

## Elevated Glucocorticoid Receptor Concentrations before and after Glucocorticoid Therapy in Peripheral Mononuclear Leukocytes of Patients with Atopic Dermatitis

M. Rupprecht, R. Rupprecht, J. Kornhuber, N. Wodarz, H.U. Koch, P. Riederer, O.P. Hornstein

Department of Dermatology, University of Erlangen-Nürnberg; Department of Psychiatry, University of Würzburg;  
Max Planck Institute of Psychiatry, München, FRG

**Key Words.** Glucocorticoids · Glucocorticoid receptors · Atopic dermatitis

**Abstract.** The number and affinity of glucocorticoid binding sites in peripheral mononuclear leukocytes of patients with atopic dermatitis (AD) and healthy controls were determined under baseline conditions and after a defined oral glucocorticoid treatment. Patients with AD ( $n = 15$ ) exhibited significantly more glucocorticoid receptors (GR) per cell than the control group ( $n = 22$ ), while the GR affinity did not differ. Methylprednisolone treatment resulted in a significant reduction of the GR sites per cell in the steroid-treated control group ( $n = 10$ ) in contrast to the patients. The dissociation constant was not affected by methylprednisolone treatment in either group. In view of the therapeutic efficiency of glucocorticoids in AD and findings of abnormal cAMP and cAMP-phosphodiesterase activity, the elevated GR concentrations in AD lend support to the hypothesis of a compensatory GR upregulation due to an insufficient action of endogenous cortisol or to altered cAMP-induced GR expression.

### Introduction

Studies on patients with atopic dermatitis (AD) have revealed a variety of immunological, hormonal and psychological [1, 2] derangements including elevations of IgE levels [3, 4], disordered cell-mediated immunity [5-7], abnormal cAMP and cAMP-phosphodiesterase activity [8, 9] and an impairment of  $\beta$ -adrenoceptor function [10, 11]. Recent investigations pointed to a possible hormonal dysregulation of the hypothalamic-pituitary-adrenal (HPA) system in AD. Slightly lowered baseline values of cortisol [12] in face of a normal adrenomedullar function [13], minor imbalances in the circadian rhythm of cortisol serum levels [14] as well as a reduced urine excretion rate of steroid metabolites contrasting with normal cortisol blood levels [15] have been noted.

Topical and systemic administration of glucocorticoids is of major importance in the treatment of AD. The effects of glucocorticoids are mainly mediated via specific

intracellular receptors which have been identified in various mammalian and human tissues, e.g. the skin [16-18], lung [19], brain [20] and mononuclear leukocytes [21-23].

As the glucocorticoid receptor (GR) has been shown to underlie an autoregulatory control in skin fibroblasts [17, 18] and in human leukocytes [21-26], the present study was designed to explore the potential role of GR autoregulation for the alteration of the HPA system in AD.

### Material and Methods

#### Subjects

Fifteen inpatients (3 men and 12 women) suffering from AD and 22 healthy controls (11 men, 11 women) without personal history of asthma, hay fever or AD participated in the study voluntarily with informed consent. The patients were aged between 18 and 36 years (mean  $\pm$  SD:  $23.4 \pm 5.6$ ) and the controls for baseline studies between 19 and 42 years (mean  $\pm$  SD:  $28.5 \pm 6.3$ ). Ten of the healthy subjects (4 men, 6 women:

mean age  $\pm$  SD: 24.3  $\pm$  2.8 years), who had the same age as the patients, agreed to further participate in the study and received the same steroid dosage as the patients for the autoregulation study.

All participants were withdrawn from any systemic therapy with corticoids or adrenocorticotrophic hormone at least 2 months prior to the study. Medication, if any, with  $\beta$ -blocking and/or sleep-inducing drugs was stopped 3 or more days before entering the study. Cutaneous lesions of AD were treated only with corticoid-free ointments at least 1 week before onset and during the study.

Exclusion criteria were prevalence of severe internal illness and alcohol, drug or nicotine abuse. Seven of the patients and 4 of the 10 healthy controls were taking birth control pills.

