Photosensitivity in Lupus Erythematosus 12

Percy Lehmann, Annegret Kuhn

Photosensitivity is a characteristic feature of all forms and subsets of lupus erythematosus (LE) that has been recognized since the first phenomenologic descriptions of this complex disease. In 1881, Cazénave (Cazénave 1881) described exacerbations of the disease related to "cold, heat, fire, and direct action of the air", and Hutchinson (Hutchinson 1888) reported in 1888 that patients with LE did not tolerate the sun well. At the beginning of the 19th century, several physicians had already realized that environmental factors, such as sun exposure, play a role in the induction of LE (Pusey 1915, Macleod 1924, Freund 1929). Pusey (Pusey 1915) described in 1915 a young lady who had her first outbreak of cutaneous LE (CLE) a few days after extensive golfing in the summertime. The lesions disappeared after strict avoidance of the sun, but another exacerbation occurred during the next summer, again after a golf tournament. In 1929, Freund (Freund 1929) could clearly demonstrate in a large series of patients with LE (n=507), which he followed between 1920 and 1927, that inductions and exacerbations of this disease showed significant clustering in the spring and summer months. In agreement with earlier observations by Haxthausen from Kopenhagen, he concluded that the increasing intensity of ultraviolet (UV) irradiation in spring and summer was responsible for the deterioration and outbreak of LE. In the same year, Fuhs (Fuhs 1929) described a specifically sun-sensitive form of LE, which occurred in a 27-year-old woman. For 10 years he had regularly observed a subacute onset of the erythematosquamous lesions in the springtime subsequent to the first periods of sunny weather, and he termed this exquisitely photosensitive subset "LE subacutus".

Whereas these and other observations delineated natural physical agents as triggering factors in LE, artificial light sources were also already recognized as causative inductors of specific LE symptoms by the second decade of the 20th century. Jesionek (Jesionek 1916), a German pioneer of phototherapy, wrote in 1916 the "guidelines for the modern applications of phototherapy". He enthusiastically described several skin diseases that responded excellently to phototherapy. In contrast, he cautioned not to irradiate patients with LE, since he had observed deterioration of the disease on irradiation, and he even described two patients with discoid LE (DLE) who developed systemic manifestations of the disease after having been irradiated with therapeutic artificial lamps. Subsequently, the induction of skin lesions by artificial lamps in patients with LE was reported in a lecture delivered to the Royal Danish Medical Association. In 1929, Fuhs (Fuhs 1929) was the first to perform experimental light testing with different wavelengths to characterize the UV sensitivity in a patient with a photosensitive form of LE. He could demonstrate a high sensitivity toward unfil-

tered quartz lamps but was unable to determine further wavelength-dependent sensitivity by using different filters in these early phototesting experiments.

The appearance of suntanning parlors in the past decades led to the occurrence of inductions and exacerbations of LE by artificial irradiation units that were not medically controlled but run by commercially oriented individuals. Several reports on such events have been published, such as by Stern and Drocken (Stern and Drocken 1986) and Tronnier et al. (Tronnier et al. 1988), who described the outbreak of severe systemic LE (SLE) after the visits to suntanning parlors. Today it is generally accepted that natural and artificial UV irradiation can induce and exacerbate LE and, furthermore, that it may exert specific effects on the complex pathophysiology of this disease.

Pathophysiology of Photosensitivity in Lupus Erythematosus

Since clinical data, phototesting procedures, and experimental evidence have demonstrated the detrimental effects of sun irradiation on patients with LE, research on pathogenetic mechanisms of UV-induced LE has become an increasingly dynamic field; this research was additionally fueled by the immense progress of the relatively young discipline of photoimmunology. Initiation and perpetuation of autoimmune responses by UV irradiation have been the subjects of extensive in vivo and in vitro studies (Norris 1993, Orteu et al. 2001, Sontheimer 1996). In summary, UV irradiation may cause the formation of molecules by different epidermal and dermal cells. These molecules have the capacity to up-regulate (prostaglandin E_2, reactive oxygen species [ROS], tumor necrosis factor [TNF]-α, interleukin [IL]-1, intercellular adhesion molecule-1) or down-regulate (IL-10, IL-1 receptor antagonist) inflammatory processes. Since genetic regulation is crucial for the induction of these molecules, a putative genetic polymorphism in LE may play an important role in the specific photosensitivity of LE (Ollier et al. 1996, von Schmiedeberg et al. 1996).

