

THE SIGNIFICANCE OF LONG WAVE UVL (320-400 NM; UVA) IN LIGHT INDUCED DISEASES

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Abstract. The histopathologic response to a fixed dose of ultraviolet radiation in the long wave ultraviolet (UVA) range was studied. Specimens from control subjects, as well as an individual who presented with a photoallergic contact dermatitis (PACD) to tribromsalicylanilide (TBS), showed only an increase in the number of epidermal clear cells. In an erythematous response to UVA a significant dermal perivascular inflammatory response was seen. The subjects who reacted clinically as persistent light reactors all developed papulovesicular responses to UVA, mimicking the clinical and histopathologic state. The demonstration of abnormal reactions to UVA irradiation in those individuals in whom no specific photoactive agent was found suggests the need for a modified definition of persistent light reaction. This definition should unify the biophysical concepts with the clinical picture. It would appear that by using a high intensity source of UVA, more abnormal reactions to light alone will be disclosed.

Vascular injury progressing from a mild perivascular response to a lesion resembling the disease state has been considered to be of importance in the pathogenesis of ultraviolet (UV) injury (16). Vascular damage progressing to dilatation has been demonstrated in the vessels of the cutis (2, 13, 14). In 1957 Miescher (10) described the development of an angiitic response in the corium as a result of irradiation in the UVA¹ (320-400 nm) range.

By utilization of an instrument whose spectral

output resembles "midday" summer sunlight (1), the natural environment leading to UV-induced disease states can be reproduced. Evaluation of the response to the natural UV spectrum as it reaches Earth is thus practicable. However, since approximately 90% of the sun's UV energy reaching Earth lies in the UVA during the summer months and 98% during the winter, and since the same spectrum is often implicated in the pathogenesis of photoallergy (3, 5, 6), this study of the response to UVA was performed.

METHODS

Subjects studied were in-patients and out-patients seen at Metropolitan Hospital Center with various skin diseases unrelated to ultraviolet light (UVL) exposure. Included in this study were 2 patients who developed an erythematous response to UVA, 3 patients who developed abnormal responses to MED testing in addition to papulovesicular reactions to UVA, 1 patient who had similar abnormal reactions and whose disease was the result of ingestion of hydrochlorothiazide, 1 patient who was a persistent light reactor by the criteria of Jillson et al. (7), and 1 patient who had an uncomplicated photoallergic contact dermatitis (PACD) to tribromsalicylanilide.

A 150 W a.c. xenon arc solar simulator was used as the source ultraviolet radiation. The physics of this instrument has been described previously (1).

All subjects were irradiated on clinically uninvolved skin of the dorsal paravertebral area. MEDs were determined using the full range of the instrument (290 to 400 nm) by irradiating using dose increments of approximately 40%. Irradiation times ranged from 21 seconds to 116 seconds. All light tests were evaluated 24 hours after irradiation.

In order to evaluate the effect of UVA irradiation on human skin, the skin of the dorsal spine was also irradiated using a fixed dose of 3 minutes with the Schott WG 345 filter in place. This transmits UV only above 320 nm. This dose has been shown to produce no reac-

