants of AD²: hormonal, emotional, and irritating factors; systemic or local infections; lifestyle; and the lack of infections, pollution, and inhalant and contact allergens. The central role of immunologic abnormalities for the pathogenesis of AD has often been described.¹⁻³ In the pathophysiology of AD, activated T lymphocytes and eosinophils infiltrating the skin are relevant immunologic factors.¹⁻⁸ In addition to CD4⁺ T_H lymphocytes, CD8⁺ T cells producing high levels of IFN- γ may be relevant to the pathophysiology of AD.^{4,6,9} More than 20% of all skin-infiltrating T cells are CD8⁺, as shown by immunohistology.¹⁰ In addition, we have found that more than 20% of allergen-specific T cells cloned directly from lesional skin in the presence of allergen are CD8⁺ and secrete IFN- γ .⁹ Those cytotoxic T cells are probably recruited from the circulation (the aspect that we studied).

CD8⁺ lymphocytes can be differentiated into 2 groups by the density of CD8 expression on the cell membranes (ie, CD3⁺ CD16⁻ CD8^{high}⁺ T lymphocytes and CD3⁻ CD16⁺ CD8^{low}⁺ natural killer [NK] cells¹¹). CD11b⁺ is expressed on a subpopulation of CD8⁺ T lymphocytes and on CD16⁺ NK cells.¹² In some studies T-suppressor activity has been found in CD11b⁺ T cells and cytotoxic activity in CD11b⁻ T cells, although in more recent studies both cell types showed cytolytic activity.¹²

Different studies have focused on the importance of mental stress as a cause of exacerbations of AD or

From ^athe Department of Psychosomatic Medicine and ^bthe Department of Dermatology, Hannover Medical School.

Received for publication June 22, 2000; revised September 18, 2000; accepted for publication September 18, 2000.

Reprint requests: Gerhard Schmid-Ott, MD, Department of Psychosomatic Medicine, Hannover Medical School, Carl-Neuberg-Straße 1, 30625 Hannover, Germany.

Copyright © 2001 by Mosby, Inc.

0091-6749/2001 \$35.00 + 0 1/85/111850

doi:10.1067/mai.2001.111850

bronchial asthma in children^{13,14} and adults.^{5,15-19} However, until now only a few studies have examined possible psychoneuroendocrinologic mechanisms underlying the link between stress and exacerbation or maintenance of AD.^{20,21} For psoriasis, another chronic inflammatory skin disease, the effect of psychosocial stressors, such as daily hassles or life events, on the illness outcome and coping has been described,²²⁻²⁴ and psychoneuroendocrinologic mechanisms have also been discussed.^{25,26}

This study was designed to analyze the physiologic response to evoked psychological stress (public speaking, mental arithmetic) in patients with AD, and both patients with psoriasis and healthy volunteers were used as control subjects. Lymphocyte subpopulations were analyzed 1 hour before, immediately after, and 1 hour after stress exposure. This study focuses on the effects of psychological stress on circulating lymphocyte subpopulations and eosinophils, which are of pathophysiologic relevance in AD. Patients with AD are compared with healthy volunteers and patients with psoriasis.

METHODS

Subjects and procedure

Fifteen untreated patients with AD (9 women and 6 men aged 20-48 years), 15 untreated patients with stable chronic plaque psoriasis vulgaris, and 15 healthy control subjects, matched by sex and social status and comparable by age to the patients, participated in this study after giving their informed consent. None of the patients or control subjects received medications such as corticosteroids, retinoids, methotrexate, or cyclosporin A or had another chronic disease. Furthermore, subjects and patients with alcohol or drug abuse problems were excluded from the study.

Experiments were conducted between 11.30 AM and 1.30 PM. On arrival in the laboratory, volunteers were seated and allowed to rest for 20 minutes. After this resting period, a butterfly needle was inserted into an antecubital vein, and the blood pressure cuff was placed on the other arm. Twenty minutes after insertion of the needle, a first blood sample (baseline) was drawn to analyze lymphocyte subpopulations (CD4⁺ T_H, CD8⁺ T and NK, CD8⁺, CD11b⁺ T and NK, and CD16⁺ NK cells). Leukocytes and eosinophils were determined by conventional white blood cell counts (hematoxylin-eosin staining).

Acute psychological stress was induced by volunteers performing public speaking and mental arithmetic.²⁷ Patients and control subjects were instructed to prepare a speech (topic: "Children's Position in Today's Society"). After 10 minutes of preparation, volunteers presented their speech in front of an audience (8-12 persons). The lecture was interrupted after 5 minutes, and volunteers were asked to subtract 13 from 1022 and to continue subtracting 13 from each subsequent number as fast as possible during the next 5 minutes. When a mistake was made, subjects were instructed to start again from 1022. Immediately after the end of the mental arithmetic task, a second blood sample (stress) was drawn. Subjects were then asked to be seated, and a third blood sample was drawn 60 minutes after the stress exposure (follow-up).