Despite these general possibilities of UV-induced autoimmunity, more specific pathogenetic pathways have been experimentally demonstrated. Thus, Furukawa et al. (Furukawa et al. 1990) could show in the absence of apoptosis the cellular redistribution of the Ro/SSA antigen on UV irradiation, which enables its presentation to the immune system as a possible first step in the autoimmune response cascade. Although the four-step model for the pathogenesis of UV-induced LE based on the translocation of the Ro/SSA antigen, which was developed by Norris and Lee (Norris and Lee 1985), has been widely referred to and agreed on, it is limited to the Ro/SSA-positive forms of LE, such as subacute CLE (SCLE) and neonatal LE (NLE).

Bennion and Norris (Bennion and Norris 1997) have also discussed in depth the role of UV irradiation in the induction of cytokine mediator release and adhesion molecules in the epidermis and dermal vessels. Recent studies have demonstrated that adhesion molecules are not only induced secondary to cytokines (TNF-α, IL-1) but also directly through transcriptional activation. This activation occurs by formation of transcriptional factors such as activator protein-2 in a single oxygen-dependent mechanism (Grether-Beck et al. 1996). Growing evidence suggests the link between UVA sensitivity and free oxygen radical formation (Krutmann 2000). Chemicals with the ability to scavenge free radicals may, therefore, be of special potential

value, that is, as additives in sunscreen products to prevent UV-induced LE lesions (McVean and Liebler 1997, Steenvorden and Beijersbergen van Henegouwen 1999, Tebbe et al. 1997, Trevithick et al. 1992). A potentially crucial role in the initiation of the autoimmune reaction cascade has been attributed to UV-induced keratinocyte apoptosis in several studies and reviews (Norris 1993, Orteu et al. 2001, Sontheimer 1996). Casciola-Rosen et al. (Casciola-Rosen et al. 1994) have demonstrated the clustering of autoantigens at the cell surface of cultured keratinocytes with apoptotic changes due to UV irradiation. These autoantigens were found within two distinct forms of blebs, the smaller ones containing Ro/SSA, calreticulin, ribosomes, and endoplasmatic reticulum and the larger ones containing Ro/SSA, La/SSB, and nucleosomal DNA. This localized concentration of autoantigens may be able to break self-tolerance, thus leading to autoimmunity (Sontheimer 1996). Using a standardized photoprovocation test protocol, our group was able to detect increased numbers of apoptotic keratinocytes in CLE after UVA and UVB irradiation compared with control subjects (Kuhn et al. 1998a). Since the cytokine-inducible nitric oxide synthase (iNOS) is believed to play an important role in the course of various autoimmune diseases and in the regulation of apoptosis (Kolb and Kolb-Bachofen 1998), we studied in further experiments, using this photoprovocation test model, the expression of iNOS at the messenger RNA and protein levels in UV-induced LE (Kuhn et al. 1998b). The results of this study demonstrated a delayed iNOS-specific signal after UV irradiation in patients with LE compared with controls, suggesting that the kinetics of iNOS induction and abnormalities in the apoptotic pathway seem to play an important role in the pathogenesis of UV-induced LE. Further elucidation of the various factors that contribute to the UV initiation and perpetuation of the autoimmune response may lead to the future development of effective strategies to prevent induction and exacerbation of LE (Furukawa 1997, Gil and Kim 2000, Golan et al. 1994, LeFeber et al. 1984, Lehmann and Ruzicka 2001, Nyberg et al. 1998). It is conceivable that the prevention of sunburn cell formation (apoptotic keratinocytes) by simple photoprotection measures and strategies significantly reduces disease activity (Sontheimer 1996, Orteu et al. 2001). According to the presented evidence, a further beneficial effect could be achieved by additional use of oxygen scavengers, that is, nitric oxide via chemical donors. Since DNA is a primary target for UV insults, leading to DNA damage with higher antigenicity, a very interesting and elegant photoprotection concept includes the addition of DNA repair enzymes into sunscreens (Stege et al. 2000, Yarosh et al. 2000). However, clinical data on this hypothetical treatment strategy are still lacking.