¹ Abbreviations

UVA = long wave ultraviolet; 320-400 nm

MED = minimal erythema dose

UVB = 290-320 nm; midrange ultraviolet

TCSA = tetrachlorosalicylanilide

TBS = tribromsalicylanilide

DBS = dibromsalicylanilide

BT = bithionol

PACD = photoallergic contact dermatitis

PLR = persistent light reactor

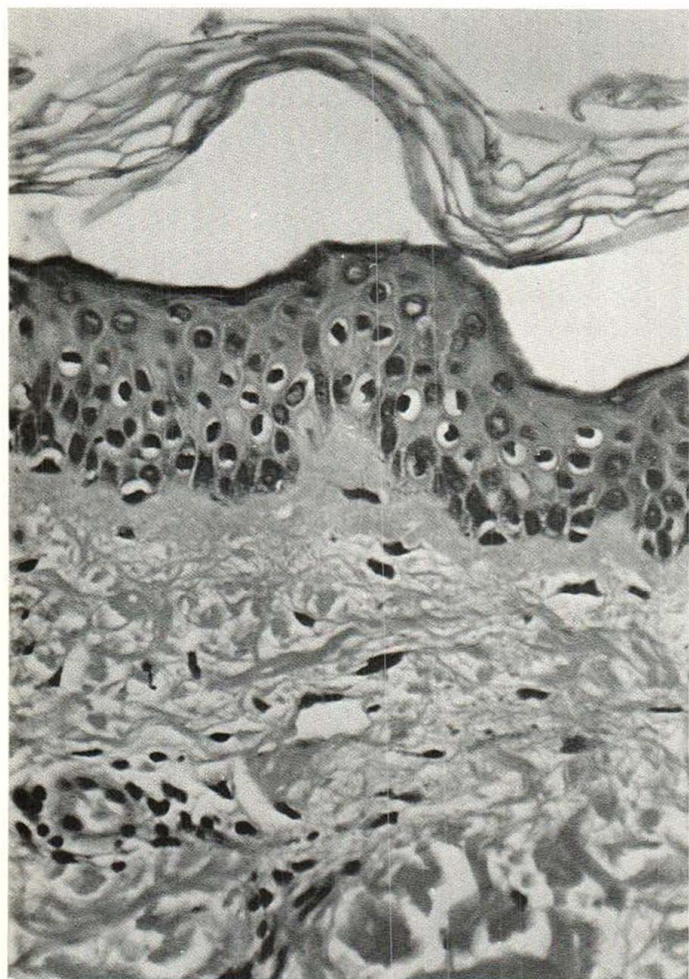


Fig. 1. No clinical response to UVA. There is an increase in the number of epidermal clear cells. H & E, $\times 150$.

tion in normal individuals yet is sufficient to elicit an abnormal reaction in susceptible individuals. The energy output of the instrument as used here is 72.8 mW/cm^2 with 56.3 mW/cm^2 in the UVA.

Photopatch tests to the halogenated salicylanilides (TCSA TBS DBS BT) 0.1% in hydrophilic petrolatum were performed on the skin overlying the dorsal spine on all individuals suspected of being light reactors as well as on 2 control patients. Duplicate rows of the test substances were applied, covered, and allowed to remain in place for 24 hours. At that time one row was irradiated using UVA and then recovered. Twenty-four hours later the tests were evaluated. If the UVA irradiation elicited an abnormal response, then the dose used for photopatch testing was titrated down to the dose which in itself produced no clinical response. A photopatch test was considered a positive reaction if the disease state was reproduced. In order to facilitate proper evaluation, the control 48-hour closed patch test must be negative at the same time as a photopatch test is positive.

Biopsies were taken from the site of UVA irradiation at the same time of evaluation in 5 subjects without light-associated disease who developed no clinical response;

from 2 subjects who developed an erythematous response (one of whom has used chlorpromazine for several years, and one subject who can only be classed as a photosensitivity reaction of undetermined type); from 4 subjects who developed papulovesicular responses (one of whom was a persistent light reactor with positive photopatch tests to several of the halogenated salicylanilides, two were clinically persistent light reactors with no demonstrable contact photoallergen, and one subject who had a photoallergy to hydrochlorothiazide). This latter subject presented with an apparent clinical reaction to light which developed after being placed on the medication for 2 weeks for an unrelated disorder. Light testing was performed while he was still using the diuretic.

In addition, biopsies were performed from the sites of non-reactive photopatch tests to TCSA in 2 patients; from a papulovesicular photopatch test reaction to TSCA in 1 subject (a persistent light reactor); and from a positive photopatch test to TBS in 1 patient with a photoallergic contact dermatitis to TBS.

Contralateral normal skin was also biopsied in those individuals who developed no clinical reaction to UVA as well as in one who developed an erythemic response.