Endocrine analyses. All blood samples were centrifuged at 4°C, and plasma was stored at -70°C. Catecholamine plasma levels were analyzed by high-pressure liquid chromatography (electrochemical detector).

Cardiovascular parameters. Heart rate and blood pressure were continuously recorded (Criticon Dinamap; Johnson & Johnson, Norderstedt, Germany) and analyzed in parallel with the time points of blood sampling.

Preparation and cultivation of PBMCs. PBMCs were isolated from heparinized blood samples by density centrifugation on Ficoll Hypaque (Nycomed Pharma AS, Oslo, Norway) (density = 1.077 g/mL).

Immunofluorescence staining of PBMCs and flow cytometry. PBMCs were stained with a combination of labeled mAb and measured by flow cytometry as described.⁹ Expression of surface antigens on gated lymphocytes was assessed by flow cytometry with the following antibodies: CD3⁺ (Leu4, IgG1; Becton Dickinson, Heidelberg, Germany), CD4⁺ (13B8.2, IgG1; Immunotech, Hamburg, Germany), CD8⁺ (DAKO, Hamburg, Germany), CD11b⁺ (DAKO), and CD16⁺ (ION16, IgG1; Immunotech). The absolute numbers of circulating lymphocyte subpopulations and eosinophils were calculated from the results of standard white blood cell counts and differential analysis from blood smears.

Statistical analysis

Statistics of the courses of the means over time and contrasts for single groups (AD, psoriasis, and control) were calculated by 1*3-ANOVAs (assessment of 1 group with 3 repeated measures). In addition, statistical analysis of the data was performed with 2*3-ANOVAs (assessment of 2 groups [patients and control subjects] with 3 repeated measures). Because of missing cases for some analyses, the sample sizes were reduced by 1 or 2 cases. In general, 3 kinds of stress effects are presented and discussed. First, we show significant contrasts ($P_{T[B-S]}$ within the 1*3-ANOVAs) between 2 measures within 1 group (eg, a stress-induced increase of a parameter between the measures baseline and stress in AD patients). Second, significant time effects (P_T within the 2*3-ANOVAs) indicate stress-induced alterations of a parameter (between 3 measures: baseline, stress, and follow-up) of 2 groups. There is, for example, a significant stress-induced increase of a parameter between patients with AD and healthy control subjects but no significant difference between the two groups. Third, and of main interest, are significant interaction effects (P_I within the 2*3-ANOVAs). They reveal significantly different stress-induced alterations of a parameter between the 3 measures of the 2 groups (eg, AD patients reveal significantly higher changes of a parameter than healthy volunteers).

RESULTS

There were comparable and significant increases of the blood pressures and the heart rates induced by public speaking and mental arithmetic in AD patients and healthy control subjects ($P_T < .01$) as well as in psoriasis patients and healthy volunteers ($P_T < .01$, Table I). Endocrine analysis also showed significant stress-induced increases in the plasma concentrations of noradrenaline in all 3 groups ($P_T < .01$, Tables II and III). These results indicate that our stress model worked.

The stress situation induced an increase of the absolute number of circulating CD8⁺ T lymphocytes in both patient groups and in the healthy volunteers; however, it was significant only in AD patients ($P_{T[B-S]} < .01$, Fig 1). Interestingly, in AD patients the stress-induced increase of CD8⁺ lymphocytes remained high at follow-up (1 hour), whereas in psoriasis patients a decrease (indicated by a significant contrast) was observed shortly after stress (Fig 1). In summary, the results suggest a higher ability of CD8⁺ T lymphocytes in AD patients than in healthy volunteers to react to psychological stress.

We also investigated stress-induced changes in the number of the CD11b⁺ subpopulation of CD8⁺ T cells.

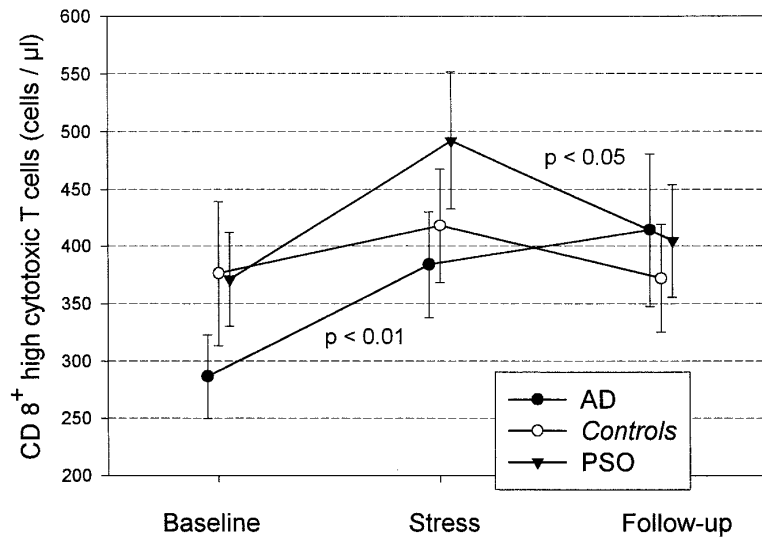


FIG 1. Number of CD8⁺ high lymphocytes 1 hour before (*Baseline*), during (*Stress*), and 1 hour after (*Follow-up*) stress exposure in patients with psoriasis (*PSO*), patients with AD, and the accompanying healthy control subjects (mean $\pm$ SE). Significant contrasts between baseline and stress as well as between stress and follow-up are marked.