The diagnosis of AD was based on the history of recurrent flexural eczema, personal and/or family history of atopy and clinical criteria of AD as established by Hanifin and Rajka [27]. The severity of cutaneous involvement was evaluated according to Costa et al. [28] and revealed moderate to marked disease activity. The score ranged between 37 and 69 points (mean  $\pm$  SD: 47.6  $\pm$  10.6) before therapy and between 11 and 55 points (mean  $\pm$  SD: 27.9  $\pm$  10.7) at the end of the study. None of the patients suffered from actual bronchial asthma.

*Study Design*

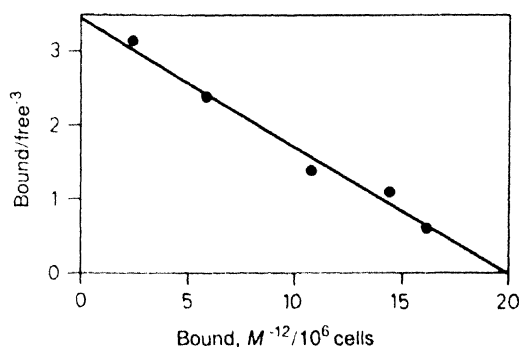
After obtaining the baseline GR and hormone parameters, all patients and the steroid-treated controls underwent a 1-mg dexamethasone suppression test (DST) and subsequent oral methylprednisolone therapy as shown in table 1. The DST was used to evaluate the integrity of the feedback regulation of the HPA system.

For determination of GR binding characteristics and hormone data peripheral venous blood samples were collected into EDTA-containing plastic tubes (Sarstedt, FRG).

*Cell Preparation and Binding Assay*

Mononuclear cell fraction was prepared by sodium metrizoate-Ficoll (Sigma, St. Louis, Mo., USA) density gradient centrifugation [29]. Cells were washed twice in phosphate-buffered saline (PBS, pH 7.4; Boehringer, Mannheim, FRG) for 10 min, incubated for 60 min at 37 °C in PBS and then washed again to allow sufficient dissociation of endogenous hormone. The final concentration of cells was determined using a Coulter counter (Model S5, Coulter Electronics Ltd. UK). Viability of cells exceeded 95%, as judged from their ability to exclude trypan blue. Contamination by erythrocytes was < 10%, by granulocytes and monocytes < 8%.

Binding experiments as described by Rupprecht et al. [25] were carried out at 37 °C in plastic microtiter plates in a total volume of 0.25 ml. The displacing compound in a final concentration of 10  $\mu$ M unlabeled dexamethasone (Sigma, St. Louis, Mo., USA) solved in 5% ethanol, containing 5 mM D-glucose, was added to half of the samples to determine nonspecific binding immediately prior to the addition of [<sup>3</sup>H]dexamethasone (Amersham, UK). Increasing concentrations of [<sup>3</sup>H]dexamethasone (specific activity: 84 Ci/mmol) from 1 to 40 nM were used. Saturation experiments were carried out at equilibrium after 90 min incubation in PBS with 5 mM D-glucose at 37 °C. After incubation, bound ligand was separated from free ligand by rapid filtration through Scatron filters (No. 11731) with a Titertek cell harvester by two 5-second washes with PBS at room temperature. The filters were transferred into plastic vials. 5 ml of a toluene-based scintillation cocktail was added (Rotiszint 22; Roth, Karlsruhe, FRG) and they were monitored for tritium in a Beckman LS 1801 counter at about 54% efficiency. All samples were assayed in triplicate with a variation coefficient < 7%.



**Fig. 1.** Scatchard plot of [<sup>3</sup>H]dexamethasone binding to human mononuclear leukocytes. Specifically bound/free [<sup>3</sup>H]dexamethasone is plotted versus specifically bound [<sup>3</sup>H]dexamethasone.

