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Alteration in Murine Epidermal Langerhans Cell Population by Various UV Irradiations: Quantitative and Morphologic Studies on the Effects of Various Wavelengths of Monochromatic Radiation on Ia-Bearing Cells

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The present study was undertaken in order to clarify the exact mode of the Langerhans cell (LC) depleting process caused by UV irradiation. Following irradiation with a single dose of various wavelengths of monochromatic UV radiation (UVR), we studied the number of Ia-positive cells in mouse epidermal sheets quantitatively, particularly with regard to dose-response relationship, action spectrum, and time course change. In addition, we studied morphologic alterations of these cells using electron- and immunoelectron microscopy (EM and IEM).

We obtained the following results after a single dose of UVB radiation (200 mJ/cm² of 300 nm) or PUVA (1% of 8-methoxypsoralen (8-MOP) 20 μl and 1 J/cm² of 360 nm): (1) EM and IEM showed that while some LCs simply lost their Ia marker without any structural alterations, the majority of the LCs disappeared due to actual cell damage. (2) During an "injury phase," the initial 48 h, and a "recovery phase," lasting from 4–14 days after irradiation, enlargement of the size of remaining Ia-positive LCs occurred. The degree of enlargement was closely related to the degree of reduction in number, suggesting a process compensating for the loss of the LC population. (3) It was found that the recovery rate of LCs after irradiation damage was slower than that of keratinocytes, indicating different cell kinetics between these distinct cell populations in the epidermis, i.e., restoration of LCs after irradiation seems to be achieved at least partially through a repopulation process originating in the bone marrow.

Studies with irradiation of various monochromatic wavebands, with or without topical 8-MOP, showed that the action spectrum for Ia-positive cell depletion activity lay within the spectrum shorter than 300 nm for UVR alone, and between 320–380 nm for 8-MOP plus UVR. Since the action spectra were similar to those for keratinocyte damage, i.e., sunburn cell formation, induction of unscheduled DNA synthesis, and to those for UVR-induced erythema, we conclude that common mechanisms underlie these types of tissue damage.

Recent studies have demonstrated that epidermal Langerhans cells (LCs) are a population of cells derived from the bone marrow [1] and they bear Fc and C3 receptors [2] and Ia (immune-response associated) antigens [3] on their surface. Functionally, LCs are required as antigen-presenting cells for the initiation of immune response, i.e., contact hypersensitivity [4], skin graft rejection [5], and also are required as stimulator cells in the epidermal cell-lymphocyte reaction [3,6].

Because of their location within the epidermis, these cells are affected by various environmental injuries. For example, UV radiation (UVR) from sunlight and from artificial sources during photochemotherapy may cause various degrees of functional and morphologic alterations of these cells. Using a specific histochemical marker, ATPase for LC, Aberer et al [7] found that ATPase-positive LCs in mouse epidermis decreased in number with a complete disappearance at 24 h after a moderate dose of UVB radiation. However, this feature was not paralleled by the actual loss of the LC population at the ultrastructural level, and they concluded that particular susceptibility of LCs to UVR did not necessarily represent a substantial depletion of LCs themselves, but was mainly due to a loss of their membrane markers. However, some conflicting results have been reported. Nordlund et al [8], examining the effect of UVR on Ia-bearing cells, observed that single and cumulative doses of short-wave UVR and UVB increased the density of these cells. Moreover, Kristian [9] and Friedmann et al [10] have recently provided ultrastructural evidence of the depletion of LCs after PUVA (psoralen plus UVA) treatment. Thus there is basic disagreement as to the effect of UVR on LCs.

In the present study, in order to characterize the exact mode of the LC depletion process following UV irradiation, we performed a quantitative analysis of Ia-positive cells in mouse epidermal sheets. Moreover, to study the relation between the loss of Ia marker from LCs and the structural alterations of these cells, we also carried out electron microscopic (EM) as well as immunoelectron microscopic (IEM) observations.

MATERIALS AND METHODS

Animals

Six- to ten-week-old, male C3H/He mice were used. For all experiments, there were a minimum of 4 mice in each experimental group. Each group of mice was separately housed in a cage and received standard laboratory food and drinking water.

Radiation Source

A grating monochromator (CT-25N, Jasco, Japan) with a 2 kW xenon lamp was used. Specifications of the diffraction grating were as follows: number of grooves = 1200 line/cm, biased wavelength = 200 nm, and spectral range = 200–700 nm. All irradiation was performed under constant conditions with a current of 64 A, a slit width of 3.0 mm, and a half-band width of 9.6 nm. The irradiated area of the skin was approximately 1 cm². Irradiance of the skin varied from 0.38 mW/cm² at 260 nm to 1.95 mW/cm² at 300 nm to 3.25 mW/cm² at 360 nm.