Table I

Subject	Response to UVA	Comment
65 WM	No response	MED normal
37 WM	No response	MED normal
23 WM	No response	MED normal
47 PRF	No response	MED normal
59 PRM	No response	MED normal
57 WF	Erythema	Psoriatic, using chlorpromazine, MED normal
60 WM	Erythema	Non-specific photosensitivity reaction, MED normal
43 PRM	Papulovesicles	PLR with positive PPT, abnormal MED
56 PRM	Papulovesicles	PLR, no demonstrable photoallergy, abnormal MED
73 PRM	Papulovesicles	PLR, no demonstrable photoallergy, abnormal MED
65 WM	Papulovesicles	Photoallergic response to hydrochlorothiazide, abnormal MED

WM=white male, WF=white female, PRM=Puerto-Rican male, PRF=Puerto-Rican female, PPT=photopatch test.

RESULTS (Figs. 1-9; Table I)

No clinical response to UVA

All of the individuals so tested, those considered as "normals" as well as the subject who presented

as a PACD to TBS, presented a similar picture and will be discussed together. The epidermis showed an increase in the number of clear cells over the unirradiated site. In addition, rare dyskeratotic cells were seen. In the dermis there was a perivascular infiltrate consisting of lymphocytes. This vascular response was not significantly greater than at the unirradiated sites.

Erythematous response to UVA

There were 2 subjects who developed an erythematous response. One was a psoriatic patient who had used chlorpromazine for several years and the other developed erythema in the sun-exposed areas after minimal exposure to midday sunlight. Both of the biopsies were rather similar in quality to those in the previous group. However, the dermal perivascular reaction in the upper dermis was increased in intensity, the cellular infiltrate now appearing to involve the vessel walls. This was not seen in contralateral unirradiated skin.

Papulovesicular response to UVA

In this category were 4 patients who react clinically as persistent light reactors. One of these patients developed positive photopatch tests to the

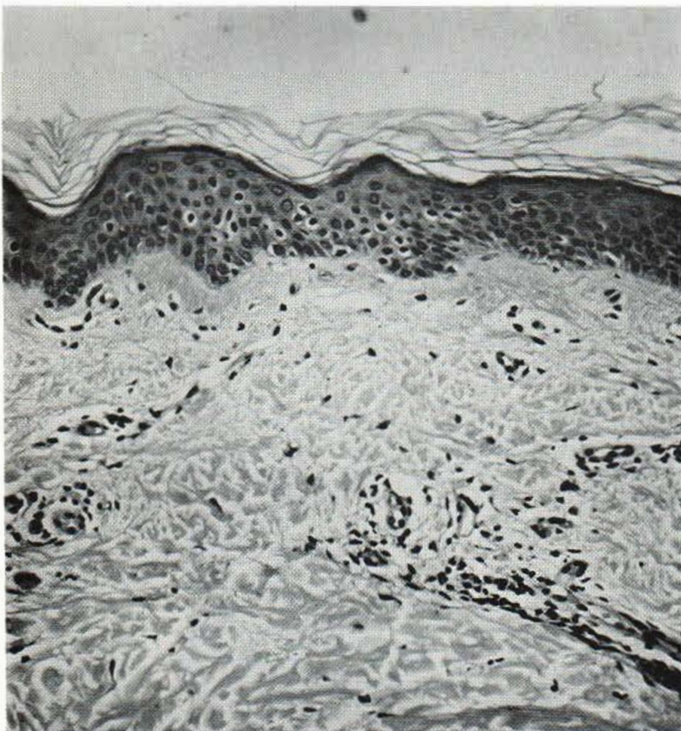


Fig. 2. Biopsy from erythematous response to UVA in a patient using chlorpromazine, H & E, $\times 75$.

