

# Ultraviolet A1 (340–400 nm) Irradiation and Systemic Lupus Erythematosus

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Short wavelengths of ultraviolet (UV) light are clearly harmful in systemic lupus erythematosus (SLE), but the action of long UV wavelengths in SLE is more enigmatic. In a series of animal and human studies, long-wavelength UV radiation, i.e., radiation in the ultraviolet-A1 (UVA1) range (340–400 nm), has proven effective in the treatment of SLE. Disease amelioration and a marked decrease in mortality followed ultraviolet-A (UVA) radiation (320–400 nm) of the New Zealand White/New Zealand Black mouse model of lupus. A follow-up study in the same animal suggested that the longer wavelengths (UVA1, 340–400 nm) in the UVA wave band were primarily responsible. There followed four human studies. The first three of these provided data indicating that low-dose UVA1 radiation significantly reduced constitutional

symptoms, joint pain, rashes, and the systemic lupus activity measures, a validated gauge of disease activity in SLE. The fourth human study showed that the therapeutic action of low-dose UVA1 action persisted or progressed long term, a period averaging 3.4 y. UVA1 effects on DNA repair, cell-mediated immunosuppression, tumor necrosis factor alpha release, and apoptosis contrast markedly with those of ultraviolet B (UVB, 280–320 nm) radiation and afford a possible basis for the salutary action of this modality of treatment. The unique features of UVA1 wavelengths may be suited to further therapeutic use, not only in SLE but also in other immunologic disorders. **Key words:** light therapy/photosensitivity/systemic lupus erythematosus/ultraviolet A1. *Journal of Investigative Dermatology Symposium Proceedings* 4:79–84, 1999

## THE TOXICITY OF ULTRAVIOLET RADIATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Sensitivity to ultraviolet (UV) radiation is characteristic in systemic lupus erythematosus (SLE) and the systemic expression of photosensitivity is unique to this disease. SLE photosensitivity has long been attributed to the UV wavelengths below 320 nm (Kochevar, 1985), and abnormal morphologic and histologic responses were generated with wavelengths up to 320 nm (Epstein *et al*, 1965). For example, erythema has been produced by exposing SLE patients to wavelengths up to 330 nm (Cripps and Rankin, 1973), and while repeated exposure of SLE patients to monochromatic light of 300 nm generated lesions, exposure to radiation 340 nm or above did not (Freeman *et al*, 1969). Additionally, single ultraviolet-B (UVB) exposures induced prolonged erythema in 62.5% of SLE patients (Wolska *et al*, 1989); ultraviolet-C (UVC) *in vitro* degraded DNA in SLE peripheral blood lymphocytes 4-fold over that in normal peripheral blood lymphocytes (Compton *et al*, 1984); and finally, UVC but not ultraviolet-A (UVA) was toxic to fibroblasts in MRL/Mp-lpr/lpr lupus mice but not in BALB/C mice (Furukawa *et al*, 1989).

In more recent studies, wavelengths in the UVA range, if inclusive of the shorter portion of the UVA spectrum, also induced photosensitive reactions. For example, high intensity (100 J per cm<sup>2</sup>) UVA radiation from 330 to 460 nm produced lesions in approximately half of SLE

patients who responded adversely to UVB radiation (Lehmann *et al*, 1990), and UVA exposure of photosensitive SLE patients to wavelengths from 320 to 340 nm in doses of 4.2–25.2 J per cm<sup>2</sup> induced erythema, that lasted 2 wk in some (Nived *et al*, 1993); cutaneous lupus erythematosus was exacerbated by the UVA wavelengths from a photocopier (Klein *et al*, 1995); exposure to a mixture of UVB/UVA irradiation in a tanning salon provoked a response in an SLE patient (Stern and Docken, 1986); and lupus erythematosus (LE) like lesions were induced in 20 of 24 photosensitive SLE patients using wavelengths of 330–440 nm and in four patients using visible light (van Weelden *et al*, 1989). Fibroblasts from patients with SLE were more sensitive to UVC (254 nm) and UVA (320–400 nm) radiation than were normal cells (Zamansky *et al*, 1985), although the repair mechanisms appeared to remain intact (Zamansky, 1986). Lymphocytes from SLE patients were more sensitive to UVA1 radiation in the 360–400 nm range, related to the presence of clastogenic factor in the serum, a sensitivity due possibly to the generation of reactive oxygen species (Emerit and Michelson, 1981). The data from the three studies is summarized in **Table I**.