Experimental Procedures

The dorsal surface of mouse ears was irradiated with UVR at a constant angle of 90°. Animals were held in a plastic case and their ears were held immobile with double sticky tape. Depilation before irradiation was unnecessary because hair on the ear was sparse. In the case of topical 8-methoxypsoralen (8-MOP) and UVR treatment, 20 μl of 1% 8-MOP (Oxysoralen, Taisho Pharm. Co, Japan) was applied epicutaneously 30 min before irradiation. Animals were sacrificed by

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Abbreviations:
- EM: electron microscopy (-ic)
- Ia: immune-response associated
- IEM: immunoelectron microscopy (-ic)
- KC: keratinocyte
- LC: Langerhans cell
- 8-MOP: 8-methoxypsoralen
- PBS: phosphate-buffered saline
- PUVA: psoralen plus UVA
- UVR: ultraviolet radiation

neck fracture and the ears were amputated at the base with scissors at various time intervals after irradiation ranging from 0 h to 14 days. These samples were processed for immunohistochemistry and EM and IEM.

Immunohistochemistry

Epidermal sheets of the ears were examined using an antimouse Ia^k (specificity 2) monoclonal antibody (Becton Dickinson, U.S.A.) and an avidin-biotin-peroxidase complex technique (ABC system, Vecton, U.S.A.) [11]. A piece measuring approximately 4 × 4 mm was taken from the center of each ear and incubated with 25 mM Na_4-EDTA in phosphate-buffered saline (PBS), pH 7.2, for 2 h at 37°C. Thereafter, epidermal sheets were fixed in ethanol for 20 min at room temperature, rinsed for 30 min in PBS, incubated with diluted normal goat serum, and then incubated for 16 h at 4°C in anti-Ia^k Ab diluted 1:100 in PBS. Subsequently, sheets were incubated in biotinylated goat antimouse IgG serum diluted in PBS for 30 min and an avidin-biotin-peroxidase complex diluted in PBS for 60 min. At each step, samples were incubated at room temperature. Sheets were rinsed for 20 min in PBS between incubations. The reaction products were revealed with 3,3′-diaminobenzidine (DAB, Sigma) and H_2O_2 in 0.05 M Tris-HCl buffer (pH 7.6) and then mounted in glycerol:PBS (9:1, V:V).

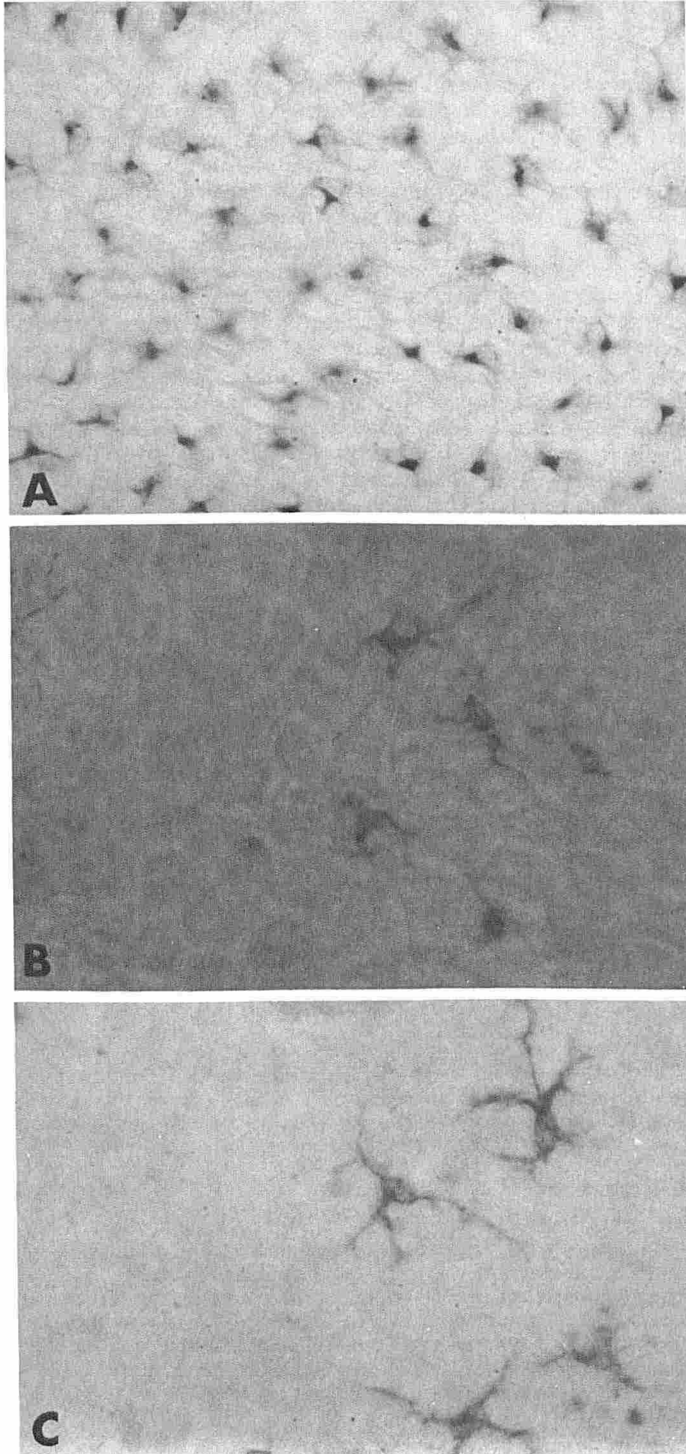
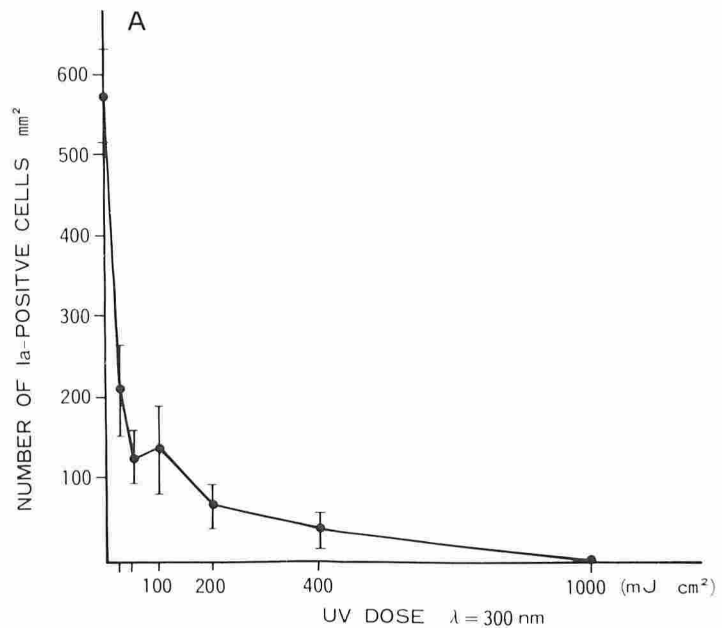


