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# Modulation of Expression of Epidermal Langerhans Cell Properties Following in Situ Exposure to Glucocorticosteroids

BRIAN BERMAN, M.D., PH.D., DENNIS S. FRANCE, B.A., GIORGIO P. MARTINELLI, PH.D., D.SC., AND ADA HASS, M.D.

*Departments of Dermatology (BB, DSF, AH) and Surgery (GPM), Mount Sinai School of Medicine, New York, New York, U.S.A.*

**Langerhans cells (LC) have been implicated as antigen-presenting and target cells in contact allergic, cell-mediated reactions. We have examined the effects in guinea pigs, rats, and humans of in situ (epicutaneous) exposure to glucocorticosteroids (GCS) on the expression of epidermal LC markers. Reductions in the number of Fc-rosetting, C3b-rosetting, and immune-associated (Ia) antigen-bearing LC occurred in a dose-related fashion, with the degree of such reductions dependent upon the specific GCS employed. These reductions were determined to be reversible following cessation of exposure to GCS. T6 antigenicity, another cell surface marker of human LC, was little affected by GCS exposure.**

**Simultaneous immunofluorescent staining for T6 and Ia antigenicity within human epidermis of amcinonide-treated skin detected reduced numbers of $T6^+/Ia^+$ cells with a concomittant increase in $T6^+/Ia^-$ cells. The data presented suggest a selective reduction in the expression of immunologically important receptors and antigens by LC which may be involved in steroid-responsive contact allergic reactions.**

Keratinocytes, melanocytes, and suprabasal dendritic Langerhans cells (LC) are the 3 populations of cells present in the mammalian epidermis. Although the main localization of LC under "normal" conditions is the epidermis, where they are seen principally in the suprabasal and lower epidermal sites [1], they are also seen in much smaller numbers in the dermis [2], epithelia of skin appendages, oral and pharyngeal mucosal epithelium, esophagus, uterine cervix, lymph nodes, tonsils, and thymus, and constitute the infiltrating cells in histiocytosis X [1,3]. For many decades attempts were made to fit the dendritic LC into one of two already established systems of dendritic cells but most authors now believe that LC are mesodermal in origin and certainly unrelated to the neural and pigmentary systems [4,5]. With the acceptance of a mesodermal derivation of LC their possible significance was reconsidered and it was suggested that LC may represent immunocompetent cells [6], capturing antigenic material, and possibly serving as epidermal macrophages [7,8].

Evidence favoring the concept that LC play a significant role in certain immunologic reactions was put forward by Silberberg [9] when she reported close apposition of mononuclear lymphocyte-like cells to LC within 3–5 h of topical application of mercury bichloride, with ultrastructural evidence of LC damage by 6 h. Similar results were obtained at reaction sites with other contact allergens (gold chloride, hexachlorophene, mercaptobenzothiazole, nickel sulfate, paraphenylenediamine, and pyrethrum) and not with contact primary irritants [10].

Although the origin and function of LC had been a matter of conjecture and theory ever since their discovery by Paul Langerhans [11], similarities between LC and macrophages have been reported recently. These similarities include plasma membrane 5′-adenosine triphosphatase (ATPase) activity [12], ability to migrate [13], Ia-histocompatibility antigens [14,15], Fc receptors [16], C3b receptors [17], nonspecific esterase activity [18], the ability in vitro to transfer antigen in lymphocyte stimulation [19], and bone marrow derivation [4]. The finding that the LC of nonsensitized guinea pigs selectively bind certain common contact allergens led Shelley and Juhlin [20] to coin the term "reticuloepithelial system" for these cells, a system that traps and processes external contact allergens, thus playing a pivotal role in the primary immune response and in the pathogenesis of skin diseases such as contact allergic dermatitis.