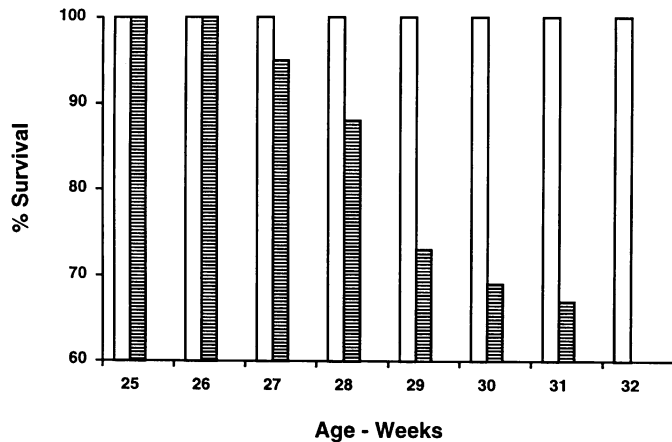
When combined with psoralens, UVA forms photoadducts in DNA, which are useful in slowing down DNA replication and mitosis and thereby useful in diseases such as psoriasis and vitiligo. Because psoralen and UVA (PUVA) make the photoproduct antigenic by altering DNA structure (Zarebska *et al*, 1978), the concern arose that PUVA would aggravate SLE. Several case reports provided evidence that this was so (Dowdy *et al*, 1989; McGrath *et al*, 1990); however, the further concern that PUVA might induce the disease proved to be unfounded (McGrath *et al*, 1990).

Complicating the entire issue of photosensitivity in SLE are polymorphous light eruptions (PLE) and drug-induced photosensitivity. An overlap of photosensitivity in SLE with that of PLE became evident after a study of 67 LE patients with a positive UV provocative test

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Abbreviations: ADCC, antibody dependent cellular toxicity; SCLE, subacute cutaneous lupus erythematosus; SLAM, systemic lupus erythematosus measures.



**Figure 1.** Survival of New Zealand Black/New Zealand White F<sub>1</sub> mice exposed or not exposed to ultraviolet-A radiation. □, exposed; ▨, not exposed.

showed that most had a PLE-like histology on biopsy, and that in over half these patients PLE coexisted with LE (Hasan *et al*, 1997). Moreover, PLE usually starts years before the systemic and cutaneous LE, and possibly predisposes to it (Nyberg *et al*, 1997). Wavelengths in the UVA range most often generate the drug-induced photosensitivities, which are becoming more common as the list of frequently used photosensitizing drugs, now well over 100, continues to grow.

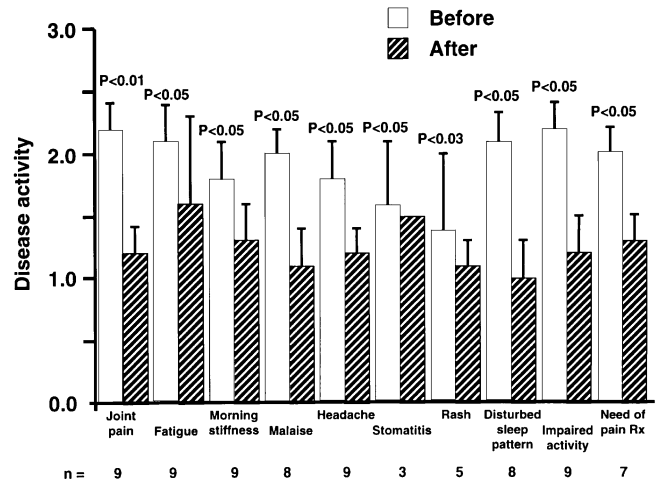
#### THE SALUBRIOUS ACTION OF UV RADIATION IN SLE