FIG 1. *A*, Dendritic Ia-positive cells in the epidermal sheet of the normal ear (× 300). *B*, Epidermal sheet obtained 24 h after a single dose of 200 mJ/cm^2 of 300 nm irradiation. Ia-positive cells markedly decreased in number (× 300). *C*, Giant Langerhans cells in the sheet from the ear treated with PUVA 4 days before sampling (× 300).

Quantitative Analysis

Sheet preparations were examined with a light microscope at a magnification of 400×. In each specimen of the experimental group



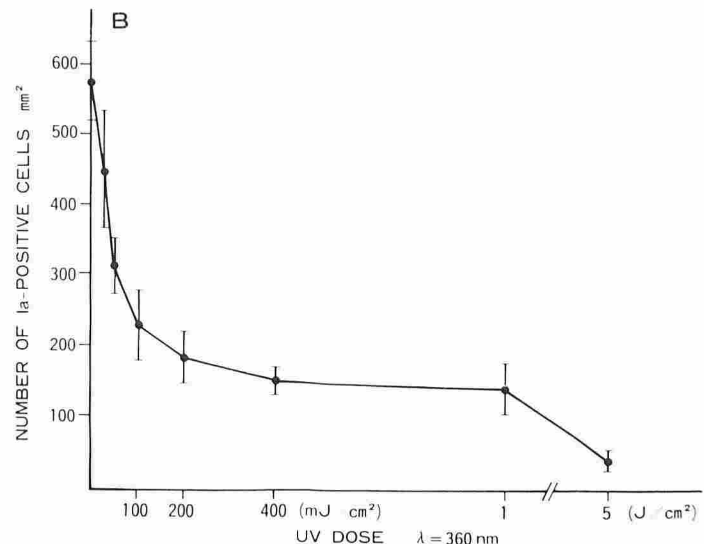


FIG 2. *A*, Dose-response curve for Ia-positive cell depletion effects at 24 h after irradiation with various doses of 300 nm irradiation. *B*, Dose-response curve for Ia-positive cell depletion effects at 24 h after topical 8-MOP and 1 J/cm^2 of 360 nm irradiation. Values are mean ± SD.