Clinical Photosensitivity in Lupus Erythematosus

Despite the numerous anecdotal reports and the overwhelming clinical evidence demonstrating the clear relationship between sunlight exposure and the manifestations of LE, almost no systematic studies on photobiologic reactivity in patients with this disease existed until the early 1960s (Hasan et al. 1997, Millard et al. 2000, Leenutaphong and Boonchai 1999, Walchner et al. 1997). The first group to phototest a larger number (n=25) of patients with LE was Epstein et al. (Epstein et al. 1965). They introduced the repeated exposure technique, which made it possible to induce spe-

cific lesions of LE in the test area in 5 of the 25 tested patients. The eliciting wavelengths were in the UVB range. In the same year, Everett and Olson (Everett and Olson 1965) demonstrated that 1 minimal erythema dose (MED) of hot quartz UV light exposure produced an increase in the size of skin lesions in patients with DLE. Baer and Harber (Baer and Harber 1965) administered phototests to 29 patients with LE by applying one to six times the MED of UVB in single exposures to multiple test sites. An abnormal reaction was detected in only one patient with SCLE, and it consisted of a markedly decreased erythema threshold dose and persistence of the erythema for 4 weeks. Wavelengths longer than 315 nm were not evaluated in this study. Freeman et al. (Freeman et al. 1969) used monochromatic light to determine the wavelength dependency of phototest reactions in 15 patients with LE by also applying the repeated UV exposure technique, which became a valuable tool later on for photoprovocation tests in several photosensitive disorders, such as polymorphous light eruption (PLE) (Lehmann et al. 1986). However, the UVA doses used in only a few patients with LE were probably too low for positive photoprovocation reactions. Cripps and Rankin (Cripps and Rankin 1973) also used monochromatic light between 250 and 330 nm in an attempt to determine the erythema action spectrum; specific lesions of LE were reproduced in the UVB range by applying 8–13 times the MED. At 330 nm (UVA), only a persistent erythematous response but no LE lesions could be detected. Because of these studies, the action spectrum of LE was ascribed to the UVB range despite experimental evidence from in vitro and animal studies indicating that UVA irradiation also had specific detrimental effects in LE (Doria et al. 1996, Friou 1957, Sontheimer 1996, Zamansky et al. 1980). However, the clinical phototesting experiments had shortcomings in that either only a very limited number of patients had been tested or the UVA testing was insufficient (Cripps et al. 1973, Epstein et al. 1965, Freeman et al. 1969, van Weelden 1989).

The description by Sontheimer et al. (Sontheimer et al. 1979) of SCLE as a very photosensitive subset marked a major step forward in the photobiology of this disease. Evidence of a role for UV irradiation in the pathogenesis of SCLE came from the observations of patients that sun exposure resulted in lesion formation, the limitation of SCLE lesions to sun-exposed skin, and the predilection for fair-skinned individuals with skin type I or II (David-Bajar et al. 1992, Sontheimer 1989). The observation that certain photosensitizing drugs, such as thiazide diuretics and sulfonylureas, can induce SCLE is also an indication that sun exposure plays an important role in the pathogenesis of this disease (Reed et al. 1985). Further experiments evolving from these clinical results have led to the concept that keratinocytes damaged by antibody-dependent cellular cytotoxicity might be a mechanism in photosensitive LE (Lee et al. 1986, LeFeber et al. 1984, Norris and Lee 1985).

In 1986, our group (Kind et al. 1993, Lehmann et al. 1986, 1990) was the first to demonstrate experimental reproduction of skin lesions by UVB and UVA irradiation using a standardized test protocol on a large number of patients with the disease. A total of 128 patients with different forms of LE underwent phototesting with polychromatic UVB and long-wave UVA irradiation, and characteristic skin lesions clinically and histologically resembling LE were induced in 43% of patients (Fig. 12.1). Subsequent investigators confirmed UVA reactivity in LE by phototesting (Nived et al. 1993, Wolska et al. 1989). In the following years, this testing regimen received much attention because the reproduction of skin lesions in patients with LE by UVB and

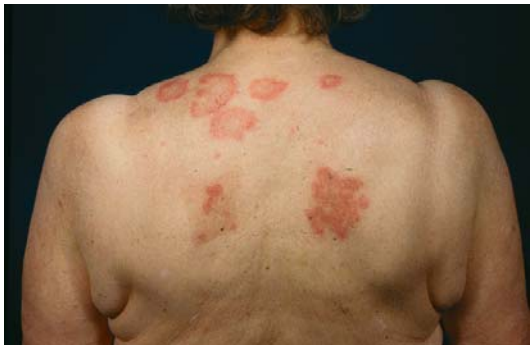

Fig. 12.1. Photoprovocation of subacute cutaneous lupus erythematosus (SCLE) with UVA (left test field) and UVB (right test field). Picture taken 10 days after the last irradiation. Characteristic genuine annular SCLE lesions on the shoulder of the patient.