TABLE I. Blood pressure and heart rate values 1 hour before (*Baseline*), during (*Stress*), and 1 hour after (*Follow-up*) stress exposure in AD patients, psoriasis patients, and healthy control subjects (mean $\pm$ SD)

	Baseline	Stress	Follow-up	2*3-ANOVA		
				P_G (df = 1)	P_T (df = 2)	P_I (df = 2,56)
RR systole (mm Hg)						
AD	126.8 $\pm$ 13.5	146.9 $\pm$ 11.4	125.7 $\pm$ 13.1	—	<.01	—
Control	128.3 $\pm$ 14.6	144.9 $\pm$ 14.6	128.1 $\pm$ 13.7			
Psoriasis	125.1 $\pm$ 13.3	145.4 $\pm$ 17.7	127.0 $\pm$ 13.6			
RR diastole (mm Hg)						
AD	74.5 $\pm$ 10.4	85.4 $\pm$ 11.3	72.5 $\pm$ 11.3	—	<.01	—
Control	75.4 $\pm$ 11.7	82.4 $\pm$ 11.2	73.7 $\pm$ 12.5			
Psoriasis	76.6 $\pm$ 14.0	84.1 $\pm$ 13.0	76.5 $\pm$ 13.5			
Heart rate (beats/min)						
AD	76.4 $\pm$ 9.7	98.6 $\pm$ 17.0	72.0 $\pm$ 11.4	—	<.01	—
Control	73.5 $\pm$ 13.3	89.2 $\pm$ 18.7	68.8 $\pm$ 9.9			
Psoriasis	76.5 $\pm$ 9.4	88.9 $\pm$ 13.1	74.5 $\pm$ 7.5			

P_G , Significant differences between the 2 groups (over all measures); P_T , stress-induced alterations of a variable over time (for both groups); P_I , stress-induced alterations of a variable being significantly different between both groups.

This lymphocyte subpopulation has been found in previous studies¹² to display “suppressive” activity. An increase of CD8⁺/CD16⁺/CD11b⁺ T cells after stress exposure (ie, between baseline and stress) was revealed in patients with AD and psoriasis ($P_{T[B-S]} < .05$, $P_{T[B-S]} < .01$), but not in healthy persons (Fig 2). This suggests a higher ability of CD8⁺/CD16⁺/CD11b⁺ T lymphocytes in patients with AD and psoriasis to react to mental stress than those in healthy control subjects.

As shown previously, lower numbers of circulating CD16⁺ NK cells are detectable in AD patients than in healthy volunteers. Here we found significant stress-induced changes of NK cells over the 3 measures for psoriasis patients and healthy control subjects ($P_T < .01$,

Table III)²⁶ and also for AD patients ($P_T < .01$, Tables II and III). However, the increase of circulating CD16⁺ NK cells during stress was transient in all 3 groups (Tables II and III).

In AD patients the stress-induced alterations of CD8⁺ lymphocytes (ie, T and NK cells) were significantly more pronounced over the 3 measures than in healthy control persons ($P_I < .05$, Table II).

As expected, the numbers of circulating eosinophils were higher in patients with AD than in healthy subjects (Fig 3). We found an increase of circulating eosinophils after acute stress (ie, between baseline and stress) in AD patients ($P_{T[B-S]} < .05$). This effect was also statistically significant when baseline and follow-up results were