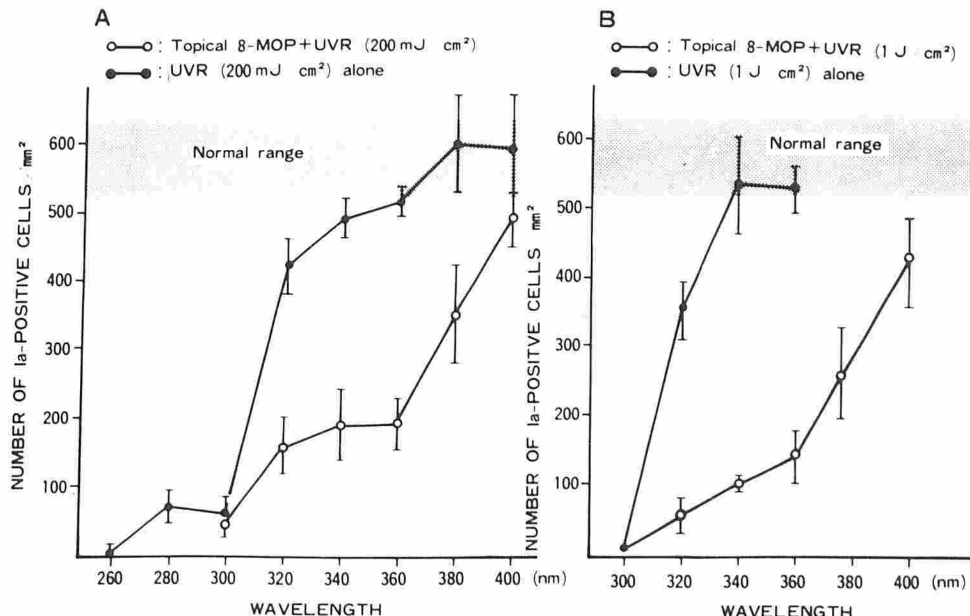


FIG 3. Action spectrum curves for Ia-positive cell depletion effects of 200 mJ/cm² (*A*) and 1 J/cm² (*B*) of various monochromatic wavelengths, with or without topical 8-MOP application. Values are mean ± SD.

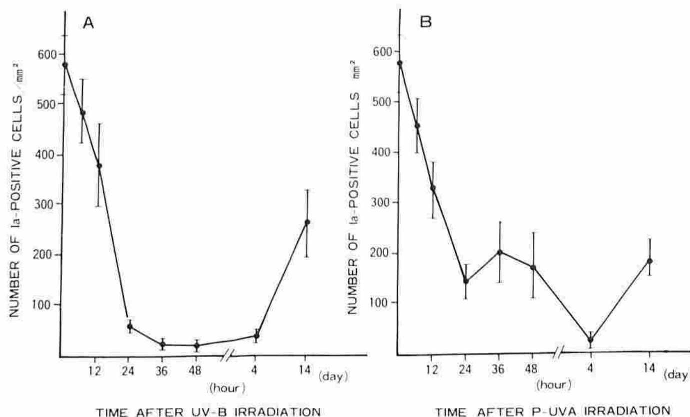


FIG 4. Time course changes of Ia-positive cell number after a single dose irradiation of UVB (200 mJ/cm² of 300 nm) (*A*) and PUVA (8-MOP + 1 J/cm² of 360 nm) (*B*). Values are mean ± SD.

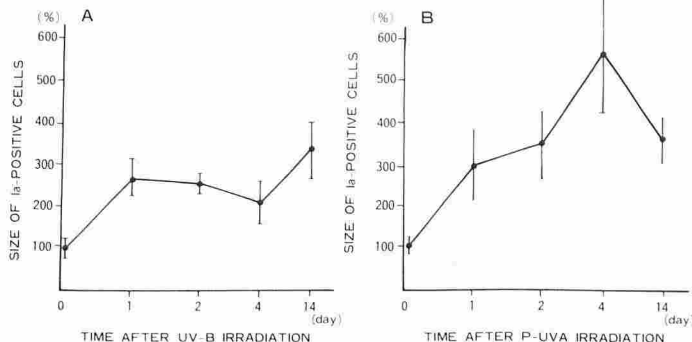


FIG 5. Time course change of Ia-positive cell size after a single dose of UVB (300 nm, 200 mJ/cm²) (*A*) and PUVA (8-MOP + 360 nm, 1 J/cm²) (*B*). Values are mean ± SD.

(number = 4), Ia-positive cells present in 10–20 fields were counted and expressed as the number of cells (mean ± SD) per mm². (One field at a magnification of 400× corresponds to an area 0.599 mm².)

Sizes of the Ia-positive cells were also analyzed quantitatively. Microscopic slides were projected onto a paper with a projection microscope and the outlines of Ia-positive cells, including their dendritic processes, were traced with a pencil. These were clipped from the paper with a razor and their weight was measured using a microbalance. Changes of cell size were expressed as a percentage increment ± SD to normal control.

Electron Microscopy

Ultrastructural changes after a single exposure of UVB (200 mJ/cm² of 300 nm) and PUVA (topical 8-MOP and 1 J/cm² of 360 nm) were examined by EM procedures. Samples were taken at 12, 24, and 48 h and at 4 and 14 days after irradiation.

For IEM, ears were incubated in 25 mM EDTA solution and then epidermal sheets were separated and processed for the following IEM procedures. Sheets were fixed in periodate-lysin-paraformaldehyde (PLP) fixative [12] at 4°C for 30 min, thereafter, they were processed for the multistep immunoperoxidase technique as described above, but all steps were performed at 4°C. Samples were postfixed with 2% osmium tetroxide for 30 min, then dehydrated and embedded in epoxy resin. Thin sections were examined at 60 kV before staining and 80 kV after staining. Instead of anti-Ia^k Ab, OKT 3 monoclonal Ab (Ortho) was used as a control.