UVA irradiation is an optimal model for clinical and experimental studies (Beutner et al. 1991, Hasan et al. 1997, Kind et al. 1993, Kuhn et al. 1998a, b, Leenutaphong and Boonchai 1999, van Weelden et al. 1989, Walchner et al. 1997). Meanwhile, provocative phototesting in patients with LE has become routine at our department, and protocols for phototesting have become optimized by taking into account multiple factors (Table 12.1). Nonlesional, non-sun-exposed areas of the upper back or extensor aspects of the arms were used for performance of the phototest reactions because other parts of the skin might not react to the same extent, probably owing to some kind of local predisposition of unknown nature other than UV irradiation, such as thickness of the stratum corneum, vascularization, presence of antigens, or distribution of antigen-presenting cells (Walchner et al. 1997). Furthermore, it is important to use a defined test area, which should be sufficiently large to provide reactions. The initial observable response following exposure to UV irradiation is an erythema reaction that most commonly arises with the normal time course. Although the duration of the erythema was not studied in particular, a prolonged erythematous response was not a conspicuous feature. In contrast to other photodermatoses, such as PLE, the development of skin lesions in patients with LE is characterized by a latency of several days to 3 weeks or even longer, and it might persist in some cases for several months (Kuhn et al. 2001a, Lehmann 1996). In addition, phototesting has been crucial in further characterizing a highly photosensitive form of CLE, namely, LE tumidus (LET) (Kuhn et al. 2000, 2001b). LET was first described by Gougerot and Bournier (Gougerot and Bournier 1930) and has since been somewhat "forgotten" or rarely described and diagnosed. In 1990, Goerz et al. (Goerz et al. 1990) emphasized for the first time that extreme photosensitivity is a major characteristic of LET, and a few further case reports of this disease followed from groups other than our own (Alexiades-Armenakas et al. 2003, Dekle et al. 1999). According to our experience, we regard LET to be an unusual clinical variant of CLE, and skin lesions of LET consist of sharply demarcated, smooth, red-violet, infiltrated plaques with hardly any scaling and no scarring. The lesions usually disappear on therapy with antimalarials and sun avoidance. It could be shown that this form is even more UV sensitive than SCLE, which, until recently, was believed to be the most photosensitive LE subset (Sontheimer et al. 1979). Using a standardized protocol, reproduction of characteristic skin lesions occurred in 76% of patients with LET, 63% with SCLE, 45% with DLE, and 41% with other forms of CLE, such as LE profundus and Chilblain LE (Kuhn et al. 2001a).

Table 12.1. Provocative phototesting in patients with lupus erythematosus (LE): optimized protocol (modified from Kuhn et al. 2001a)

Criteria	Protocol	Comments
Test site	Non-sun-exposed, unaffected areas of the upper back or extensor aspects of the arms	Other parts of the skin might not react to the same extent
Size of test field	Defined test areas that should be sufficiently large to provide reactions (4×5 cm)	Test areas that are too small or different in size might not show reproducible results
Pretesting	MED, IPD, MTD	Testing of the MED is necessary to make data comparable; a prolonged erythematous response is not a conspicuous feature
Dosage	60–100 J/cm^2 UVA and/or 1.5 MED UVB on 3 consecutive days	Single UV exposure is unlikely to induce positive reactions in all possible patients
Light sources	UVA: UVASUN 3000 (330–460 nm), Mutzhas or UVA1 Sellas 2000 (340–440 nm), Sellas UVB: UV-800 with fluorescent bulbs, Philipps TL 20 W/12 (285–350 nm), Waldmann	Different light sources with a different action spectrum can result in different numbers of positive phototests
Pretreatment	No pretreatment	Any topical or systemic pretreatment might affect the phototesting procedure
Medication	If possible, no systemic medication for skin disease	Systemic medications, such as antimalarial agents, corticosteroids, and immunosuppressive drugs, might lead to false-negative results
Evaluation	24, 48, 72 h up to 4 weeks after last irradiation	Follow-up shorter than 3 weeks might miss positive provocative phototest results in some patients
Criteria for positive photoprovocation	Induced skin lesions clinically resemble LE Skin lesions develop slowly over several days or weeks Skin lesions persist up to several months Clinical diagnosis is confirmed by histologic analysis	Positive phototest reactions are considerably slower and persist longer than other photodermatoses, such as polymorphous light eruption, persistent light reaction, photoallergy, hydroa vacciniforme, and solar urticaria