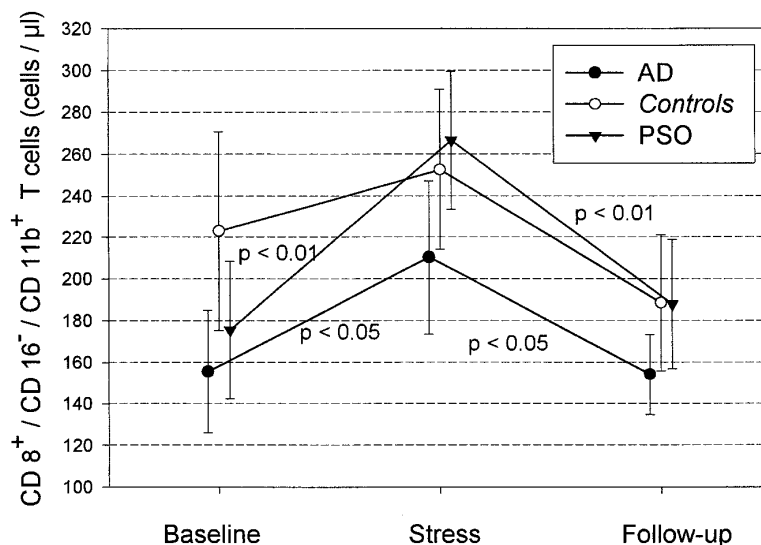


FIG 2. Number of CD8⁺/CD16⁻/CD11b⁺ lymphocytes 1 hour before (*Baseline*), during (*Stress*), and 1 hour after (*Follow-up*) stress exposure in patients with psoriasis (*PSO*), patients with AD, and the accompanying healthy control subjects (mean $\pm$ SE). Significant contrasts between baseline and stress as well as between stress and follow-up are marked.

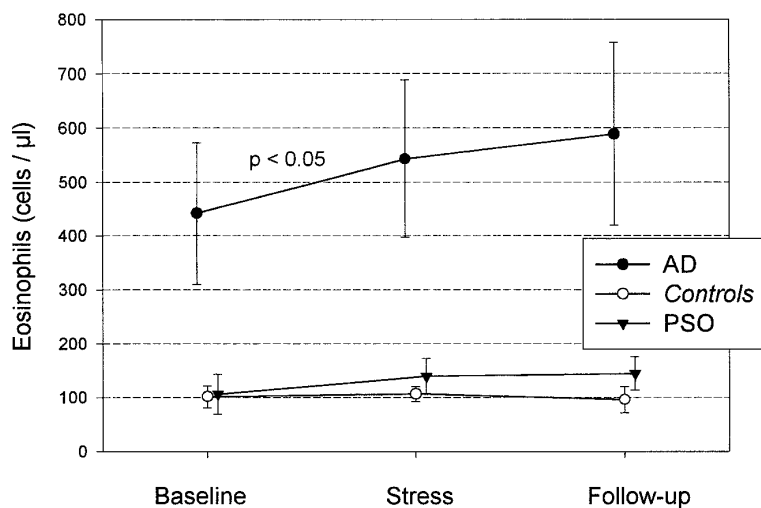


FIG 3. Number of eosinophils 1 hour before (*Baseline*), during (*Stress*), and 1 hour after (*Follow-up*) stress exposure in patients with psoriasis (*PSO*), patients with AD, and the accompanying healthy control subjects (mean $\pm$ SE). Significant contrasts between baseline and stress as well as between stress and follow-up are marked.

compared [$P_{T[B-FU]} < .05$]. The results suggest a more marked stress-induced increase and a longer lasting elevation of eosinophils after stress only in AD patients but not in psoriasis patients or healthy persons.

DISCUSSION

The chosen design is an adequate psychological stressor, as proved by the stress-induced effects on blood pressure, heart rate, and noradrenaline levels.²⁷ However, beyond the stress-induced time effects for these parameters in AD and psoriasis patients as well as in the healthy

volunteers, no significant differences between the matched groups of patients with a chronic skin disease and the control subjects were found. The insertion of a butterfly needle into the veins before the stress protocol could have caused a significant stress; however, blood pressure and heart frequency were measured continuously from the beginning of the protocol (ie, the first measure includes the time point from 20-minute pause after the insertion until the beginning of the stress itself, altogether 50 minutes). Besides, only the mean baseline systolic blood pressures were minimally raised. The baseline diastolic blood pressures and the baseline heart rates were within the normal

TABLE II. Numbers of different lymphocytes and leukocytes (cells/ μ L), as well as noradrenaline levels before (*Baseline*), immediately after (*Stress*), and 1 hour after (*Follow-up*) stress exposure in AD patients (n = 15) and control subjects (n = 15) (mean $\pm$ SD)