RESULTS

Langerhans Cells in the Epidermis

In untreated normal epidermis, darkly stained Ia-positive cells were evenly spread over the epidermis, exhibiting a regular distribution among basal keratinocytes (KCs) (Fig 1*A*). Some dendritic melanocytes were also present but easily distinguishable from Ia-positive LCs because of their numerous intracytoplasmic pigment granules.

UVR-treated epidermis showed a remarkable decrease in the density of Ia-positive cells and a change of appearance (Fig 1*B*), the degree of which seems to be clearly related to the wavelengths, dose, and time intervals after irradiation. Thus, dose-response and action spectrum studies were performed for the samples taken 24 h after irradiation, and a time course study was carried out for those taken 0 h to 14 days after irradiation.

Dose-Response Relation

A single dose of UVB and PUVA caused a marked decrease in Ia-positive cell density according to administered dosage. Following relatively low doses (25, 50 mJ/cm²) of 300 nm radiation (Fig 2*A*), the density of Ia-positive cells decreased to about 30% of normal density. A high dose (1 J/cm²) of 300 nm irradiation caused complete disappearance of these cells. PUVA also had similar depletion effects on Ia-positive cells. A gradual increase in dosage up to 100 mJ/cm² of UVA radiation resulted

in about a 60% reduction of cell number, and the rate of reduction reached a plateau between 100 mJ/cm^2 and 1 J/cm^2 (Fig 2*B*).

Action Spectrum for Ia-Positive Cell Depletion Effects

Action spectrum studies were performed following 200 mJ/cm^2 or 1 J/cm^2 of irradiation by various monochromatic wavebands with or without topical 8-MOP application (Fig 3*A*,*B*). In groups treated with UVR alone, action spectrum curves showed that a spectral range shorter than 300 nm was very effective, whereas UVA ranging from 320–400 nm was almost ineffective. 8-MOP plus UVR treatment caused a significant reduction of cell number only within the UVA spectrum. Judging from the two curves in Fig 3, the action spectrum of PUVA seems to lie between 320–380 nm.

Time Course Study

Changes in number and size of Ia-positive cells at 6, 12, 24, 36, and 48 h and at 4 and 14 days after UV irradiation (Figs 4*A*,*B* and 5*A*,*B*) were studied. Following irradiation with each dose of 200 mJ/cm^2 of the 300 nm band and 1 J/cm^2 of the 8-MOP plus 360 nm band, Ia-positive cells gradually decreased in number until 24 h after irradiation, reaching a nadir between 36 h and 4 days with the 300 nm band, and on day 4 with PUVA (Fig 4*A*, *B*). Incomplete recovery in cell number but with a restoration of regular distribution of Ia-positive cells was observed after 14 days in both cases.

It is of interest that an increment in cell size occurred, which was closely associated with the reduction in cell number (Fig 5*A*,*B*). This was observed with both UVB and PUVA treatment. The most prominent changes were observed on day 4 after PUVA treatment (Fig 1*C*), when a few remaining Ia-positive cells enlarged roughly 5 times normal size, displaying elongated dendritic processes. By 14 days after PUVA treatment such giant cells began to decrease in size, whereas some increase was still visible on the same day after UVB irradiation.

Ultrastructural Changes in LC

Time sequence changes of epidermis, especially with regard to LCs, following a single dose of UVB and PUVA, were examined in Epon-embedded 1-μm sections (Fig 6*A*–*C*) and by EM. Results are summarized in Table I. Untreated ears revealed a regular occurrence of clear cells without any pigment granules in every 7–10 basal cells (Fig 6*A*). In EM, classical LCs with Birbeck granules were scattered throughout the basal layer (Fig 7*A*).

Morphologic alterations produced by UVB and PUVA were essentially the same. In the acute "injury phase," ranging up to 48 h after irradiation, similar degenerative changes were noted in both LCs and KCs, though these changes were much more prominent in LCs. Some KCs showed distinct signs of degeneration or cell death, i.e., sunburn cell formation (Fig 6*B*). Many LCs also showed various degrees of degenerative changes such as swelling and rupture of mitochondria and lysosomes (Fig 7*B*), while more severely damaged cells revealed condensation of cytoplasm with the appearance of many vacuoles and pyknotic nuclei or nuclear fragments evenly scattered throughout the cytoplasm (Fig 7*C*). Although some of the LCs seemed intact morphologically, the number decreased to approximately 20–30% of the normal number in both UVB- and PUVA-treated skin.

IEM was carried out for samples taken before and 24 h after UVB or PUVA treatment. No Ia-positive cells were found before any treatment (negative:positive = 0:14) and the majority of the remaining LCs were Ia-positive in both UVB- and PUVA-treated sites (UVB, negative:positive = 2:16; PUVA, negative:positive = 0:8). Electron-dense deposits consisting of reaction products including their dendrites were seen on the cell surface membrane (Fig 8*B*). A small number of remaining LCs were Ia-negative (Fig 8*B*), although they showed no marked structural alterations. These Ia-negative LCs were located near the Ia-positive LCs in the same section.