Despite the toxicity of short wavelength radiation in SLE, the relatively benign effects of UVA radiation prompted a study of UVA wavelength action in the New Zealand Black/New Zealand White F<sub>1</sub> hybrid mouse model of SLE (McGrath *et al*, 1987). Unexpectedly, low-dose (35 kJ per m<sup>2</sup>) daily exposure for 32 wk to predominately UVA-emitting black lamps eliminated mortality and significantly decreased autoimmunity in these mice over an 8-mo period during which 60% of the nonirradiated control mice died (Fig 1), in line with an established mortality rate for these animals (Dixon, 1985). In a follow-up study using the same animals exposed for a longer time to cool white fluorescent lamps, filtered to transmit only visible light and low levels of UV radiation, it appeared that the UVA1 wavelengths were responsible for the benefits observed (Rihner and McGrath, 1992).

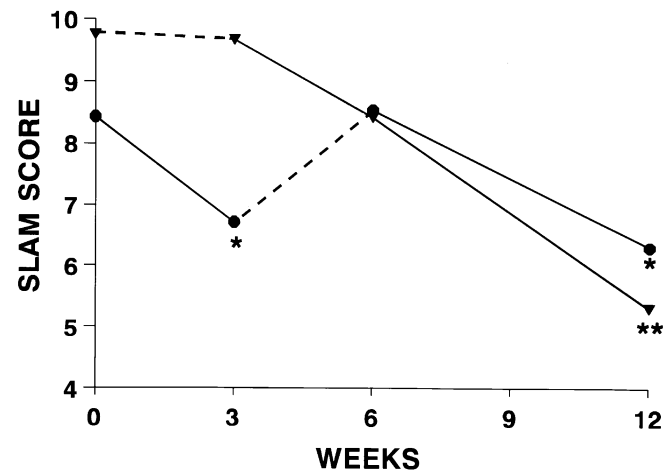
These observations generated a series of four human studies, the first two open (McGrath *et al*, 1994a; McGrath, 1994), the third double-blinded and placebo controlled (McGrath *et al*, 1996), and the fourth long term (Molina and McGrath, 1997). In the aggregate, these human studies presented a picture as encouraging as that drawn from the animal studies. The lamps used for the human studies, TL/10R (Philips Company, Eindhoven, The Netherlands), primarily emitted UVA1 radiation and only low levels (0.06% and 0.03%) of UVB and UVA2 (UVA2, 320–340 nm) wavelengths that were present in the black lamp emissions used in the first mouse study.

In the first of the two open human studies (McGrath *et al*, 1994a), low-dose, 5-d-a-week TL/10R lamp irradiation of 15 SLE patients significantly ( $p < 0.05$ ) decreased clinical disease activity scores ( $p < 0.0005$ ): fatigue, joint pain, fever, malaise, and morning stiffness each decreased significantly ( $p < 0.05$ ). The efficacy and apparent safety of UVA1 radiation in this seminal study prompted the second open human study (McGrath *et al*, 1994b), which differed from the first only in that the remaining vestiges of UVB and UVA2 wavelengths were eliminated from the TL/10R lamp source with UVASUN filters (Mutzhas, Munich, Germany). Clinical responsiveness increased (Fig 2), SSA antibody titers and photosensitivity decreased; in one patient, striking amelioration of a severe annular subacute cutaneous lupus erythematosus rash occurred.

Following the open studies, we undertook a prospective, placebo-controlled, double-blind, cross-over study comparing UVA1 irradiation with visible light (McGrath *et al*, 1996). In this trial we substantiated



**Figure 2.** Second open human study (UVASUN filters added). Changes in 10 specific clinical disease activity scores following 3 wk of 5-d-a-week UVA1 radiation averaging 60 kJ per m<sup>2</sup> per d.