**Table 1.** Study design

Day	Time	Glucocorticoid doses	Blood samples
1	7 a.m.	1 mg dexamethasone	hormone data
	4 p.m.		hormone + receptor data
	11 p.m.		
2	7 a.m.		hormone data
	4 p.m.		hormone data
3-6	7 a.m.	8 mg methylprednisolone	
7-8	7 a.m.	4 mg methylprednisolone	
8	4 p.m.		hormone + receptor data

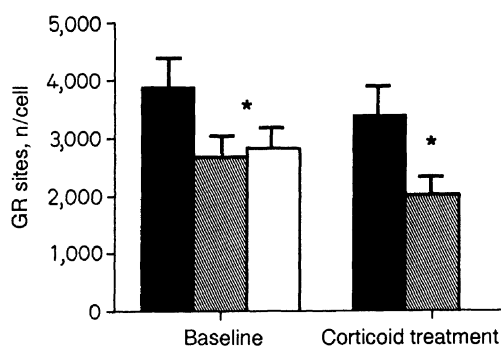
**Table 2.** Cortisol mean  $\pm$  SD values ( $\mu$ g/dl) inpatients (n = 15) and controls (n = 10)

	A		B		C
	7 a.m.	4 p.m.	7 a.m.	4 p.m.	4 p.m.
Patients	27.5 $\pm$ 13.8	13.4 $\pm$ 11.3	1.6 $\pm$ 1.4	4.1 $\pm$ 4.0	5.6 $\pm$ 6.9
Controls	25.1 $\pm$ 8.6	14.6 $\pm$ 6.9	2.3 $\pm$ 1.5	3.3 $\pm$ 3.3	7.7 $\pm$ 5.7

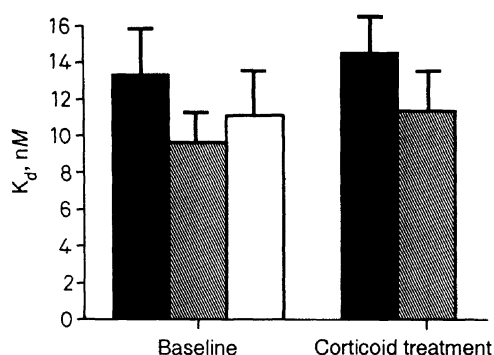
A = Baseline levels; B = after oral administration of 1 mg dexamethasone; C = after oral methylprednisolone treatment.

**Table 3.** GR sites in female patients and female controls taking and not taking birth control pills under baseline conditions and after methylprednisolone treatment

	Pill	No pill
Patients	n = 7	n = 5
Baseline	3,783 $\pm$ 1,658	3,886 $\pm$ 1,537
Prednisolone	3,353 $\pm$ 1,105	3,250 $\pm$ 1,643
Controls	n = 4	n = 2
Baseline	2,642 $\pm$ 567	2,764 $\pm$ 859
Prednisolone	2,030 $\pm$ 470	2,087 $\pm$ 14



**Fig. 2.** GR sites per cell. Means  $\pm$  SE, in patients with AD (■,  $n = 15$ ), the corticoid-treated controls (▨,  $n = 10$ ) and the whole control group (□,  $n = 22$ ) before (baseline) and after glucocorticoid treatment. The asterisks indicate significant differences ( $p < 0.02$ ).



**Fig. 3.**  $K_d$ . Means  $\pm$  SE, in patients with AD (■,  $n = 15$ ), the corticoid-treated controls (▨,  $n = 10$ ) and the whole control group (□,  $n = 22$ ) before (baseline) and after glucocorticoid treatment.

Receptor levels and the dissociation constant ( $K_d$ ) were determined by Scatchard plots [30]. A typical Scatchard plot of [ $^3$ H]dexamethasone is shown in figure 1.

Specific binding was determined by subtracting the nonspecific from total binding. Nonspecific binding (in percent of total binding) at a concentration of 10 nM [ $^3$ H]dexamethasone was  $28 \pm 18\%$  in patients and  $26 \pm 15\%$  in controls.

#### Cortisol Assay

Cortisol was measured by an enzyme-linked immunoassay (Elias, Freiburg, FRG). The lower detection limit was 22 nmol/l, and the intra- and interassay coefficients of variation were 6% for both.

Cortisol nonsuppression was defined as the inability to suppress both postdexamethasone cortisol levels to below 5  $\mu$ g/dl [31].