The therapeutic mainstay for allergic contact dermatitis is the administration of glucocorticosteroids (GCS), most often via epicutaneous application. GCS have been long known to suppress delayed hypersensitivity in the guinea pig [21] and in humans [22], which is probably due, at least in part, to their profound effects on macrophages and monocytes. In addition to the ability to suppress inflammation by decreasing mononuclear cell chemotaxis [23] and the inhibition of the response to macrophage inhibitory factor and macrophage activating factor [24,25], GCS influence macrophage integrity and function. The expression of human monocyte-macrophage membrane-bound Fc and C3b receptors is diminished following in vitro and in vivo exposure to GCS in a dose-dependent fashion [26–32]. It has been reported that topical application of betamethasone dipropionate (BD) [33] and triamcinolone acetonide (AM) [34] to the skin of mice induced an inability to be sensitized to dinitrofluorobenzene, and a decrease in immune-associated (Ia) antigen-bearing LC, respectively. Belsito and coworkers [35] have recently shown a decrease in guinea pig LC as detected by cell surface ATPase activity and Ia antigenicity following exposure to GCS. We report here studies of guinea pigs, rats, and humans undertaken to assess the effects of in situ exposure to different GCS on the expression of LC Fc and C3b receptors and other membrane-bound antigens.

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Reprint requests to: Dr. Brian Berman, Mount Sinai Medical Center, Department of Dermatology, One Gustave Levy Place, New York, New York 10029.

Abbreviations:
AM: amcinonide
ATPase: 5′-adenosine triphosphatase
BD: betamethasone dipropionate
BEIgG: bovine erythrocytes sensitized with IgG antibody
ΔFCS: heat-inactivated fetal calf serum
FITC: fluorescein isothiocyanate
GCS: glucocorticosteroid(s)
GPEC: guinea pig epidermal cells
HEC: human epidermal cells
Ia: immune-associated
LC: Langerhans cell(s)
MEM: minimal essential medium with Earle's salts
PBS: phosphate-buffered saline
REC: rat epidermal cells
SEIgMC′: SEIgM sensitized with fresh mouse serum
TRITC: tetramamethyl rhodamine isothiocyanate

## MATERIALS AND METHODS

### *Buffers and Tissue Culture Medium*

Sterile minimal essential medium (MEM) with Earle's salts supplemented with 100 units penicillin/ml + 2.5 μg amphotericin B/ml + 100 units streptomycin/ml + 60 μg tylocine/ml was prepared from stock solutions (Grand Island Biological Company, Grand Island, New York). Supplemented MEM was used throughout and is designated as MEM. Heat-inactivated fetal calf serum (ΔFCS) was obtained from Grand Island Biological Co., as was Dulbecco's phosphate-buffered saline (PBS), calcium- and magnesium-free. Trypsin (type XI; Sigma Chemical Co., St. Louis, Missouri) was sterilized by filtration through 0.20 Nalgene filters (Nalge Co., Rochester, New York). Antibodies were diluted in PBS containing 5% bovine serum albumin (Cohn fraction V; Sigma).

### *Preparation of Epidermal Cell Suspensions*

Single cell suspensions of Hartley strain guinea pig and ACI strain rat epidermal cells (GPEC and REC, respectively) were prepared according to the method of Stingl et al [14] with the minor modification that MEM was used instead of TC 199 medium. Resultant cell suspensions were 98–100% viable as determined by trypan blue exclusion. Human epidermal cell (HEC) suspensions were similarly prepared, either from freshly excised neonatal foreskin or from upper arm skin, with the modification of an 18-h incubation of 4°C in 0.5% trypsin in PBS.

### *Antibodies*

The following antibodies were obtained commercially: rabbit anti-bovine erythrocyte IgG (Cordis Laboratories, Miami, Florida), rabbit antisheep erythrocyte IgM (Cordis Laboratories), monoclonal mouse antihuman Ia $IgG_{2b}$ (1 mg/ml; New England Nuclear, Boston, Massachusetts), monoclonal mouse antihuman T6 $IgG_1$ (50 μg/ml; Ortho Pharmaceuticals, Raritan, New Jersey), goat antimouse IgG IgG-FITC (F/P = 4.7; Meloy Laboratories, Springfield, Virginia), monoclonal mouse antihuman T1 IgG (1 mg/ml), monoclonal mouse antihuman T6 IgG-FITC (Ortho Pharmaceuticals), and rabbit antimouse IgG IgG-TRITC (Cappel Lab., Cochranville, Pennsylvania). Guinea pig strain 2 anti-guinea pig Ia 1.3.7 serum was raised by immunization of inbred strain 2 with strain 13 bone marrow cells by an otherwise unmodified procedure [36]. Prior to use, this serum was incubated at 56°C for 30 min and ultracentrifuged at 100,000 *g* for 30 min.