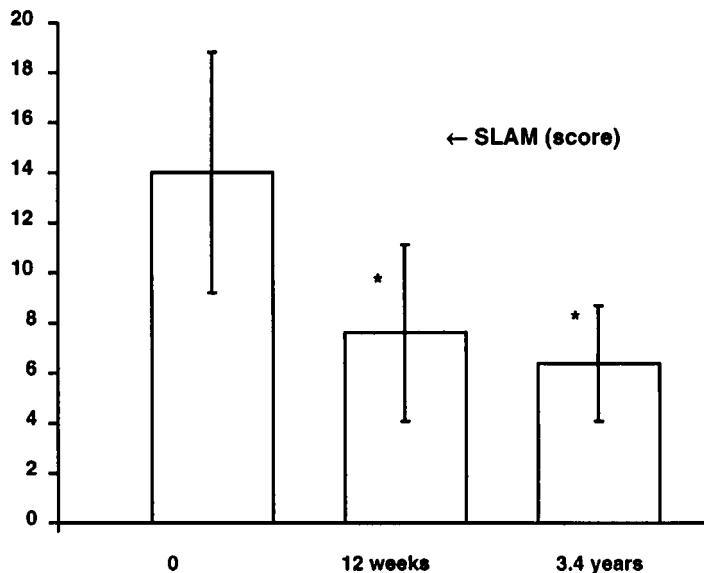


**Figure 3.** SLAM scores. During the first 6-wk, double-blind, 5-d-a-week irradiation phase of the study, Group A (●) patients received UVA1 (—) for 3 wk and were then crossed over to receive placebo (---) for 3 wk. Group B (△) patients received placebo irradiation for the first 3 wk and were then crossed over to receive UVA1 for 3 wk. During the unblinded phase of the study, starting at week 6, all patients received UVA1 irradiation 3 d a week: \* $p > 0.05$ ; \*\* $p < 0.01$ . (Reprinted with permission from *Lupus*, Stockton Press.)

that low-dose UVA1 irradiation emitted from UVASUN-filtered TL/10R lamps effected clinical and serologic benefits in patients with SLE. Specifically, the treatment significantly reduced the systemic lupus activity measures (SLAM) and ameliorated fatigue, arthritis, mouth ulcers, photosensitivity, and acute and subacute but not discoid cutaneous lupus rashes (Fig 3). The data from the three studies is summarized in Table 1.

We followed six patients for an average of 3.4 y and observed that twice-a-week therapy maintained or increased the gains initially obtained and that discontinuance of therapy brought relapses (Molina and McGrath, 1997) (Fig 4). One of our long-term patients, a woman with fair skin and red hair whose severe photosensitivity had been virtually eliminated with UVA1 therapy, developed two lentigos after 5 y of therapy, during which time she had intentionally increased her natural sun exposure. Biopsy evidence of dysplastic changes in these lentigos, although benign, prompted the discontinuance of therapy. Fortunately, by this time, the patient appeared to have gone into remission.

Although UV-sensitive and SSA Å patients responded slightly better to the UVA1 therapy than did nonphotosensitive patients, the difference



**Figure 4. Long-term UVA1 radiation therapy.** Depicted are the changes in disease activity as measured by the SLAM in six patients treated with low-dose UVA1 radiation 3–5 times a week for 12 wk and then 1–3 times a week for an average of 3.4 y. \* $p < 0.05$ .

was not significant. These study patients tolerated plaquenil, prednisone, and NSAID but in our most recent studies, drugs such as thiazides and calcium channel blockers, known to be photosensitizers for patients with subacute cutaneous lupus erythematosus (SCLE), occasionally resulted in rashes. As mentioned above, because drug-induced photosensitivity is becoming more common, patients taking such drugs are observed closely for any sign of drug-induced photosensitivity.

#### ACCOUNTING FOR THE DIFFERENCES IN THE PROPERTIES OF DIFFERENT UV WAVELENGTHS

The UV spectrum, comprising UVA, UVB, UVC, and vacuum UV, was only recently subdivided. The UVA band was separated into UVA2 (from 320 to 340 nm) and UVA1 (from 340 to 400 nm). This division was recommended, at least in part, because it had become evident that UVA2 was, in effect, an extension of UVB (Kochevar *et al*, 1992) and that UVA1, as is evident from our own studies, had its own set of properties, some of which overlapped with those of visible light (Brainard *et al*, 1992). For this reason, the 340 nm demarcation became more useful than 320 nm for separating UV wavelengths according to their photobiologic properties and their effect in SLE.