#### Statistical Analysis

Preliminary estimates of binding parameters from saturation experiments were provided by the EBDA program. Final estimates of binding parameters were determined with a computerized nonlinear, least-square regression analysis [32]. This weighted curve fitting program assumes binding according to the law of mass action to independent classes of binding sites. The results are expressed as the mean  $\pm$  SD, and as the mean  $\pm$  SE in the figures.

Data were analyzed using the t-test for paired or group samples and Pearson's product moment correlation. All significance levels are two-tailed.

## Results

Cortisol mean values of the patients and the controls did not differ significantly at any of the blood sampling time points during the 1-mg DST (table 2). Three of the patients and 2 of the controls fulfilled the criterion for cortisol nonsuppression.

Comparison of the postmethylprednisolone cortisol levels to the 4 p.m. baseline levels revealed significant reduction in patients and controls ( $p < 0.03$ ).

The patients had significantly ( $p < 0.02$ ) more GR sites per cell than controls (fig. 2). After methylprednisolone therapy the patients revealed a slightly smaller mean number of GR sites per cell in relation to the baseline values (mean baseline:  $3,894 \pm 1,521$ ; after treatment:  $3,394 \pm 1,189$ , not significant), whereas in the controls ( $n = 10$ ) a significant reduction of the GR sites was found (mean baseline:  $2,695 \pm 582$ ; after treatment:  $2,036 \pm 410$ ,  $p < 0.02$ ).

The significantly more GR binding sites per cell persisted after therapy in the patient group when compared with the steroid-treated control group ( $p < 0.002$ ).

There was no difference in baseline or methylprednisolone-treated GR sites between female subjects taking birth control pills and those who did not (table 3).

The  $K_d$  did not differ at baseline condition and after methylprednisolone treatment in both groups (fig. 3). No relations were found between age, sex, cortisol levels, severity of the skin disorder and GR binding parameters under the conditions studied.

## Discussion

Although slightly lowered baseline cortisol serum concentrations in patients with AD have been observed [12], our study is in accordance with reports on normal cortisol levels in AD [15]. Twenty percent of the patients with AD and 20% of the controls showed no suppression of cortisol

to below 5 µg/dl after 1 mg dexamethasone. However, abnormal DST data may not only occur in various diseases but can also be induced by multiple interference factors such as stress and weight loss in healthy subjects [33, 34]. Therefore, the abnormal DST results obtained in AD and healthy controls may represent an unspecific finding.

As no data are available on GR binding characteristics in AD we used peripheral blood mononuclear leukocytes to study GR pharmacology, partly for their easy accessibility but also for their relevance to the pathogenesis in AD [35] as emphasized by the finding that bone marrow transplantation for other reasons could either confer the state of atopy to former nonatopics [36, 37] or may clear AD in patients with a concomitant immune deficiency disorder [38].

The elevated GR concentrations found in the patients with AD are probably not representing a causal factor, otherwise worsening of the skin lesions would be expected at the beginning of glucocorticoid treatment due to an increased number of activated hormone-receptor complexes. An upregulation of the glucocorticoid binding sites as a compensatory mechanism is more likely. Possible hypotheses for such an upregulation may be alterations in cAMP-induced GR expression [39], activation of the GR synthesis by unspecific mediators [40] or a relative biological inefficiency of endogenous corticoids. The latter hypothesis might be supported by the well-known benefit of glucocorticoids for the treatment of AD and also by the frequent occurrence of a rebound phenomenon after discontinuation of glucocorticoid administration. An increase in receptor protein half-life [39, 41] due to reduced cortisol-receptor interactions as supposed after depletion of endogenous cortisol following metyrapone administration [26] or adrenalectomy [42], or an enhanced transcription rate for the GR [43] may also be responsible for the elevated GR sites in AD.

No correlations were found between endogenous cortisol levels and GR binding sites in the control and patient group. This result is in accordance with previous studies in healthy and asthmatic subjects [26, 44, 45] and indicates that the plasma concentrations of endogenous glucocorticoids at the time of the GR assay are of minor importance for the estimation of GR number.