Table 12.1. Provocative phototesting in patients with lupus erythematosus (LE): optimized protocol (modified from Kuhn et al. 2001a) (continued)

Criteria	Protocol	Comments
Results of phototesting (different wavelengths)	UVA and UVB: 20%–53% UVB: 25%–72% UVA: 0%–55%	Differences in phototest results are found because of different protocols and the age of the patients at onset of disease
Results of phototesting (different LE subtypes)	LET: 70%–81% SCLE: 50%–100% DLE: 10%–64% SLE: 25%–85%	Differences in phototest results are found because of different protocols; in our studies, LET patients are the most photosensitive patients
Local side effects	Persistence of hyperpigmentation and hypopigmentation for several months after irradiation	Patients should be reminded of these possible side effects because they might lead to cosmetic problems
Induction of disease	Exacerbation of cutaneous lesions in a few patients, no provocation of systemic disease in our studies	Follow-up of SLE patients after phototesting is very important because reports in the literature describe exacerbation of systemic disease under phototesting
History of photosensitivity	LET: 43%–50% SCLE: 27%–100% DLE: 25%–90% SLE: 6%–94%	Positive phototesting results are not always associated with a positive history of photosensitivity; it might be difficult for patients to recognize the association between sun exposure and induction of skin lesions

DLE, discoid LE; IPD, immediate pigment darkening; LET, LE tumidus; MED, minimal erythema dose; MTD, minimal tanning dose; SCLE, subacute cutaneous LE; SLE, systemic LE.

Results of reported phototesting in patients with LE often differ between various groups because there are numerous technical differences between the studies that could explain the different findings (Beutner et al. 1991, Hasan et al. 1997, Kind et al. 1993, Kuhn et al. 2001a, Lehmann et al. 1990, Nived et al. 1993, Van Weelden et al. 1989, Sanders et al. 2003, Walchner et al. 1997, Wolska et al. 1989). Varying factors are light source, energy dose, wavelength, time points of provocation and evaluation, and location and size of the test area. Most studies were conducted in white patients; however, there is one recent article on phototesting in 15 oriental patients with LE using exactly the same test protocol as our group (Leenutaphong and Boonchai 1999). The incidence of positive phototest reactions in these patients seemed to be similar to or a little lower than that in white patients, and there was no correlation between a positive history of UV sensitivity and phototest reactions. However, classification of positive test results might be difficult in some patients because persistent erythema can develop, which is even histologically hard to interpret. It is also unclear why skin lesions cannot always be reproduced under the same conditions several months after the initial phototest and why phototesting results are not positive in all patients with LE tested, providing indirect evidence for variant factors in the pathophysiology of this disease (Higuchi et al. 1991).