### *Fc-Mediated Rosette Formation*

One- to 2-day-old bovine erythrocytes (BE) collected in citrated saline were washed 4 times and resuspended in 4°C PBS as a 2.5% suspension. An equal volume of a 1:20 dilution of rabbit anti-BE IgG in PBS was added to the 2.5% BE suspension and incubated for 30 min at 37°C with constant shaking (BEIgG). The cells were then washed 3 times in 4°C PBS and resuspended in MEM as a 1% suspension. No bound C3 was detected by immunofluorescence. These cells were incubated at 37°C with epidermal cells in a 50:1 ratio, and pelleted and incubated at 4°C as described elsewhere [17]. A minimum of 1000 nucleated cells were counted, and those binding 5 or more erythrocytes were considered to be rosetted.

### *Complement-Mediated (C3b) Rosette Formation*

Four- to 5-day-old sheep erythrocytes (SE) collected in citrated saline were washed 4 times and resuspended in 4°C PBS as a 2.5% suspension. An equal volume of 1:10 dilution of rabbit anti-SE IgM in PBS was added to the 2.5% suspension, incubated for 30 min at 37°C with constant shaking, washed, and sensitized with fresh mouse serum (SEIgMC′) [16]. These cells were then handled and incubated with epidermal cells as described above for Fc-mediated rosette formation.

### *Preparation of Frozen Skin Sections and Epidermal Sheets*

Six-micron-thick frozen skin sections were prepared using an American Optical cryostat at −30°C. Incubation of skin samples in 2 M NaBr at 37°C for 30 min allowed for manual removal of intact epidermal sheets.

### *Immunofluorescence*

Fresh preparations of HEC or freshly prepared human epidermal sheets were incubated in a 1:100 dilution of monoclonal mouse antihuman Ia $IgG_{2b}$ or a 1:500 dilution of monoclonal mouse antihuman T6 $IgG_{2b}$ for 60 min at 37°C and were washed exhaustively in PBS. The samples were then incubated in a 1:10 dilution of rabbit antimouse IgG IgG-FITC for 60 min at 37°C and washed in PBS. Fresh preparations of Hartley GPEC were handled in an identical fashion with Δ guinea pig strain 2 antiguinea pig strain 13 serum for the primary incubation and staphylococcal Protein A-FITC for the secondary incubation. Human epidermal sheets were examined with epifluorescence microscopy and the number of fluorescing dendritic cells per 0.5 $mm^2$ determined using a calibrated reticle. Cytocentrifuge preparations were first viewed with phase contrast microscopy, and the same field was then examined under ultraviolet light so that a percentage of fluorescence-positive cells could be determined. AT least 1000 cells were counted for each determination. Simultaneous detection of T6 and Ia antigen-bearing epidermal cells was achieved as follows. Epidermal sheets were sequentially incubated at 37°C for 60 min in 1:10 dilution of mouse monoclonal antihuman Ia $IgG_{2b}$, 1:20 dilution of rabbit antimouse IgG IgG-TRITC, and 1:25 dilution of monoclonal mouse antihuman T6 IgG-FITC and were washed 3 times in PBS following each incubation. Fluorescing cells in 10 400× power fields were enumerated under epifluorescence microscopy using appropriate excitation and barrier filters, and the density of the phenotyped cells per 0.5 $mm^2$ calculated.

### *In Situ Exposure to Epicutaneously Applied GCS*

*Human*: Four × 10 cm areas of skin of the medial aspect of opposite upper arms of healthy volunteers were treated epicutaneously twice daily for 10 days with either BD (1.28 mg/2 g white petrolatum) or AM (2.0 mg/2 g hydrophilic base) and their respective vehicle (2 g). Subjects were between the ages of 18 and 35, of both sexes, not pregnant, without known medical diseases, and not using any prescribed medications. Approximately 4 × 5 mm samples of skin were excised under 1% lidocaine anesthesia from the treated areas upon completion of applications, either dispersed epidermal cells or epidermal sheets, and frozen sections were prepared and assessed for the presence of LC properties; a percent control (vehicle) was calculated for each subject.