	Baseline	Stress	$P_{T(B-S)}$	Follow-up	$P_{T(S-FU)}$	1*3-ANOVA ($P_{T(B-S-FU)}$) (df = 2)	2*3-ANOVA		
							P_G (df = 1)	P_T (df = 2)	P_I (df = 1,86)
CD4 ⁺									
AD	957.5 $\pm$ 418.1	1043.9 $\pm$ 520.4	NS	1116.8 $\pm$ 446.2	NS	NS	—	—	—
Control	957.4 $\pm$ 457.8	910.8 $\pm$ 282.6	NS	833.1 $\pm$ 318.3	NS	NS			
CD8 ⁺									
AD	366.5 $\pm$ 150.5	538.0 $\pm$ 195.7	<.05	483.1 $\pm$ 200.5	NS	<.05	—	<.01	<.05
Control	631.5 $\pm$ 387.9	713.6 $\pm$ 283.8	NS	524.2 $\pm$ 263.4	<.01	<.05			
CD11b ⁺									
AD	283.3 $\pm$ 167.0	514.6 $\pm$ 221.0	0	252.2 $\pm$ 97.4	<.01	<.01	<.01	<.01	—
Control	614.1 $\pm$ 419.9	781.3 $\pm$ 278.2	NS	400.6 $\pm$ 233.5	<.01	<.01			
CD16 ⁺									
AD	166.4 $\pm$ 96.8	335.4 $\pm$ 136.2	<.01	155.1 $\pm$ 60.9	<.01	<.01	<.01	<.01	—
Control	420.8 $\pm$ 269.7	585.1 $\pm$ 216.9	NS	290.6 $\pm$ 141.1	<.01	<.01			
Leukocytes									
AD	6460.0 $\pm$ 1835.7	6946.7 $\pm$ 1885.6	<.01	7426.7 $\pm$ 1786.2	NS	<.05	—	<.01	—
Control	5573.3 $\pm$ 1148.0	6053.3 $\pm$ 968.7	<.01	6473.3 $\pm$ 954.3	NS	<.01			
Noradrenaline (ng/L)									
AD	794.0 $\pm$ 213.2	995.1 $\pm$ 224.2	<.01	947.4 $\pm$ 301.6	NS	<.01	—	<.01	—
Control	762.1 $\pm$ 195.0	923.6 $\pm$ 297.9	<.05	936.2 $\pm$ 350.4	NS	<.05			

P_G , Significant differences between the 2 groups (over all measures); P_T , stress-induced alterations of a variable over time (for both groups); P_I , stress-induced alterations of a variable being significantly different between both groups.

TABLE III. Numbers of different lymphocytes and leukocytes (cells/ μ L), as well as noradrenaline levels before (*Baseline*), immediately after (*Stress*), and 1 hour after (*Follow-up*) stress exposure in psoriasis patients (n = 15) and control subjects (n = 15) (mean $\pm$ SD)

	Baseline	Stress	$P_{T(B-S)}$	Follow-up	$P_{T(S-FU)}$	1*3-ANOVA ($P_{T(B-S-FU)}$) (df = 2)	2*3-ANOVA		
							P_G (df = 1)	P_T (df = 2)	P_I (df = 1,86)
CD4 ⁺									
Psoriasis	1190.6 $\pm$ 606.5	1328.9 $\pm$ 473.3	NS	1209.6 $\pm$ 403.5	NS	NS	<.05	—	—
Control	929.1 $\pm$ 452.4	908.2 $\pm$ 271.7	NS	833.9 $\pm$ 305.9	NS	NS			
CD8 ⁺									
Psoriasis	580.0 $\pm$ 215.5	927.8 $\pm$ 292.8	<.01	640.6 $\pm$ 187.2	<.01	<.01	—	<.01	<.01
Control	615.9 $\pm$ 377.2	714.2 $\pm$ 272.7	NS	531.4 $\pm$ 254.5	<.01	<.05			
CD11b ⁺									
Psoriasis	453.6 $\pm$ 247.3	831.9 $\pm$ 316.3	<.01	385.4 $\pm$ 157.4	<.01	<.01	—	<.01	—
Control	614.1 $\pm$ 419.9	781.3 $\pm$ 278.2	NS	400.6 $\pm$ 233.5	<.01	<.01			
CD16 ⁺									
Psoriasis	328.1 $\pm$ 194.9	637.6 $\pm$ 280.6	<.01	266.7 $\pm$ 142.7	<.01	<.01	—	<.01	—
Control	420.8 $\pm$ 269.7	585.1 $\pm$ 216.9	NS	290.6 $\pm$ 141.1	<.01	<.01			
Leukocytes									
Psoriasis	6993.3 $\pm$ 1452.4	7653.3 $\pm$ 1395.8	<.01	8153.3 $\pm$ 1891.3	NS	<.01	<.01	<.01	—
Control	5573.3 $\pm$ 1148.0	6053.3 $\pm$ 968.7	<.01	6473.3 $\pm$ 954.3	NS	<.01			
Noradrenaline (ng/L)									
Psoriasis	611.8 $\pm$ 192.4	762.1 $\pm$ 304.0	<.01	779.6 $\pm$ 262.9	NS	<.01	—	<.01	—
Control	744.1 $\pm$ 199.1	909.5 $\pm$ 291.1	<.01	902.8 $\pm$ 359.1	NS	<.05			

P_G , Significant differences between the 2 groups (over all measures); P_T , stress-induced alterations of a variable over time (for both groups); P_I , stress-induced alterations of a variable being significantly different between both groups.

range (Table I). The high values of noradrenaline at rest (baseline) compared with values in other studies²⁸ could be due to an unspecific preactivation of patients and control subjects in the context of the experiment.