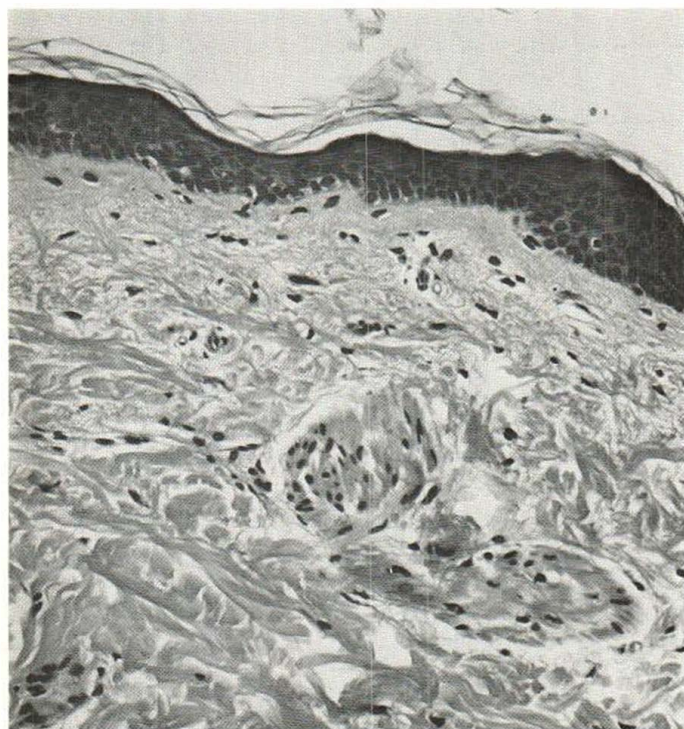


Fig. 3. Contralateral unirradiated skin biopsy from patient who developed erythematous response. H & E, $\times 75$.



Fig. 4. Papulovesicular response to UVA in a patient with a photoallergy to hydrochlorothiazide and an abnormal MED. H & E, $\times 92$.

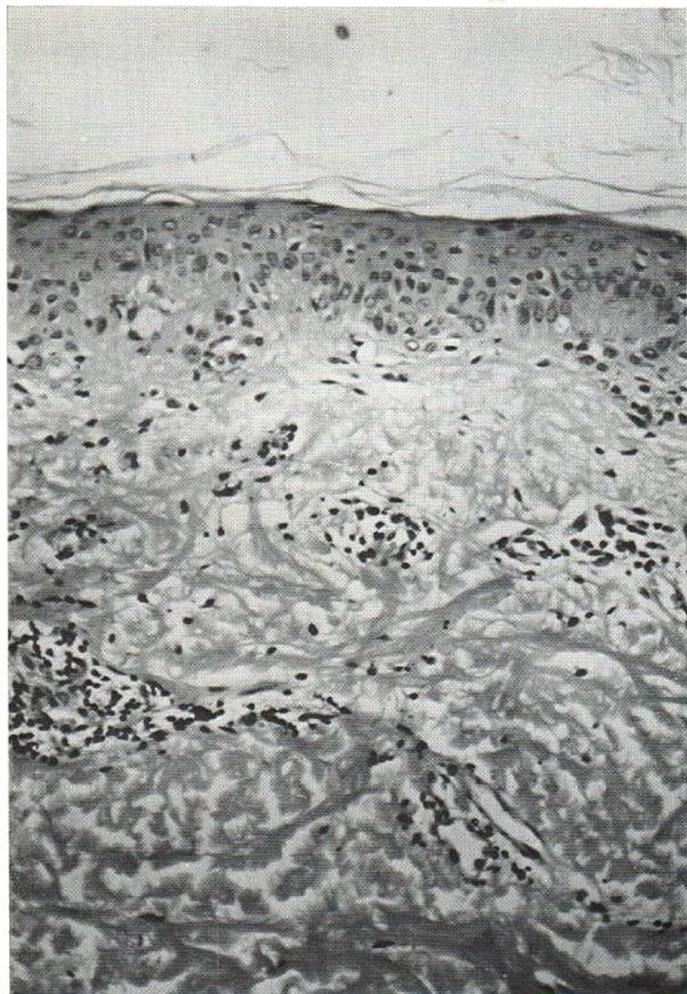


Fig. 5. Papulovesicular response to UVA in a patient with no demonstrable photoallergy and an abnormal MED. H & E, $\times 75$.

halogenated salicylanilides, 2 had no demonstrable photoallergy, and another developed a photoallergy to hydrochlorothiazide. All of these patients also had abnormal responses to MED testing. All of the biopsies showed a similar picture but in varying degrees of intensity. The 2 subjects who had no demonstrable photoallergy had the mildest reactions while the most severe reactions were seen in the individual who developed positive photopatch tests. The light reactor whose disease was due to hydrochlorothiazide ingestion was intermediate. All showed epidermal changes of spongiosis, exocytosis, liquefaction degeneration of the basal layer, and scattered dyskeratotic cells. In the dermis was a perivascular infiltrate of lymphocytes and endothelial proliferation. Involvement of the blood vessels by lymphocytes

was prominent. In all of these instances the clinical disease state was mimicked.