*Guinea pig*: Opposite flanks of groups of 4 Hartley guinea pigs were treated either once daily or twice daily for various periods of time with topical application of either BD (1.28 mg in 2 g petrolatum) or petrolatum (2 g). Upon completion of treatment, epidermal cells were isolated from opposite flank skin from each guinea pig and the percent forming rosettes upon incubation with BEIgG (Fc) and SEIgMC′ (C3b), and expressing Ia antigens were determined in triplicate. The values obtained for the steroid-treated flank were compared to those of the petrolatum-treated control flank and a percent control for each animal, and an average percent control ± SEM for the group of 4 guinea pigs was calculated.

*Rat*: Opposite flanks of a pair of ACI strain rats were treated twice daily for 21 days with topical application of either BD (1.28 mg in 2 g petrolatum) or petrolatum (2 g). At various times following discontinuance of topical steroid and petrolatum treatments, epidermal cells were isolated from opposite flank skin from each rat, and the percent forming rosettes upon incubation with BEIgG (Fc) and SEIgMC′ (C3b) were determined in triplicate. The values obtained for the steroid-treated flank were compared to those of the petrolatum-treated, control flank, and a percent control and an average percent control ± SEM were calculated.

## RESULTS

### *Effects of in Situ Epicutaneous Application of BD on Expression of LC Properties by GPEC*

Opposite flanks of Hartley strain guinea pigs were treated with either BD or petrolatum. As shown in Table I the percent of epidermal cells, isolated from BD-treated flanks, capable of forming Fc and C3b rosettes was decreased from control levels as determined with cells isolated from petrolatum-treated flanks. More frequent and/or extended applications of BD resulted in more pronounced reductions in LC rosetting. Decreased Ia expression in BD-treated epidermal cells was detected in those guinea pigs reacting with anti-guinea pig Ia 1.3.7 serum.

### *In Situ Epicutaneous Application of BD and AM Selectively Diminishes the Expression of Certain LC Properties by HEC*

When compared with petrolatum treatment, twice daily application of BD (1.25 mg/2 g petrolatum) to upper arm skin (40

TABLE I. *Effects of in situ epicutaneous application of BD on expression of LC properties by GPEC*

| BD application[a] | Percent control (SEM)[b] | | |
|---|---|---|---|
| | % Fc rosetted (SEM) | % C3b rosetted (SEM) | % Ia positive[c] |
| Daily × 9 days | 93.3 (2.3) | 93.0 (0.1) | 61.5 |
| b.i.d. × 9 days | 65.2 (2.8) | 66.9 (4.1) | 47.0 |
| b.i.d. × 14 days | 39.0 (2.6) | 59.1 (2.5) | NR[d] |
| Daily × 20 days | 43.9 (6.1) | 34.3 (3.4) | NR |

[a] Opposite flanks of groups of 4 Hartley guinea pigs were treated either once daily or twice daily (b.i.d.) for the indicated number of days with topical application of either BD (1.28 mg in 2 g petrolatum) or petrolatum (2 g).

[b] Upon completion of treatment, epidermal cells were isolated from opposite flank skin from each guinea pig and the percent capable of forming rosettes upon incubation with BEIgG (Fc) and SEIgMC′ (C3b), and expressing Ia antigens were determined in triplicate. The values obtained for the steroid-treated flank were compared to those of the petrolatum-treated, control flank and a percent control calculated. The indicated values represent the average percent control (SEM) of the group of 4 guinea pigs.

[c] Expression of certain guinea pig Ia antigens was detected by indirect immunofluorescence using guinea pig strain 2 anti-strain 13 serum followed by FITC-conjungated staphylococcal Protein A. The epidermal cells of 2 guinea pigs reacted under these conditions.

[d] Nonreactive.