In the "recovery phase," 4 days after irradiation, epidermis showed marked proliferative changes such as acanthosis, enlargement of individual KCs, and occasional mitotic figures (Fig 6*C*). Although degenerative changes were no longer seen, the LC population greatly decreased. A few of the remaining LCs showed signs of activation, i.e., enlargement of cell size and elongation of dendrites (Fig 7*E*), but there were no mitotic figures in LCs. Fourteen days after irradiation, when the thickness of the epidermis decreased and appearance became nearly normal, LCs with Birbeck granules were noted by EM and

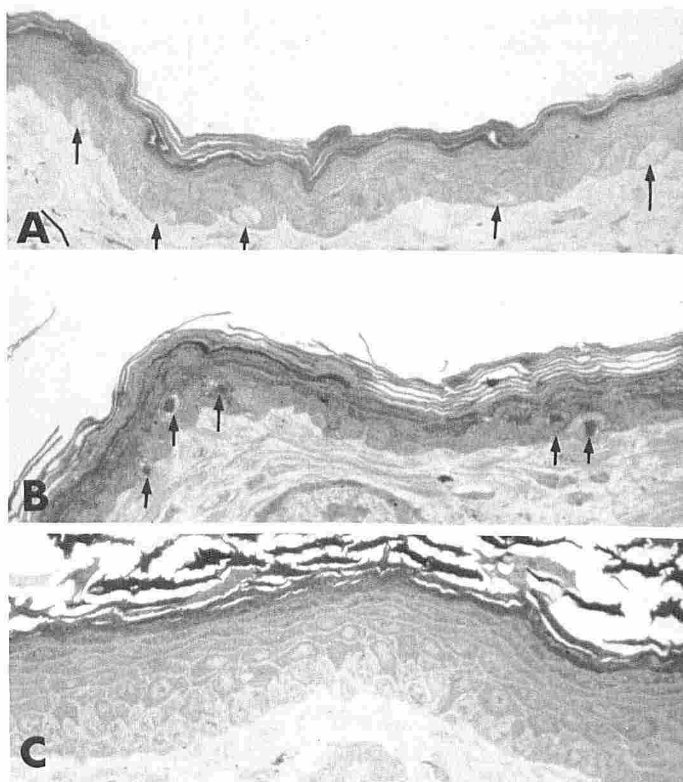


FIG 6. Light microscopic view of toluidine blue-stained 1-μm Epon-embedded section. *A*–*C* × 300. *A*, Normal epidermis. Clear cells (*arrows*), probably Langerhans cells, are present scattered among 7–10 basal cells. *B*, Epidermis at 24 h after a single dose of 200 mJ/cm^2 of 300 nm irradiation. This section shows the degenerating cells with condensed nuclei (so-called sunburn cells, *arrows*), scattered throughout the basal layer. *C*, Epidermis 4 days after PUVA treatment (8-MOP + 1 J/cm^2 of 360 nm). Epidermis shows marked acanthosis. There are no clear cells in this photograph.

TABLE 1. *Morphologic changes after UVB (300 nm, 200 mJ/cm^2) and PUVA (1% 8-MOP plus 360 nm, 1 J/cm^2) treatment*

		12 h	24 h	48 h	4 days	14 days
Epidermal hyperplasia	UVB	+	−	−	++	+
	PUVA	−	−	+	+++	+
Sunburn cells	UVB	+	++	+	−	−
	PUVA	+ or −	+	+	−	−
Langerhans cells:						
Reduction in number	UVB	+	++	++	+++	−
	PUVA	+	++	++	+++	−
Degeneration of organella	UVB	+	++	+	−	−
	PUVA	+	+	+	−	−
Condensation, cytolysis	UVB	+	++	++	−	−
	PUVA	+ or −	+	+	−	−

+++ = Marked; ++ = moderate; + = few; − = negative.