Results using photoactive agents

A closed patch test biopsy to halogenated salicylanilides was carried out in 2 individuals. One of these was a control patient without light-associated disease, and one was a subject who developed an abnormal photopatch test to TBS. Both of these biopsies were unremarkable.

Non-reactive photopatch tests performed on 2 subjects without light-associated disease also revealed a picture similar to UVA alone. Two papulovesicular photopatch tests were also biopsied. One of these was from a persistent light reactor who developed an abnormal response to TCSA and the other developed a photoallergic contact

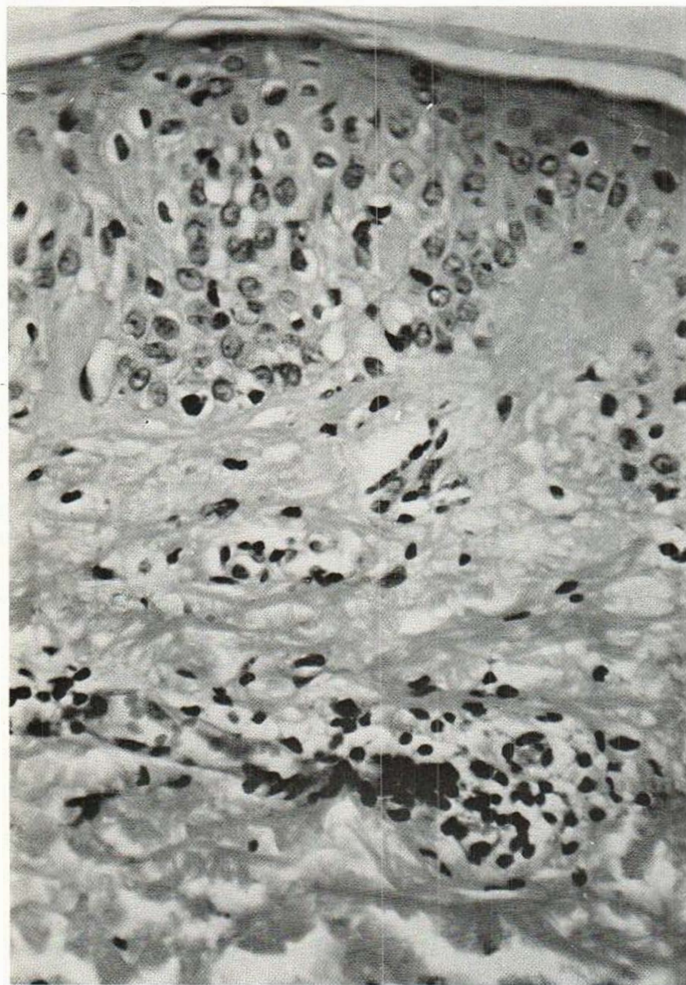


Fig. 6. Papulovesicular response to UVA in a patient with no demonstrable photoallergy and an abnormal MED. H & E, $\times 150$.

dermatitis to TBS. His response to UVB testing and UVA testing was normal. Although both showed similar findings, the markedly greater intensity seen in the persistent light reactor was striking. Epidermal changes consisted of exocytosis, spongiosis, and a marked increase in the number of clear cells. In the dermis was a perivascular infiltrate of lymphocytes, endothelial proliferation and endothelial thickening.

COMMENT

By using a light source whose spectral output resembles "midday summer sunlight" and whose output lies predominantly in the UVA portion of the ultraviolet spectrum, the histopathologic responses to UVA were studied. At the outset it must be emphasized that almost all UVA which

is incident on the skin penetrates through the epidermis to reach the dermis (4). The vascular reaction which occurs with no obvious clinical response is intensified in subjects who developed an erythematous response. There is now involvement of the papillary vessel walls, a phenomenon not observed in normal subjects.