TABLE II. *Effect of in situ epicutaneous exposure to AM 0.1% on Ia and T6 antigen expression by HEC*

| Subject | Treatment[a] | Number of cells per 0.5 mm$^{2}$[b] (SEM) | | Percent control number of cells | | Average percent control number of cells (SEM) | |
|---|---|---|---|---|---|---|---|
| | | Ia$^+$ | T6$^+$ | Ia$^+$ | T6$^+$ | Ia$^+$ | T6$^+$ |
| 1 | Vehicle | 156 (10) | 255 (9) | | | | |
| | AM | 27 (4) | 239 (14) | 17.3 | 93.7 | | |
| 2 | Vehicle | 126 (7) | 337 (10) | | | | |
| | AM | 32 (5) | 266 (11) | 25.3 | 78.9 | 25.8 (5.1) | 90.5 (6.0) |
| 3 | Vehicle | 126 (10) | 197 (7) | | | | |
| | AM | 44 (4) | 195 (6) | 34.9 | 98.9 | | |

[a] Four × 10 cm areas on the medial aspects of the opposite arms of 3 human volunteers were treated twice daily for 10 days with topical applications of either AM (2.0 mg in 2 g hydrophilic base) or the hydrophilic base vehicle.

[b] Upon completion of treatment, superficial 4 × 5 mm biopsies of treated skin were performed. The skin biopsies were incubated for 30 min at 37°C in 2 N NaBr and epidermal sheets prepared. Ia and T6 antigen-bearing LC were detected by indirect immunofluorescence employing monoclonal mouse antihuman Ia or T6 IgG followed by rabbit antimouse IgG-FITC. Fluorescing dendritic cells were enumerated, the numbers within steroid-treated skin compared with control-treated skin, a percent control calculated for each volunteer, and an average percent control (SEM) calculated.

cm$^2$) of 3 volunteers induced parallel reductions in the percent of epidermal cells capable of forming Fc rosettes (55.4% ± 2.0 SEM), forming C3b rosettes (56.6% ± 5.1 SEM), or bearing Ia antigen (58.8% ± 2.0 SEM). As shown in Table II, following similar treatment of a second set of volunteers with AM, a marked decrease (74.2% ± 5.1 SEM) from control numbers of Ia-bearing LC was detected in the steroid-treated skin, with the number of T6-bearing LC being only minimally decreased (9.5% ± 6.0 SEM). Although these findings were suggestive that AM induces a selective reduction in expression of Ia antigens, it was necessary to determine the degree of the coincidence of Ia and T6 antigenicity of LC within epidermis following AM and/or control treatments. As shown in Table III, in control epidermis all Ia-positive cells were also T6-positive (T6$^+$/Ia$^+$) although there were T6-positive cells on which Ia was not detected (T6$^+$/Ia$^-$). In skin treated with AM the density of T6$^+$/Ia$^+$ epidermal cells decreased with a concomitant increase in T6$^+$/Ia$^-$ cells. As previously noted (Table II), the total number of T6-bearing cells was only slightly diminished (a 3.9% reduction from control), suggesting a selective reduction in Ia antigenicity.

*Reversibility of in Situ BD-Induced Reductions in REC Fc and C3b Rosette Formation*

Having demonstrated in guinea pigs and humans a diminished expression of certain LC properties following exposure to GCS, we attempted to determine the susceptibility of rat LC to these effects as well as to assess the reversibility of these reductions over time. As shown in Table IV, BD applied to flanks of ACI rats twice daily for 21 days reduced the percent of Fc- and C3b-rosetting LC to approximately 50% of that detected in petrolatum-treated control flanks. Within days following discontinuation of steroid application a return of Fc- and C3b-rosetting LC was detected and petrolatum-treated control levels were attained within 28 days.