Skin biopsy specimens could be an alternative to our examination of the stress-induced change of immunocompetent cells in the circulation. However, the kinetics of infiltration of the skin by these cells under stress are

not known in persons with AD, persons with psoriasis, or healthy persons. To study this, a large number of repeated skin biopsies would be necessary, which would be a much larger stressor than collecting blood from a butterfly needle lying in a vein. Nevertheless, the modes of infiltration of immunocompetent cells into the skin have to be the subject of further studies to elucidate the connection between changes in the blood and inflammation processes in inflammatory cutaneous diseases.

The stress-induced increases of the CD16⁺ NK cells in the patient groups of this study are of potential immunologic relevance in AD and psoriasis, especially when the IFN- γ production of CD16⁺ NK cells is considered.²⁹ A pathophysiologic effect on inflammation is discussed for IFN- γ in chronic AD^{2,4,30,31} and in psoriasis.^{32,33} The transient increase of NK cells may be traced back to the noradrenaline plasma level. This is in accordance with other reports indicating the determining role of catecholamines for the increase of NK cell numbers during acute stress in healthy volunteers³⁴ and confirms the observations for psoriasis patients compared with controls.²⁶ Stress probably results in a catecholamine-mediated detachment of NK cells from the endothelium of the vascular walls in AD and psoriasis patients, comparable to findings published for healthy volunteers.³⁵ The results for NK cells of AD patients at rest are in accordance with those of studies describing an NK cell deficiency in unstressed AD patients.³⁶⁻³⁸ Interestingly, the NK cell numbers in AD patients also show a stress-induced increase up to the number of circulating NK cells comparable to those of healthy control subjects and psoriasis patients *before* stress.

The results of this study demonstrate an increase of CD8⁺ T-lymphocytes levels in the circulation upon acute psychosocial stress that remained high for at least 1 hour in patients with AD but not in healthy control subjects or patients with psoriasis. The effects of different types of acute psychosocial stress on CD8⁺ cells often have been described.^{26,28,39} However, because 30% to 50% of NK cells express CD8 antigen in low densities, the stress-induced increase of CD8⁺ cells in these studies is probably mainly due to changes in NK cell numbers. So far, the effect of acute psychological stress on CD8⁺ T lymphocytes has only been differentiated by double-staining (ie, identifying CD8⁺/CD16⁻ cells in patients with psoriasis²⁶ and systemic lupus erythematosus⁴⁰ compared with healthy control subjects). Stress effects on cytotoxic CD8⁺ T cells have not been studied previously. Therefore the increases of CD8⁺ cells probably induced by catecholamines as described before in human beings⁴¹ and rats⁴² cannot be related specifically to increases of cytotoxic T lymphocytes. The results of stress-induced increases of cytotoxic T lymphocytes shown here suggest a possible somatic link between psychological stress and the cutaneous inflammation in AD patients.^{1,2,4,5,12}

Inflammatory dermatoses are strongly influenced by the activity of CD8⁺ cytolytic T cells. Functionally, not only cytotoxic CD11b⁻ but also suppressor CD11b⁺ T cells seem to have cytolytic capabilities; suppression itself may

be due above all to a lytic capacity.¹² CD8⁺ cytolytic T lymphocytes have a crucial role in the pathophysiologic effects of allergen-associated skin-infiltrating T cells within the AD.^{9,10} In psoriatic epidermis CD8⁺ cytolytic T cells seem to be associated with the persistence of psoriatic lesions not undergoing resolution.^{12,43,44} A stress-induced increase of CD8⁺/CD11b⁺ T lymphocytes in patients with AD as well as in patients with psoriasis was revealed in this study.

Eosinophils in AD show a delayed cell death and a pathophysiologic relevance mediated by degranulation in AD lesional skin, releasing "toxic" factors (eg, eosinophil cationic protein⁴⁵) and mediating a late-phase allergic reaction in the skin.⁴⁶ A stress-induced increase of eosinophils only in AD shown in this study for the first time supports the hypothesis of the mediation of psychological stress effects by different immunodermatologic mechanisms including the recruitment of eosinophils.

Different cytokine profiles are suggested for the acute and chronic phases of eczema^{2,4}: In the acute phase more type 2 cytokines such as IL-4 and IL-5 are expressed than type 1 cytokine IFN- γ ; in chronic eczema type 1, cytokine IFN- γ increases, possibly induced by IL-12 and other milieu factors.

Further studies will have to focus on categorizing stress effects on T cells and eosinophils in AD not only by immunophenotype but also by demonstrating the functional role of these shifts, such as cytokine profiles in acute and chronic eczema reactions.

We thank the German Psoriasis Association, Hamburg, Germany, for its assistance in recruiting the psoriasis patients.