The individual who had a circulating photoallergen (hydrochlorothiazide); the 3 who, in addition to developing a vesicular response to UVA, had abnormal MEDs; and the patient with a positive photopatch test reaction to TCSA (a persistent light reactor) all showed a similar histopathologic picture. There is an intense vascular reaction localized to the upper dermis associated with epidermal alterations (to be discussed later). This marked reaction may well be the result of the photoreaction between UVA and a photo-

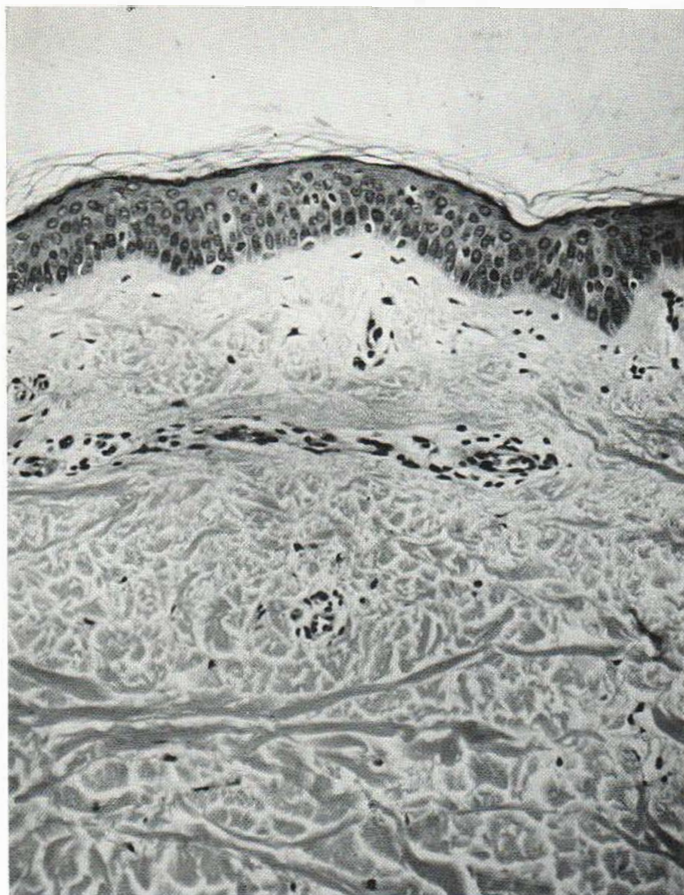


Fig. 7. Negative photopatch test to TBS. H & E, $\times 75$.

active agent present in the dermis. This agent can reach the dermis via the circulation (as did the hydrochlorothiazide) or by topical application—the positive photopatch test. The histopathology of these abnormal responses to UVA bears a strong resemblance to the biopsies of MED responses in patients with polymorphous light eruption (PMLE) (16). It would thus seem that the skin reacts in a non-specific yet similar manner to these varying wavelengths of UVR. Significantly, abnormal response to UVA without the use of added photoactive agents developed at sites distant to sun-exposed areas. (History failed to reveal ingestion of any known photosensitizer and porphyrin studies were normal.) This reactivity at distant sites suggests the likelihood that an immunologic mechanism plays a significant role. The abnormal photopatch test has the same significance as any abnormal patch test, with an additional feature. The photoantigen must be produced at the site of action. The pa-

tient must also recognize this new photoproduct as immunogenic and react accordingly. Since the case is made for some photoactive agents mediating abnormal reactions to UVA, it follows that such substance should persist long after the offending agent is withdrawn. Such a hypothesis has been proposed (17).