## DISCUSSION

The number of immune interactions and components shown to be susceptible to the influence of GCS has markedly increased over the past 25 years since the introduction of these immunomodulatory compounds. Recognition of these modulatory influences has led to the therapeutic use of GCS in a variety of disease states including cell-mediated, contact allergic reactions. Our findings further delineate the effects of GCS on the epidermal LC, a pivotal component of the peripheral arm of the immune system. We have detected a decrease in epidermal cells expressing immunologically important receptors and antigens following epicutaneous exposure to GCS. The degree of these reductions reflected the dose as well as the intrinsic clinical and vasoconstrictive potencies of the GCS used. Other investigators have shown Ia antigens on mouse [34] and guinea

TABLE III. *Simultaneous detection of T6 and Ia antigen-bearing epidermal cells in AM-treated skin*

| Epicutaneous application[a] | Mean number phenotyped cells (SEM)/0.5 mm$^{2}$[b] | | |
|---|---|---|---|
| | T6$^+$/Ia$^+$ | T6$^+$/Ia$^-$ | T6$^-$/Ia$^+$ |
| Hydrophilic vehicle | 137 (9) | 203 (10) | 0 (0) |
| AM | 46 (4) | 281 (10) | 0 (0) |

[a] Four × 10 cm areas of skin of the medial aspect of opposite upper arms of a healthy volunteer were treated twice daily for 8 days with either AM (2.0 mg/2.0 g hydrophilic base) or its hydrophilic vehicle (2.0 g).

[b] Epidermal sheets from each area were sequentially incubated in monoclonal mouse antihuman Ia antigen IgG$_{2b}$, rabbit antimouse IgG IgG-TRITC, and monoclonal mouse antihuman T6 antigen IgG-FITC, and were washed 3 times in PBS following each incubation. Fluorescing cells in 10 400× power fields were enumerated under epifluorescence microscopy, using appropriate excitation and barrier filters, and the density of the phenotyped cells calculated. Incubation of human epidermis with either rabbit antimouse IgG IgG-TRITC alone or following prior incubation with monoclonal mouse antihuman T1 antigen IgG yielded no cellular fluorescence.

TABLE IV. *Return of Fc and C3b rosetting REC following discontinuance of in situ epicutaneous application of BD*

| Days following final application[a] | Percent control[b] (SEM) | |
|---|---|---|
| | % Fc rosetted | % C3b rosetted |
| 0.5 | 48.5 (4.3) | 54.0 (4.0) |
| 2.5 | 61.3 (5.2) | 63.5 (8.2) |
| 6.5 | 64.7 (2.7) | 67.9 (2.1) |
| 15.5 | 78.5 (0.7) | 78.0 (1.9) |
| 28.5 | 94.6 (0.1) | 99.7 (7.5) |

[a] Opposite flanks of a pair of ACI strain rats were treated twice daily for 21 days with topical applications of either BD (1.28 mg in 2 g petrolatum) or petrolatum (2 g).

[b] At the indicated times following discontinuance of topical steroid and petrolatum treatments, epidermal cells were isolated from opposite flank skin from each rat, and the percent capable of forming rosettes upon incubation with BEIgG (Fc) and SEIgMC′ (C3b) were determined in triplicate. The values obtained for the steroid-treated flank were compared to those of the petrolatum-treated, control flank and a percent control (SEM) calculated.

pig [35] epidermal LC to be reduced following in situ exposure to GCS. Our findings expand this Ia susceptibility to include those on human LC. In addition, we have found Fc and C3b rosetting by LC isolated from guinea pig, rat, and human epidermis to be reduced following GCS exposure.

The observed reductions in Ia antigen-bearing and Fc- and C3b-rosetting epidermal cells do not appear to be due to disappearance of LC since the continued presence of virtually all T6-positive cells following GCS treatment suggests the persistence of LC. In fact, Belsito et al [35] observed no irreversible ultrastructural changes within GCS-treated guinea pig LC. We have found similar qualitative ultrastructural changes in GCS-treated rat epidermal LC (unpublished observations). The results of our quantitative assessment of coincidental Ia and T6 staining (Table III) support the notion of the continued presence of LC, with a selective reduction in other immunologically important LC markers.