REFERENCES

1. Leung DYM. Atopic dermatitis: new insights and opportunities for therapeutic intervention. *J Allergy Clin Immunol* 2000;105:860-76.
2. Werfel T, Kapp A. Environmental and other major provocation factors in atopic dermatitis. *Allergy* 1998;53:731-9.
3. Leung DYM, Gatley M, Trumble A, Ferguson-Darnell B, Schlievert PM, Picker LJ. Bacterial superantigens induce T cell expression of the skin-selective homing receptor, the cutaneous lymphocyte-associated antigen, via stimulation of interleukin 12 production. *J Exp Med* 1995;181:747-53.
4. Grewe M, Bruijnzeel-Koomen CA, Schoepf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, et al. A role for T_H1 and T_H2 cells in the immunopathogenesis of atopic dermatitis. *Immunol Today* 1998;19:359-61.
5. Kodama A, Horikawa T, Suzuki T, Ajiki W, Takashima T, Harada S, et al. Effect of stress on atopic dermatitis: investigation in patients after the great Hanshin earthquake. *J Allergy Clin Immunol* 1999;104:173-6.
6. Lonati A, Licenziati S, Canaris AD, Fiorentini S, Pasolini G, Marcelli M, et al. Reduced production of both Th1 and Th2 lymphocyte subsets in atopic dermatitis (AD). *Clin Exp Immunol* 1999;115:1-5.
7. Strickland I, Hauk PJ, Trumble AE, Picker LJ, Leung DYM. Evidence for superantigen involvement in skin homing of T cells in atopic dermatitis. *J Invest Dermatol* 1999;112:249-53.
8. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999;104:466-72.
9. Werfel T, Morita A, Grewe M, Renz H, Wahn U, Krutmann J, et al. Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in chronic skin lesions of atopic dermatitis. *J Invest Dermatol* 1996;107:871-6.
10. Zachary CB, MacDonald DM. Quantitative analysis of T-lymphocyte subsets in atopic eczema, using monoclonal antibodies and flow cytometry. *Br J Dermatol* 1983;108:411-22.