However, prolonged glucocorticoid administration results in downregulation of the number of GR [18, 21, 24] by influencing GR gene transcription [46] without significantly affecting the binding affinity. In the controls methylprednisolone administration was followed by a significant decrease in GR binding, whereas in the patients with AD only a slight reduction of GR binding was

observed. This finding might be interpreted as a diminished downregulation of GR by exogenous glucocorticoids which could be due to the heterogeneity of the patient group shown by the greater standard deviation and might also be compatible with the hypothesis of a cAMP-induced overdrive of GR expression [39] or a relative biological inefficiency of endogenous cortisol which would require a greater amount of exogenous glucocorticoids to downregulate the GR. However, it cannot be excluded that an eventual displacement of receptor-bound methylprednisolone by dexamethasone during the assay may underlie different kinetics in patients with AD which might affect the estimation of  $K_d$  and  $B_{max}$  values. The use of monoclonal antibodies for quantification of GR expression [47] might overcome the difficulties with ligand exchange assays and furnish a direct proof for the hypothesis of a decreased GR downregulation in AD.

As no data are available on GR in other inflammatory skin diseases so far, the specificity of the present findings is still questionable. However, although AD and bronchial asthma are often closely associated [48] and glucocorticoid therapy is efficient in both diseases [44], normal lymphocyte GR content and affinity has been described in asthmatic subjects [44, 45].

In line with observations that patients with AD exhibit a minor derangement of the HPA system shown by imbalances of the circadian rhythm of cortisol [14] and may have a reduced excretion of glucocorticoids [15], the here reported alterations in GR binding characteristics on mononuclear leukocytes lend further support to the view of AD as being a systemic rather than a mere cutaneous disease.

Future perspectives might be the concomitant analysis of GR behavior in mononuclear leukocytes and cells of both involved and uninvolved skin areas of patients with AD.

### Acknowledgements

We thank Miss Nistelweck for excellent technical assistance. The Johannes and Frieda Marohn Stiftung of the University of Erlangen-Nürnberg provided financial support.

### References

- 1 Faulstich ME, Williamson DA, Duchmann EG, Conerly SL, Brantley PP: Psychophysiological analysis of atopic dermatitis. *J Psychosom Res* 1985;29:415-417.
- 2 Whitlock FA: Psychophysiologische Aspekte bei Hautkrankheiten: Atopische Dermatitis; in Bosse K, Hünecke P (eds): *Beiträge zur Dermatologie*. Erlangen, Perimed, 1980, vol 6, pp 141-159.