The immunofluorescent assay for human Ia expression detected approximately 50% of the number of LC determined by immunofluorescent detection of human T6 antigen. One could speculate that these assays differ in their ability to detect two different subpopulations of LC: indeterminate LC, which have been suggested to be immature LC, and Birbeck granule-containing LC. The possibility exists that T6 antigens are expressed by all LC [37] with the expression of Ia antigens, Fc and C3b receptors being restricted to differentiated or activated LC. Differences in assay sensitivities as the basis for the differences in LC detection cannot be ruled out.

The loss of Fc- and C3b-rosetting capabilities of LC exposed to GCS may indeed be due to a decrease in surface Fc and C3b receptors. The addition of GCS does not immediately inhibit LC Fc and C3b rosetting and results of indirect immunofluorescence testing with aggregated IgG for Fc receptors and of testing with a radioimmunochemical assay for C3b receptors suggest a reduction in such receptors following in vitro LC exposure to GCS [38].

In light of our demonstration of the susceptibility of LC Fc and C3b rosetting following GCS exposure, experiments dealing with LC phagocytosis of, and damage by, immune complexes in vivo are interesting [39]. Immune complex uptake by, and migration of, epidermal LC appear to be independent of the presence of circulating C3 and C4, whereas subsequent LC cellular damage, leading to lysosomal disruption, is dependent upon the presence of these complement components. The depletion of Fc and C3b receptors following exposure to GCS may interfere with LC as targets of immune complex reactions, or with LC "activation."

Finally, GCS perturbation of LC with resultant reduction in the number of Ia-bearing LC may allow antigens to escape presentation via LC, causing failure to induce [33,40] or elicit contact sensitization.