UVB encompasses wavelengths absorbed chiefly by nucleic acids and proteins in the epidermis (Setlow, 1974). These wavelengths promote DNA pyrimidine dimer formation (Sutherland, 1996), release tumor necrosis factor (Skov *et al*, 1998), trigger translocation of nuclear antigens to cell surfaces (Golan *et al*, 1992), and suppress cell-mediated immunity (Kripke and Applegate, 1991); all these actions have the potential to exacerbate disease activity in SLE.

In contrast, UVA1 photons bypass nucleic acids (Sutherland and Griffen, 1981), penetrating more deeply than those of UVB and reaching putative non-DNA endogenous chromophores in the dermis and its circulating blood and lymph cells (Bruls *et al*, 1984). Although capable of engendering their own brand of DNA damage, UVA1 photons also give rise to photoreactivation (Sutherland and Bennett, 1995), a light-dependent mechanism for the repair of DNA, the major autoimmune antigen in SLE (Tan and Miescher, 1971). These photons also inhibit the release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ; Skov *et al*, 1998), thus inhibiting UVB-generated increases in vascular permeability factor (Longuet-Perret *et al*, 1998), a TNF- $\alpha$ -generated mediator of solar-induced erythema. Broadband UVA photons do not suppress cell-mediated immunity (Aubin and Kripke, 1992), which is already suppressed in SLE (Horowitz, 1972), and, in fact, UVA photons inhibit UVB radiation- or cis-urocanic acid-induced suppression of cell-

mediated immunity (Reeve *et al*, 1998). Furthermore, wavelengths in the UVA1 range actually enhance cell-mediated immunity (McGrath *et al*, 1987; Hager *et al*, 1989), due, at least in part, to their capacity to increase numbers of immunoenhancing CD1a+ dendritic epidermal cells in irradiated skin (Krutman *et al*, 1992).

#### UVA1'S ROLE IN TRANSLOCATION AND APOPTOSIS

In determining pathways by which UVA1 radiation may elicit benefits, the responsiveness of SCLE is telling. This disorder, characterized by the presence of high levels of circulating precipitating antibodies to SSA<sup>1</sup> and, as determined by fluorescence studies, epidermal deposition of Ig (Nieboer *et al*, 1988),<sup>1</sup> presumably anti-SSA, resolves during UVA1 radiation treatment, which decreases levels of anti-SSA antibodies (McGrath, 1994).

We speculate that antibodies to SSA and some other nuclear antigens are pivotal in converting translocation, a normally physiologic process, into a pathologic one. During exposure to UVB radiation (Golan *et al*, 1992; Jones, 1992) or to estrogens (Furukawa *et al*, 1988), viruses (Baboonian *et al*, 1989), or other cell stresses (Kaufmann, 1990), the nuclear antigens SSA, SSB, RNP, and Sm translocate from the nucleus to the cytoplasm and from there to the cell membrane, apparently as an early stage of an apoptotic process that manifests in the formation of apoptotic blebs on the cell surface (Rosen *et al*, 1995). In SLE, if these antigens are bound after translocation to the cell surface by their respective autoimmune antibodies, they can either activate complement-dependent, antibody-dependent cellular cytotoxicity (ADCC)-induced cell necrosis (Norris *et al*, 1984), or facilitate passage of the antigen-antibody complexes into the cell (Lee *et al*, 1989). Cell necrosis releases immunogenic autoantigens, inflammatory mediators, and perhaps viruses (Rosen *et al*, 1995) into the circulation, while entry of antigen-antibody into the cell presumably leads to cell dysfunction. UVA1 radiation has the potential to offset both of these eventualities, first, through initiation of "immediate" apoptosis (Godar, 1996) that preempts completion of translocation, and second, by reducing interleukin-12 (IL-12), a key mediator of ADCC.