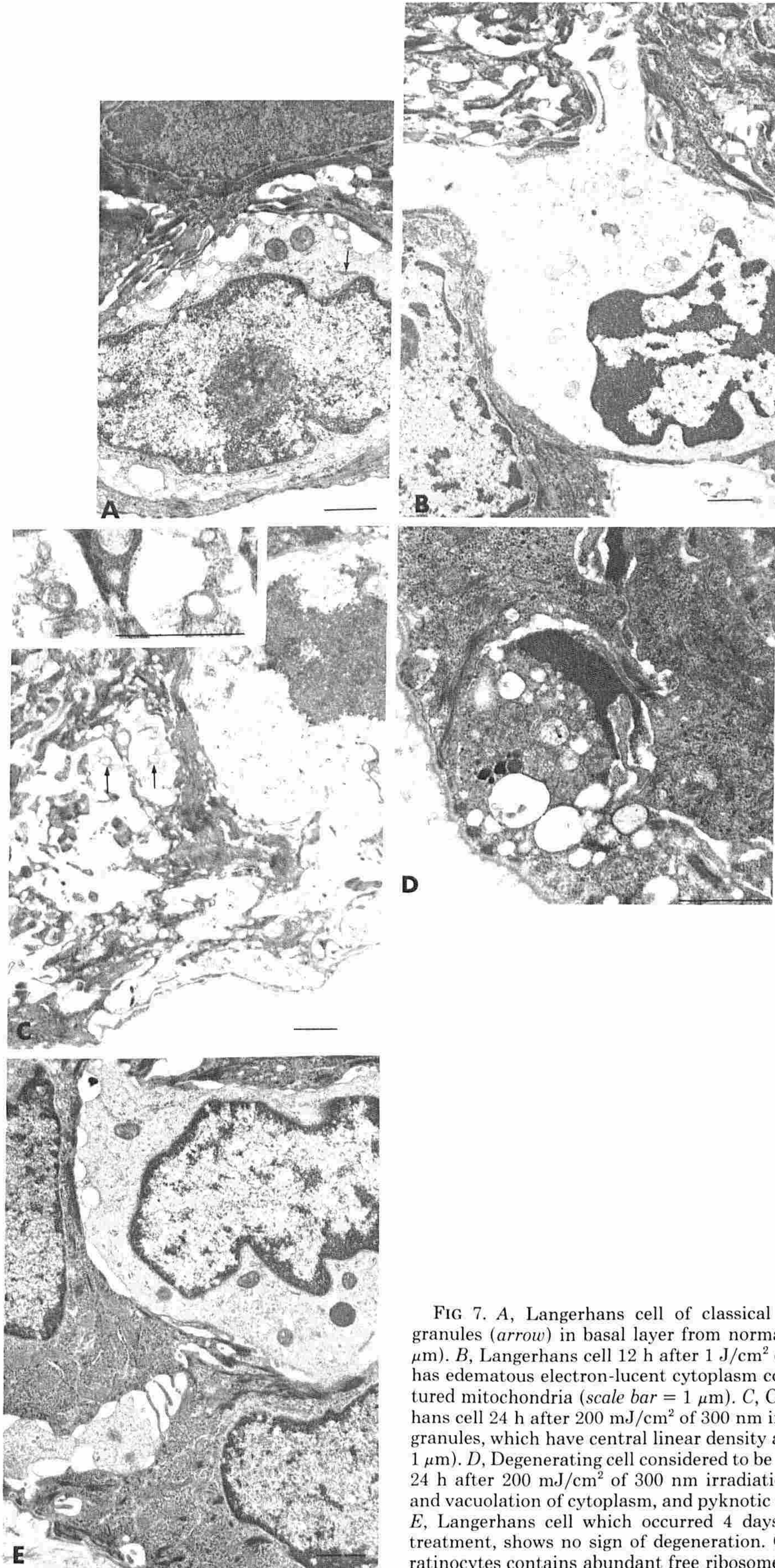


FIG 7. *A*, Langerhans cell of classical appearance with Birbeck granules (*arrow*) in basal layer from normal epidermis (*scale bar* = 1 μm). *B*, Langerhans cell 12 h after 1 J/cm^2 of PUVA treatment, which has edematous electron-lucent cytoplasm containing swollen and ruptured mitochondria (*scale bar* = 1 μm). *C*, Cytolytic change of Langerhans cell 24 h after 200 mJ/cm^2 of 300 nm irradiation. *Arrow* indicates granules, which have central linear density and periodicity (*scale bar* = 1 μm). *D*, Degenerating cell considered to be a Langerhans cell occurred 24 h after 200 mJ/cm^2 of 300 nm irradiation. It shows condensation and vacuolation of cytoplasm, and pyknotic nucleus (*scale bar* = 1 μm). *E*, Langerhans cell which occurred 4 days after 1 J/cm^2 of PUVA treatment, shows no sign of degeneration. Cytoplasm of adjacent keratinocytes contains abundant free ribosomes (*scale bar* = 1 μm).