## REFERENCES


1. Wolff K: The Langerhans cell, Current Problems in Dermatology. Edited by JWH Mali. Basel, S Karger, 1972, p 79–145
2. Zelickson AS: The Langerhans cell. J Invest Dermatol 44:201–212, 1965
3. Berman B, Chang DL, Shupack JL: Histiocytosis X: treatment with topical nitrogen mustard. J Am Acad Dermatol 3:23–29, 1980
4. Katz SI, Tamaki K, Sachs DH: Epidermal Langerhans cells are derived from cells which originate in the bone marrow. Nature 282:324–326, 1979
5. Billingham RE, Silvers WK: Some unsolved problems in the biology of skin, Biology of the Skin and Hair Growth. Edited by AG Lyne and B Short. Syndney, Angus and Robertson, 1965, pp 1–24
6. Prunieras M: Interactions between keratinocytes and dendritic cells. J Invest Dermatol 52:1–17, 1969
7. Hashimoto K, Tarnowski WM: Some new aspects of the Langerhans cell. Arch Dermatol 97:450–464, 1968
8. Tarnowski WM, Hashimoto K: Langerhans cell granules in histocytosis X. Arch Dermatol 96:298–304, 1967
9. Silberberg I: Ultrastructural studies of Langerhans cells in contact sensitive and primary irritant reactions to mercuric chloride. Clin Res 19:715–717, 1971
10. Silberberg I: Apposition of mononuclear cells to Langerhans cells in contact allergic reactions. An ultrastructural study. Acta Derm Venereol (Stockh) 53:1–12, 1973
11. Langerhans P: Uber die Nerven der menschlichen Haut. Virchows Arch [Pathol Anat] 44:325–327, 1868
12. Wolff K, Winkelmann RK: Ultrastructural localization of nucleoside triphosphatase in Langerhans cells. J Invest Dermatol 48:50–54, 1967
13. Silberberg I: Apposition of mononuclear cells to Langerhans cells in contact allergy. I. An ultrastructural study in actively induced contact dermatitis in guinea pigs. Acta Derm Venereol (Stockh) 54:321–331, 1973
14. Stingl G, Katz SI, Shevach EM, Wolff-Schreiner E, Green I: Detection of Ia antigens of Langerhans cells in guinea pig skin. J Immunol 120:570–578, 1978
15. Rowden G, Lewis MG, Sullivan AK: Ia antigen expression on human epidermal Langerhans cells. Nature 268:247–248, 1977
16. Stingl G, Wolff-Schreiner E, Pichler WJ, Gschnait F, Knapp W, Wolff K: Epidermal Langerhans cells bear Fc and C3b receptors. Nature 268:245–246, 1977
17. Berman B, Gigli I: Complement receptors on guinea pig epidermal Langerhans cells. J Immunol 124:685–690, 1980
18. Berman B, France DS: Histochemical analysis of Langerhans cells. Am J Dermatopathol 1:215–221, 1979
19. Stingl G, Katz SI, Clement L, Green I, Shevach EM: Immunological functions of Ia-bearing epidermal Langerhans cells. J Immunol 121:2005–2013, 1978
20. Shelley WB, Juhlin L: Langerhans cells form a reticuloepithelial trap for external contact antigens. Nature 261:46–47, 1976
21. Harris W, Harris TN: Effect of cortisone on some reactions of hypersensitivity in laboratory animals. Proc Soc Exp Biol Med 74:186–189, 1950
22. Solomon H, Angel JH: Corticotropin-induced changes in the tuberculin skin test. Am Rev Respir Dis 83:235–242, 1961
23. Thompson J, van Furth R: The effect of glucocorticosteroids on the kinetics of mononuclear phagocytes. J Exp Med 131:429–442, 1970
24. Balow JE, Rosenthal AS: Glucocorticoid suppression of macrophage inhibitory factor. J Exp Med 137:1031–1041, 1973
25. Weston WL, Claman HN, Krueger CG: Site of action of cortisol in cellular immunity. J Immunol 110:880–883, 1973
26. Rinehardt JJ, Sagone AL, Balcerzak SP, Ackerman GA, LoBuglio AF: Effects of corticosteroid therapy on human monocyte function. N Engl J Med 292:236–241, 1975
27. van Furth R: Origin and kinetics of monocytes and macrophages. Semin Hematol 7:125–141, 1970
28. Bilbey DCI, Nicol T: Effect of various natural steroids on the phagocytic activity of the reticuloendothelial system. Nature 182:674, 1958
29. Vernon-Roberts B: The effects of steroid hormones on macrophage activity. Int Rev Cytol 25:131–159, 1969
30. Rinehardt JJ, Balcerzak SP, Sagone AL, LoBuglio AF: Effects of corticosteroids on human monocytes. J Clin Invest 54:1337–1343, 1973
31. Atkinson JP, Schreiber AD, Frank MM: Effects of corticosteroids and splenectomy on the immune clearance and destruction of erythrocytes. J Clin Invest 52:1509–1517, 1973
32. Schreiber AD, Parsons J, McDermott P: Effect of corticosteroids on the human monocyte IgG and complement receptors. J Clin Invest 56:1189–1197, 1975
33. Lynch DH, Gurish MF, Daynes RA: Relationship between epidermal Langerhans cell density ATPase activity and the induction of contact hypersensitivity. J Immunol 126:1892–1897, 1981
34. Nordlund JJ, Ackles AE, Lerner AB: The effects of ultraviolet light and certain drugs on Ia-bearing Langerhans cells in murine epidermis. Cell Immunol 60:50–63, 1981
35. Belsito DV, Flotte TJ, Lim HW, Baer RL, Thorbecke GJ, Gigli I: Effect of glucocorticosteroids on epidermal Langerhans cells. J Exp Med 155:291–302, 1982
36. Shevach EM, Rosentreich DL, Green I: The distribution of histocompatibility antigens on T and B cells in the guinea pig. Transplantation 16:126–133, 1973
37. Chu A, Eisinger M, Lee JS, Takezaki S, Kung PC, Edelson RL: Immunoelectron microscopic identification of Langerhans cells using a new antigenic marker. J Invest Dermatol 78:177–180, 1982
38. Berman B, France DS: Effects of *in vitro* and *in situ* exposure to corticoids on human Langerhans cells. Clin Res 30:260A, 1982
39. Silberberg-Sinakin I, Fedorko ME, Baer RL, Rosenthal SA, Berezowsky V, Thorbecke GJ: Langerhans cells: target cells in immune complex reactions. Cell Immunol 32:400–416, 1977
40. Burrows WM, Stoughton RB: Inhibition of induction of human contact sensitization by topical glucocorticosteroids. Arch Dermatol 112:175–178, 1976