The first of these, "immediate" apoptosis, is triggered by the well-established capacity of UVA1 photons to generate the reactive oxygen species singlet oxygen (Godar, 1999). By depolarizing the mitochondrial membrane, singlet oxygen interrupts the progression to cell apoptosis that is ordinarily initiated by the assembly of death-signaling complexes such as Fas/Fas ligand at the cell surface. Because immediate apoptosis is rapid, it has the capacity to come to completion prior to the completion of translocation. A recent report that Fas ligand/Fas receptor interactions in SLE are inhibited by specific antibodies (Suzuki *et al*, 1998) suggests UVA1-induced immediate apoptosis exerts another benefit: that UVA1 may be bringing about apoptosis where none would have otherwise occurred. Several other reports describe defects in the apoptotic process in humans with SLE (Cheng *et al*, 1994; Rieux-Laucet *et al*, 1995), strengthening the possibility that singlet-oxygen-induced immediate apoptosis is beneficial in SLE. We tested the action of UVA1 radiation on an indirect measure of apoptosis, the release of caspase from peripheral blood lymphocytes, and found significant increases in SLE patients and normal subjects 24 h after a 20-min total body UVA1 exposure (unpublished observation).

As for IL-12, this cytokine is a central mediator of ADCC (Trinchieri, 1995) and decreases in its level would dampen cell lysis in SLE. Interestingly, UVA1 releases IL-10 (Krutmann *et al*, 1992), a cytokine that decreases IL-12 levels (de Waal *et al*, 1993). In addition, whereas Th2-like, cytokine-directed eosinophils produce IL-12 (Grewe *et al*, 1998), UVA1 irradiation of patients with atopic dermatitis decreases levels of eosinophils (Krutmann *et al*, 1998) – observations further suggesting that UVA1 radiation can decrease IL-12 levels. Our preliminary studies indicate that low-dose UVA1 irradiation decreased IL-12 levels in normal subjects and SLE patients alike. Accordingly, UVA1's healing action in SCLE may be due to a dampening of cell necrosis

<sup>1</sup>Lee LA, Roberts CM, Frank B, McCubbin V, Rice D, Reichlin M: Autoantibody markers of cutaneous lupus erythematosus. *J Invest Dermatol* 100:573, 1993 (abstr.)

**Table I. The 11 columns depict demographic data, a brief antibody profile, the global clinical score, and the scores for joint pain and fatigue of the 51 patients studied. A blank row separates each of the three groups, made up, respectively, of the 15 patients from the first study, the 10 from the second, and the 26 from the third. The scores in the third study are based on a wider scale (SLAM) than are those in the first two studies. Because the three studies were completed 8, 6, and 4 y ago, some patients were lost to follow-up. (Two patients added more recently are listed at the end.)**