- 3 Wüthrich B: Serum IgE in atopic dermatitis. *Clin Allergy* 1978; 8:241-248.
- 4 Juhlin L, Johansson SGO, Bennich H, Högman C, Thyresson N: Immunglobulin E in dermatoses. *Arch Dermatol* 1969;100:12-16.
- 5 Lobitz WC, Honeyman JF, Winkler NW: Suppressed cell-mediated immunity in two adults with atopic dermatitis. *Br J Dermatol* 1972;86:317-328.
- 6 Rola-Pleszczynski M, Blanchard R: Abnormal suppressor cell function in atopic dermatitis. *J Invest Dermatol* 1981;76:279-283.
- 7 Schöpf E, Kapp A, Kim CW: T-cell function in atopic dermatitis - Controlled examination of concanavalin A dose-response relations in cultured lymphocytes. *Arch Dermatol Res* 1978;262:37-44.
- 8 Schwarz W, Bock G, Hornstein OP: Plasma levels of cyclic nucleotides are elevated in atopic eczema. *Arch Dermatol Res* 1987;279: S59-S62.
- 9 Holden CA, Chan SC, Hanifin JM: Monocyte localization of elevated cyclic AMP phosphodiesterase activity in atopic dermatitis. *J Invest Dermatol* 1986;87:372-376.
- 10 Szentivanyi A, Helm O, Schultze P, Szentivanyi J: Adrenoreceptor binding studies with 3-H-(dihydroalprenolol) and 3-H-(dihydroergocryptine) on membranes of lymphocytes from patients with atopic disease. *Acta Derm Venereol (Stockh)* 1980;92:19-21.
- 11 Szentivanyi A: The beta adrenergic theory of the atopic abnormality in bronchial asthma. *J Allergy* 1968;42:203-232.
- 12 van de Kerkhof PCM: Plasma aldosterone and cortisol levels in psoriasis and atopic dermatitis. *Br J Dermatol* 1981;106:423-428.
- 13 Archer CB, Dalton N, Turner C, MacDonald DM: Investigation of adrenomedullary function in atopic dermatitis. *Br J Dermatol* 1987;116:793-800.
- 14 Heubeck B, Schönberger A, Hornstein OP: Sind Verschiebungen des zirkadianen Cortisolrhythmus ein endokrines Symptom des endogenen Ekzems? *Hautarzt* 1988;39:12-17.
- 15 Buhles N, Hölzel C, Spittler G, Holzmann H, Altmeyer P: Disorders of steroid metabolism in inflammatory dermatoses. *Z Hautkr* 1987;62:1356-1363.
- 16 Smith K, Shuster S: Characterisation of the glucocorticoid receptor in human epidermis and dermis. *Clin Exp Dermatol* 1987;12:83-88.
- 17 Berkovitz GD, Carter KM, Migeon CJ, Brown TR: Downregulation of the glucocorticoid receptor by dexamethasone in cultured human skin fibroblasts: Implications for the regulation of aromatase activity. *J Clin Endocrinol Metab* 1988;66:1029-1036.
- 18 Oikarinen A, Oikarinen H, Meeker CA, Tan EML, Uitto J: Glucocorticoid receptors in human skin fibroblasts: Evidence for downregulation of receptor by glucocorticoid hormone. *Acta Derm Venereol (Stockh)* 1987;67:461-468.
- 19 Ballard PL, Ballard RA: Cytoplasmic receptors for glucocorticoids in lung of the human fetus and neonate. *J Clin Invest* 1974;53: 477-486.
- 20 Fuxe K, Wikström AC, Okret S, Agnati LF, Härfstrand A, Yu ZY, Granhol L, Zoli M, Vale W, Gustafsson JA: Mapping of glucocorticoid receptor immunoreactive neurons in the rat tel- and dien-cephalon using a monoclonal antibody against the rat liver glucocorticoid receptor. *Endocrinology* 1985;117:1803-1812.
- 21 Shipman GF, Bloomfield CD, Gajl-Peczalska K, Munck AU, Smith KA: Glucocorticoids and lymphocytes. III. Effects of glucocorticoid administration on lymphocyte glucocorticoid receptors. *Blood* 1983;61:1086-1090.
- 22 Lippman M, Barr R: Glucocorticoid receptors in purified subpopulations of human peripheral blood lymphocytes. *J Immunol* 1977; 118:1977-1981.
- 23 Brentani MM, Wajchenberg BL, Cesar FP, Martins VR: Regulation of the glucocorticoid receptor by glucocorticoids in human mononuclear leucocytes. *Horm Res* 1986;24:9-17.
- 24 Schlechte JA, Ginsberg BH, Sherman BM: Regulation of the glucocorticoid receptor in human lymphocytes. *J Steroid Biochem* 1982;16:69-74.
- 25 Rupprecht R, Kornhuber J, Wodarz N, Göbel C, Lugauer J, Sinzger C, Beckmann H, Riederer P, Müller OA: Autoregulation of the glucocorticoid receptor in man: Up-regulation by metyrapone is avoided by dexamethasone pretreatment. *J Neuroendocrinol* 1990; 2:803-806.
- 26 Rupprecht R, Kornhuber J, Wodarz N, Lugauer J, Göbel C, Haack D, Müller OA, Riederer P, Beckmann H: Disturbed glucocorticoid receptor autoregulation and corticotropin response to dexamethasone in depressives pretreated with metyrapone. *Biol Psychiatry*, in press.
- 27 Hanifin JM, Rajka G: Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)* 1980;92:44-47.
- 28 Costa C, Rilliet A, Nicolet M, Saurat JH: Scoring atopic dermatitis: The simpler the better? *Acta Derm Venereol (Stockh)* 1989;69: 41-45.
- 29 Boyum A: Separation of leukocytes from blood and bone marrow. *Scand J Clin Lab Invest* 1968;21:97-107.
- 30 Scatchard G: The attraction of proteins for small molecules and ions. *Ann NY Acad Sci* 1949;51:660-672.
- 31 Carroll BJ, Martin FI, Davis BM: Resistance to suppression by dexamethasone of plasma 11-OHCS levels in severe depressive illness. *Br Med J* 1968;iii:285-287.
- 32 McPershon GA: A practical computer-based approach to the analysis of radioligand binding experiments. *Comput Programs Biomed* 1983;17:107-114.
- 33 Berger M, Pirke KM, Doerr P, Krieg JC, Zerssen D: The limited utility of the dexamethasone suppression test for the diagnostic process in psychiatry. *Br J Psychiatry* 1984;145:372-382.
- 34 Rupprecht R, Lesch KP: Psychoneuroendocrine research in depression. I. Hormone levels of different neuroendocrine axes and the dexamethasone suppression test. *J Neural Transm* 1989; 75:167-178.
- 35 Archer CB: Cyclic nucleotide metabolism in atopic dermatitis. *Clin Exp Dermatol* 1987;12:424-431.
- 36 Saarinen UM: Transfer of latent atopy by bone marrow transplantation? *J Clin Allergy Immunol* 1984;74:196-200.
- 37 Tucker J, Barnetson R, Eden OB: Atopy after bone marrow transplantation. *Br Med J* 1985;290:116-117.
- 38 Saurat JH: Eczema in primary immune deficiencies. Clue to the pathogenesis of atopic dermatitis with special reference to the Wiskott-Aldrich syndrome. *Acta Derm Venereol Suppl (Stockh)* 1985: 114:125-128.
- 39 Dong Y, Aronsson JA, Okret S: The mechanism of cAMP-induced glucocorticoid receptor expression. *J Biol Chem* 1989;23: 13679-13683.
- 40 Damon M, Rabien M, Loubatière J, Blotman F, Crastes de Paulet A: Glucocorticoid receptors in fibroblasts from synovial tissue. Changes during the inflammatory process. Preliminary results. *Agents Actions* 1986;17:478-483.
- 41 Distelhost CW: Recent insight into the structure and function of the glucocorticoid receptor. *J Lab Clin Med* 1989;113:404-412.
- 42 Turner BB: Tissue differentiation in the up-regulation of glucocorticoid-binding proteins in the rat. *Endocrinology* 1986;118: 1211-1216.