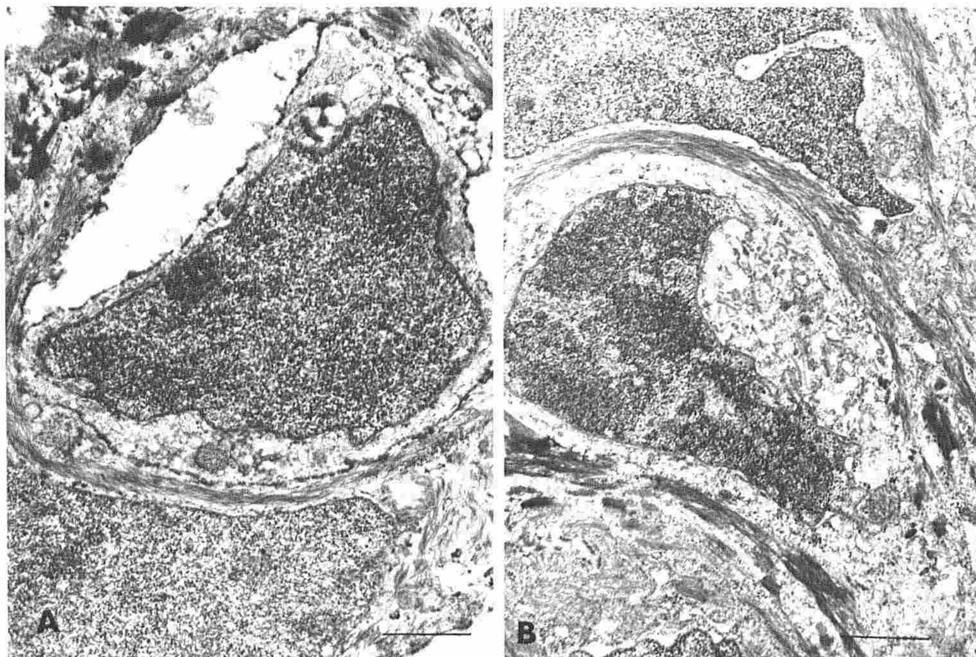


FIG 8. Immunoelectron microscopic views. Ia-positive (*A*) and Ia-negative (*B*) Langerhans cells are observed in the same section following a single dose of 200 mJ/cm² of 300 nm radiation (*scale bars* = 1 μm).

clear cells found by light microscopy also regained their normal density and distribution.

DISCUSSION

In the present study, by analysis of the action spectrum and the time course of LC depletion as well as examination of morphologic changes, we demonstrated that LCs are also damaged by UVB and PUVA in a manner similar to that observed with other epidermal cells.

The conjoint use of immunohistochemistry and EM revealed a unique pattern of LC alteration after UV irradiation. In the acute "injury phase," Ia-positive cells decreased in number in close association with the degeneration of LCs at the ultrastructural level. IEM study showed that only a small population of these cells had lost their Ia marker. These degenerative changes in the LC population paralleled those of the KC population. The degenerating cells of both populations were completely eliminated by 4 days after irradiation, probably due to an apoptotic process [13]. Whereas KCs showed marked signs of proliferation in the "recovery phase," only a few remaining LCs showed similar changes of activation at the EM level, and no mitotic LCs were observed.

An increase in LC size was more clearly visible in epidermal sheet preparations, in which remaining Ia-positive cells increased to roughly 3–5 times the normal size and had elongated dendrites (Fig 1*C*). It is of note that in the present time sequence study, enlargement of remaining Ia-positive cells was observed in every case of UVB and PUVA treatment. Such giant LCs have been reported in epidermis chronically treated with the PUVA regimen [14].

This unique pattern of destruction and recovery of LCs from the damaging effects of UVR provides interesting information on the biologic behavior of LCs in relation to UVR and on the kinetics of LCs in the epidermis. A moderate dose of UVR caused an actual decrease in their number due to cell damage, although some of LCs only lost their Ia marker without any morphologic alterations. Such a difference of cellular alteration may depend on the dose of UVR and on the time interval for sampling after irradiation. It is possible that only the surface marker is affected by lower UVR doses or earlier stages after irradiation. The slower recovery pace in the number of LCs when compared to that of KCs may be due to the different cell kinetics of these distinct cell populations in the epidermis: restoration of LCs seems to take place partly by a repopulation process originating in the bone marrow [1].

The results of this study are basically similar to those of Aberer et al [7] but with some conflicting points. The main difference may be due to the difference in staining methods for the quantitative assay and to the length of the observation period. The Ia marker used in this study is thought to be more stable with regard to UVR and more reliable than the ATPase marker [15]. In contrast to the study of Aberer et al which was conducted for only a 48-h period, our prolonged observations up to 14 days after UV irradiation revealed a distinct pattern of LC behavior that provides further evidence of actual loss of these cells following UV irradiation.

Our quantitative studies with various doses and with various wavelengths of monochromatic UVR revealed new aspects of LC depletion effects of UVR. Firstly, the obtained dose-response relation has also been observed in sunburn cell formation [16,17] and in the induction of unscheduled DNA synthesis [18]. Secondly, our action spectrum study also showed a pattern similar to that of sunburn cell formation [16,17], induction of unscheduled DNA synthesis [19], or to that of UVR-induced erythema [20]. In all of these cases, wavelengths shorter than 300 nm were most effective while all wavelengths of the UVA spectrum were entirely ineffective. Thirdly, action spectra of PUVA treatment also overlapped those for PUVA-induced sunburn cell [21] and for erythema [22]. In these cases, action spectra lie between 320–380 nm. These phenomena may be related to the fact that DNA is the primary chromophore of UVR [20].

Finally, we conclude that Ia antigens on the LC surface are useful markers for the study of the functional state of these cells because Ia antigens are essential for antigen presentation in immune responses [23].

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