Name	Age	Sex	Race	Ab to SSA	Ab to DNA	ANA	Clin. score before/after	Fatigue before/after	Joint pain before/after	Photo <sup>a</sup>
HB	55	F	A A	+	-	+	12→2	2→0	1→0	⊕
PB	53	F	C	-	+	+	19→17	3→3	3→2	⊕
GV	59	F	A A	-	+	+	18→20	2→3	2→1	⊕
AH	32	F	A A	+	+	+	14→19	2→1	1→0	⊕
DP	52	M	C	-	-	-	Dropped out	2→3	2→3	-
EK	57	F	C	-	-	-	18→10	3→1	2→1	-
DM	30	F	C	-	-	-	20→12	3→2	2→1	-
CC	30	F	C	-	-	-	18→12	3→2	1→1	+
AP	49	F	C	+	-	+	13→11	2→2	2→1	-
VM	39	F	A A	+	-	+	13→5	2→0	2→1	-
HL	58	M	C	+	+	+	12→6	2→1	2→1	-
CW	41	F	C	-	-	-	19→14	3→2	2→2	+
JL	56	F	A A	+	+	+	19→14	2→1	2→1	-
DC	31	F	C	+	+	+	9→5	2→1	0→0	+
JW	59	F	C	-	+	+	17→8	3→1	2→2	+
DL	35	F	C	-	-	+	16→7	2→1	2→1	+
AA	35	F	A A	-	-	+	20→14	3→2	3→2	+
CG	35	F	C	+	-	+	8→4	1→1	0→0	+
JD	60	F	C	-	+	+	24→11	3→2	3→1	-
SS	30	F	C	+	-	+	21→20	3→3	3→2	+
ML	35	F	A A	-	-	-	6→2	0→0	3→1	+
BT	58	F	C	+	-	+	19→10	2→1	2→1	+
DS	28	F	C	+	-	-	15→5	2→1	1→0	+
DN	47	F	A A	-	-	+	16→11	2→2	2→2	+
MM	68	M	C	-	-	+	8→9	2→2	1→1	+
LA	36	F	C	-	-	+	7→3	4→1	3→5	+
LC	34	F	A A	+	+	+	8→4	6→1	5→1	-
SH	36	F	C	+	-	+	12→6	6→4	0.5	-
PH	43	F	A A	PH	-	+	6→8	4→2	4→1	-
CH	33	F	C	-	-	+	19→20	6→5	5→5	+
DM	51	F	CC	-	-	+	8→6	0→0	0→0	-
BR	44	F	C	-	-	-	6→2	6.5→4	6→3	+
KR	48	F	C	+	-	+	15→11	8→4	5.5→3	-
MT	26	F	C	-	+	+	14→4	2.5→2	2.5→3	+
NV	47	F	C	-	-	+	7→7	4.5→7	4→8	+
WM	53	F	C	-	-	+	5→3	7→1	8→1	+
TL	33	F	A A	+	+	+	5→5	8→4	5→2	+
JF	33	F	A A	-	-	+	12→6	8→2	6→4	+
SV	36	F	C	-	-	+	9→7	4.5→5	4→4	+
DSp	23	F	C	-	+	+	9→4	8→3	6.5→3	-
KK	24	F	C	-	-	+	7→6	5→6	6.6→4	+
LD	30	F	A A	-	-	+	4→2	8→0.5	8→0.5	+
EG	38	F	C	-	-	-	7→8	5→8	3→9	+
RE	34	F	A A	-	-	+	8→7	7→5	5→2	-
TP	32	F	C	+	-	+	7→7	7→3	6.5→2	+
DSa	38	F	C	-	-	-	6→6	6→8	7→7	+
AF	66	F	C	-	-	-	7→4	10→4	6.5→6	-
BA	59	F	C	-	-	-	10→3	7.5→4	4→4	-
NL	50	F	A A	-	-	+	11→13	8.5→7	7→7	+
MF	38	F	C	-	-	-	8→8	7→3	8→4	-
BM	53	F	C	+	+	+	19→6	6→1	6→2	+

<sup>a</sup>Photosensitivity.

by three means: a decrease in levels of precipitating SSA antibody, activation of immediate apoptosis, and a reduction in IL-12 levels.

#### THE ENERGY FACTOR

It is intriguing that whereas the predominant result of UVA1 photon energy delivery in humans is the transfer of this energy to the system through the reactive oxygen species singlet oxygen, the most frequent and rewarding effect of UVA1 radiation in the SLE patient is increased energy, or conversely, decreased fatigue, as though a deficiency in SLE patients was being replaced by this oxidative source. Put another way,

singlet oxygen that is ordinarily generated endogenously as a reactive oxygen species from the respiratory chain in mitochondria, when introduced exogenously through UVA1 photon bombardment, is beneficial to SLE patients who otherwise avoid exposure to all UV sources because of short UV wavelength toxicity.

#### UNMASKING UVA1 PROPERTIES

Since the discovery of the photoelectric effect nearly a century ago, we have known but sometimes forget that the properties of different wavelengths within the UV spectrum differ qualitatively. The con-

trasting actions of UVB and UVA1 radiation in SLE underscore this. The singular nature of the UVA1 band of wavelengths is apparent not only in its actions in SLE but now in its effectiveness in the treatment of atopic dermatitis (Krutmann *et al.*, 1992), localized scleroderma (Kerscher *et al.*, 1995), urticaria pigmentosa (Stege *et al.*, 1996), and generalized granuloma annulare (Muchenberger *et al.*, 1997).