- 43 Gustafsson J, Carlstedt-Duke J, Poellinger L, Okret S, Wikstöm A, Brönnegård M, Gillner M, Dong Y, Fuxe K, Cintra A, Härfstrand A, Agnati L: Biochemistry, molecular biology, and physiology of the glucocorticoid receptor. *Endocr Reviews* 1987;8:185-234.
- 44 Tsai BS, Watt G, Koensnadi K, Townley RG: Lymphocyte glucocorticoid receptors in asthmatic and control subjects. *Clin Allergy* 1984;14:363-371.
- 45 Griese M, Kusenbach G, Lüsebring K, Köster W, Roth B, Reinhardt D: Glucocorticoid receptors in mononuclear blood cells and their correlation to endogenous and exogenous corticoids in healthy and asthmatic children. *Eur J Pediatr* 1988;147:490-495.
- 46 Rosewicz S, McDonald AR, Maddux BA, Goldfine ID, Miesfeld RL, Logsdon CD: Mechanism of glucocorticoid receptor down-regulation by glucocorticoids. *J Biol Chem* 1988;263:2581-2584.
- 47 Antakly T, Raquidan D, O'Donnell O, Katnick L: Regulation of glucocorticoid receptor expression. I. Use of a specific radioimmunoassay and antiserum to a synthetic of the N-terminal domain. *Endocrinology* 1990;126:1821-1828.
- 48 Aas K: Common immunochemistry in atopic dermatitis and bronchial asthma. *Acta Derm Venereol Suppl (Stockh)* 1980;92:64-66.

Received: October 15, 1990

Accepted: January 18, 1991

Monika Rupperecht, MD  
Department of Dermatology  
Hartmannstrasse 14  
D-W-8520 Erlangen (FRG)