11. Baume DM, Caligiuri MA, Manley TJ, Daley JF, Ritz J. Differential expression of CD8 alpha and CD8 beta associated with MHC-restricted and non-MHC-restricted cytolytic effector cells. *Cell Immunol* 1990;131:352-65.
12. De Panfilis G. CD8+ cytolytic T lymphocytes and the skin. *Exp Dermatol* 1998;7:121-31.
13. Kramer U, Schafer T, Behrendt H, Ring J. The influence of cultural and educational factors on the validity of symptom and diagnosis questions for atopic eczema. *Br J Dermatol* 1998;139:1040-6.
14. Mishoe SC, Baker RR, Poole S, Harrell LM, Arant CB, Rupp NT. Development of an instrument to assess stress levels and quality of life in children with asthma. *J Asthma* 1998;35:553-63.
15. Ginsburg IH, Prystowsky JH, Kornfeld DS, Wolland H. Role of emotional factors in adults with atopic dermatitis. *Int J Dermatol* 1993;13:656-60.
16. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol* 1995;63:624-35.
17. Ringsberg KC, Akerlind I. Presence of hyperventilation in patients with asthma-like symptoms but negative asthma test responses: provocation with voluntary hyperventilation and mental stress. *J Allergy Clin Immunol* 1999;103:601-8.
18. Koblenzer CS. Itching and the atopic skin. *J Allergy Clin Immunol* 1999;104:S109-113.
19. Schmid-Ott G, Kuensebeck HW, Jaeger B, Werfel T, Frahm K, Ruitmann J, et al. Validity study for the stigmatization experience in atopic dermatitis and psoriasis patients. *Acta Derm Venereol* 1999;17:443-7.
20. Arnetz BB, Fjellner B, Eneroth P, Kallner A. Endocrine and dermatological concomitants of mental stress. *Acta Derm Venereol* 1991;156:9-12.
21. Buske-Kirschbaum A, Jobst S, Wustmans A, Kirschbaum C, Rauh W, Hellhammer D. Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosom Med* 1997;59:419-26.
22. Gupta MA, Gupta AK, Kirkby S, Schork BS, Gorr SK, Ellis CN, et al. Psychocutaneous profile of psoriasis patients who are stress reactors. *Gen Hosp Psychiatry* 1989;11:166-73.
23. Schmid-Ott G, Jaeger B, Kuensebeck HW, Ott R, Lamprecht F. Dimensions of stigmatization in patients with psoriasis in a "Questionnaire for the experience of skin complaints." *Dermatology* 1986;193:304-10.
24. Lebowitz M, Tan MH. Psoriasis and stress [commentary]. *Lancet* 1988;350:82.
25. Arnetz BB, Fjellner B, Eneroth P, Kallner A. Stress and psoriasis: psychoendocrine and metabolic reactions in psoriatic patients during standardized stressor exposure. *Psychosom Med* 1985;47:528-41.
26. Schmid-Ott G, Jacobs R, Jaeger B, Klages S, Wolf J, Werfel T, et al. Stress-induced endocrine and immunological changes in psoriasis patients and healthy controls: an explorative study. *Psychother Psychosom* 1998;67:37-42.
27. Gerritsen W, Heijnen CJ, Wiegant VM, Bermond B, Frijda NH. Experimental social fear: immunological, hormonal, and autonomic concomitants. *Psychosom Med* 1996;58:273-86.
28. Schedlowski M, Jacobs R, Stratmann G, Richter S, Haedicke A, Tewes U, et al. Changes of human natural killer cells during acute psychological stress. *J Clin Immunol* 1993;13:119-26.
29. Orange JS, Biron CA. An absolute and restricted requirement for IL-12 in natural killer cell IFN-gamma production and antiviral defense. *Studies of natural killer and T cell responses in contrasting viral infections. J Immunol* 1996;156:1138-42.
30. Grewe M, Gyufko K, Schoepf E, Krutmann J. Lesional expression of interferon-gamma in atopic eczema. *Lancet* 1994;343:25-6.
31. Ohmen JD, Hanifin JM, Nickoloff BJ, Rea TH, Wyzkowski R, Kim J, et al. Overexpression of IL-10 in atopic dermatitis. *J Immunol* 1995;154:1956-63.
32. Szabo SK, Hammerberg C, Yoshida Y, Bata-Csorgo Z, Cooper KD. Identification and quantitation of interferon-gamma producing T cells in psoriatic lesions: localization to both CD4+ and CD8+ subsets. *J Invest Dermatol* 1998;111:1072-8.
33. Gudmundsdottir AS, Sigmundsdottir H, Sigurgeirsson B, Good MF, Valdimarsson H, Jonsdottir I. Is an epitope on keratin 17 a major target for autoreactive T lymphocytes in psoriasis? *Clin Exp Immunol* 1999;117:580-6.
34. Benschop RJ, Jacobs R, Sommer B, Schuermeyer TH, Raab HR, Schmidt RE, et al. Modulation of the immunologic response to acute stress in humans by beta-blockade and benzodiazepines. *FASEB J* 1996;10:517-24.
35. Benschop RJ, Nijkamp FP, Ballieux RE, Heijnen CJ. The effects of beta-adrenoceptor stimulation on adhesion of human natural killer cells to cultured endothelium. *Br J Pharmacol* 1994;113:1311-6.
36. Jensen JR, Sand TT, Jorgensen AS, Thestrup-Pedersen K. Modulation of natural killer cell activity in patients with atopic dermatitis. *J Invest Dermatol* 1984;82:30-4.
37. Lever RS, Lesko MJ, Mackie RM, Parrott DM. Natural-killer-cell activity in atopic dermatitis. *Clin Allergy* 1984;14:483-90.
38. Jensen JR. Reduction of active natural killer cells in patients with atopic dermatitis estimated at the single cell level. *Acta Derm Venereol Suppl* 1985;114:105-8.
39. Naliboff BD, Solomon GF, Gilmore SL, Fahey JL, Benton D, Pine J. Rapid changes in cellular immunity following a confrontational role-play stressor. *Brain Behav Immun* 1995;9:207-19.
40. Pawlak CR, Jacobs R, Mikeska E, Ochsmann S, Lombardi MS, Kavelaars A, et al. Patients with systemic lupus erythematosus differ from healthy controls in their immunological response to acute psychological stress. *Brain Behav Immun* 1999;13:287-302.
41. Kronfol Z, Nair M, Zhang Q, Hill EE, Brown MB. Circadian immune measures in healthy volunteers: relationship to hypothalamic-pituitary-adrenal axis hormones and sympathetic neurotransmitters. *Psychosom Med* 1997;59:42-50.
42. Clausen P, Ali SF, Taylor LD, Newport GD, Rybak S, Paule MG. Central and peripheral neurochemical alterations and immune effects of prenatal ethanol exposure in rats. *Int J Dev Neurosci* 1996;14:461-9.
43. Chang JC, Smith LR, Froning KJ, Schwabe BJ, Laxer JA, Caralli LL, et al. CD8+ T cells in psoriatic lesions preferentially use T-cell receptor V beta 3 and/or V beta 13.1 genes. *Proc Natl Acad Sci U S A* 1994;91:9282-6.
44. Norris DA, Travers JB, Leung DYM. Lymphocyte activation in the pathogenesis of psoriasis. *Invest Dermatol* 1997;109:1-4.
45. Elsner J, Kapp A. Regulation and modulation of eosinophil effector functions. *Allergy* 1999;54:15-26.
46. Alison J, Macfarlane AJ, Kon OM, Smith SJ, Zeibecoglou K, Khan LN, et al. Basophils, eosinophils, and mast cells in atopic and nonatopic asthma and in late-phase allergic reactions in the lung and skin. *J Allergy Clin Immunol* 2000;105:99-107.