The properties of UVA1 wavelengths are in contrast also with those of UVA2 (Hager *et al.*, 1989; Sutherland *et al.*, 1991; Skov *et al.*, 1998); however, this discordance has been underappreciated because almost all studies of wavelengths in the UVA range to date have been done with broadband UVA, 320–380 nm, while actions of the isolated UVA2 and UVA1 wavelength bands have received little attention. Whenever a UVA action is reported to differ from that of UVB, it is generally assumed that all wavelengths in the UVA wave band are responsible. The possibility that the actions of one may obscure those of the other has been ignored. For example, when it was found that UVB-generated cis-urocanic acid's immunosuppressive activity (Webber *et al.*, 1997; Reeve *et al.*, 1998) was inhibited by UVA, investigators assumed that the entire UVA spectrum was responsible. That UVA2 is virtually an extension of UVB (Kochevar, 1992) was not taken into account, nor was the fact that UVA2 should have generated immunosuppression and did not, which certainly implicated UVA1 as inhibitory. In fact, it turns out that when UVA1 irradiation is isolated, it actually enhances cell-mediated immunity, affirming a discordance with UVA2 and the potential to offset UVA2-induced immunosuppression.

To illustrate further, broadband UVA wavelengths have been reported to have no effect on TNF- $\alpha$  release (Kock *et al.*, 1990; Skov *et al.*, 1998), but since UVA1 irradiation inhibits TNF- $\alpha$  (Skov, 1998) release, UVA2 is presumably masking this inhibition. In fact UVA2, like UVB, promotes TNF- $\alpha$  release. As another example, UVA wavelengths shift the DNA repair/damage ratio toward repair, but it is actually the UVA1 wavelengths above 360 nm – those well into the UVA1 range – that account for this shift (Sutherland *et al.*, 1991). Shorter UVA wavelengths, i.e., those in the UVA2 range, foster damage as much as or more than they generate repair.

Studies to isolate these disparate properties of UVA1 and UVA2 are needed. It's even quite possible, for instance, that UVA's failure to trigger the process of translocation is due to inhibition by UVA1, inasmuch as UVA2 should, like UVB, generate translocation. Similarly, UVA photons, which cannot promote tyrosine phosphorylation as UVC and UVB photons readily do (Schieven *et al.*, 1993), may fail to do so because of an inhibitory action by UVA1 wavelengths.

Our interest in these divergent actions of UVA1 and UVA2, some demonstrated and some hypothetical, is that they hint at properties of UVA1 that may account for its salutary action in SLE. Thus, in SLE, the damaged DNA molecule is immunogenic (Tan and Miescher, 1971); TNF- $\alpha$  accelerates disease (Brennan *et al.*, 1989); translocation, which is increased in SLE (Golan *et al.*, 1992), has the potential to induce cell necrosis; and lymphocyte tyrosine phosphorylation, which is increased in SLE (Matache *et al.*, 1996), enhances immunoreactivity. A UVA1-induced inhibition or overriding of these phenomena could account for some of the UVA-induced benefits observed.

The counterbalancing actions of different bands of UV radiation, including those of UVA1 and UVA2, not only explain their different effects in SLE but reflect the balances that manifest in natural sunlight and that are important for terrestrial life and health. We envision that UVA1 wavelengths will eventually prove useful for strategically tipping photobiologic balances, not only in SLE but also in other diseases.

#### PROSPECTS

This is now the seventh year of UVA1 radiation treatment of human subjects with SLE. The gains patients undergoing this therapy have made are rewarding, the simplicity and lack of toxicity of the therapy encouraging. We are presently investigating changes in dermal and circulating cells and in humoral factors generated by these cells with UVA1 irradiation. We also are evaluating means (i.e., duration and intensity of exposure, addition or deletion of medications) to optimize its effectiveness.

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