Because incident UVA has not been shown to be appreciably absorbed in the epidermis, the significant alterations occurring in response to UVA irradiation require explanation. There is an apparent increase in the number of epidermal clear cells in response to non-erythemogenic UVA. These cells have been presumed to be melanocytes (9). On using irradiation in the UVB (290–320 nm) range, an increase in melanocytes (or melanocyte activity) was observed in response to single-dose and repeated irradiation (11, 12). Although no attempt was made to study the phenomenon of immediate pigment darkening (Meirowsky phenomenon) in response to UVA, the

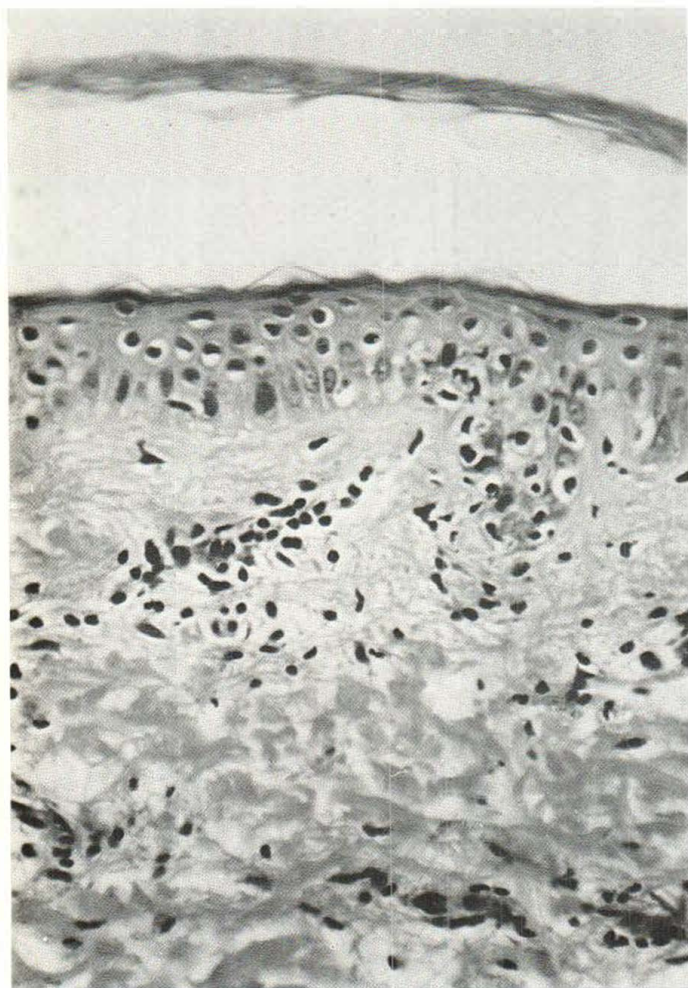


Fig. 8. Reactive photopatch test to TBS in a patient with an uncomplicated PACD to TBS. H & E, $\times 75$.

apparent increase of clear cells seen after 24 hours is striking. The presence of these cells and the epidermal changes of spongiosis, exocytosis, and liquefaction degeneration certainly suggest epidermal participation in response to UVA irradiation. This may result from direct action on epidermal DNA (Willis et al. (18) has demonstrated an increase in epidermal DNA synthesis in response to UVA) or via mediation of lysosomal liberation (8, 15). The likelihood that there is a direct effect on epidermal DNA which can be magnified by the addition of photoactive agents is underscored in the study by Zirenberg et al. (19). They demonstrated an increase in dimerization and single- and double-stranded breaks in DNA after 313 nm UV irradiation in an in vitro system to which a photosensitizer was added.

This effect was significantly greater than after UV alone. The data thus tends to confirm, rather than deny, the impression that abnormal reactions to UVA may be mediated by a photoactive agent.

Finally, the concept of what defines a persistent light reactor is in need of revision. An alternate definition, and one which coincides with the clinical picture, can now be formulated. An individual who, in response to UV testing with a source mimicking the physical environment, develops an abnormal MED response as well as an abnormal response to UVA, will react clinically as a persistent light reactor. A patient whose disorder is the result of a circulating photoantigen is thus included in such a definition. The presence of a photosensitizer is assumed, whether exogenous or



Fig. 9. Papulovesicular photopatch test to TCSCA in a patient with persistent light reaction. H & E, $\times 92$.

endogenous. It is anticipated that these criteria will be confirmed as more patients are studied, and the list of photosensitizers will increase.

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