Furthermore, a history of photosensitivity in patients with LE does not necessarily predict positive reactions on phototesting, and results of reported photosensitivity often differ between various groups (Beutner et al. 1991, Callen 1985, Callen and Klein 1988, Doria et al. 1996, Drosos et al. 1990, Grigor et al. 1978, Harvey et al. 1954, Herrero et al. 1988, Hymes et al. 1986, Kuhn et al. 2001a, Lee et al. 1977, Millard et al. 2000, Mond et al. 1989, O'Loughlin et al. 1978, Pande et al. 1993, Pistiner et al. 1991, Sontheimer et al. 1979, Sontheimer 1989, Tan et al. 1982, Tuffanelli and Dubois 1964, Vila et al. 1999, Walchner et al. 1997, Wilson and Hughes 1979, Wilson et al. 1984, Wysenbeek et al. 1989). This might be because skin lesions after UV irradiation do not develop rapidly after sun exposure, and, therefore, a relationship between sun exposure and exacerbation of LE does not seem obvious to the patient. An additional factor might be age at onset of disease, as observed by Walchner et al. (Walchner et al. 1997), demonstrating that mainly patients younger than 40 years reported photosensitivity. Furthermore, the occurrence of photosensitivity varies among different types of LE, and some ethnic groups, such as African blacks, seem to be less photosensitive than others (Mody et al. 1994, Petri et al. 1992, Shi et al. 1987, Sutej et al. 1989, Taylor and Stein 1986, Ward and Studenski 1990). Nevertheless, the term "photosensitivity" (skin rash as a result of unusual reaction to sunlight by patient history or physician observation) is poorly defined (Lee and Farris 1999), although it is listed as one of the American Rheumatism Association (ARA) criteria for the classification of SLE (Tan et al. 1982). In 1996, a large discrepancy between a personal history of photosensitivity and a decreased MED was documented by Doria et al. (Doria et al. 1996), concluding that the use of photosensitivity as a classification criterion for SLE remains questionable, at least when it is assessed according to the ARA criteria. Therefore, a detailed clinical history is important to the diagnosis and assessment of photosensitivity in patients with LE. There are several key components to a history of photosensitivity, including the morphology of the rash, duration, distribution, and the relationship to sun exposure and specific symptoms (such as pain, pruritus, burning, blistering, and swelling). Each of these symptoms may provide clues to the nature of

the photosensitive eruption and thus the diagnosis. Differentiating between the morphology and the time course of CLE and, for instance, PLE, in terms of history alone can be difficult; clinically, PLE tends to consist of an acute eruption of tiny, pruritic plaques and vesicles that lasts several days, in contrast to SCLE, which usually involves larger, nonpruritic annular or psoriasiform lesions that persist for weeks to months after UV exposure. In contrast, LET may, in some cases, be clinically very similar to PLE. A past medical history should also include a detailed drug history, particularly in temporal relation to a suspected phototoxic eruption.

Physical examination may reveal a distribution suggestive of a photosensitive condition in the absence of a history of photosensitivity. The most common areas for skin lesions in LE include sun-exposed areas such as the face, the V-area and posterior aspect of the neck, the ears, the dorsa of the hands, and the forearms. Equally helpful may be areas that are specifically spared from sun exposure, including the upper eyelids, submental areas, finger web spaces, and general creases within skin folds, where a photosensitive eruption is noticeably absent. Furthermore, investigation of patients with photosensitivity includes routine tests to establish the diagnosis and extent of disease activity, including hematology, biochemistry, serology, and complement studies. Skin biopsies and immunofluorescence may also be appropriate. Provocative phototesting is an objective means of demonstrating whether a patient has an abnormal response to UV exposure; however, phototesting does not play a role in the routine assessment or diagnosis of a patient with CLE. Indications for phototesting in patients with LE include (a) the objective demonstration of photosensitivity where there is doubt about the history and where such demonstration would support a diagnosis of LE; (b) the exclusion of other causes of photosensitivity, such as PLE, chronic dermatitis, solar urticaria, and drug-induced phototoxicity; and (c) use of the photoprovocation test as a useful research tool with which to study the immunopathology of evolving lesions of LE-specific skin disease (Millard et al. 2000).

Results of histopathologic and immunopathologic examination of UV-induced LE lesions are similar to the findings of spontaneously developing primary skin lesions but can give further insight into the earliest pathologic events of CLE lesions. Kind et al. (Kind et al. 1993) demonstrated that histopathologic examination of early UV-induced lesions (up to 10 days) in patients with CLE and SLE shows nonspecific changes such as superficial perivascular lymphocytic infiltration. On the other hand, late UV-induced lesions (more than 10 days) were characterized by parakeratosis, few necrotic basal keratinocytes, and vacuolar degeneration of the dermoepidermal zone. Furthermore, under experimental conditions, the appearance of immunoglobulins in UV-induced LE lesions has been reported as a late phenomenon, and in our study, direct immunofluorescence findings were negative in all skin lesions investigated up to 3 weeks after UV exposure. This is in accordance with Cripps and Rankin (Cripps and Rankin 1973), who detected the first immunoglobulin deposits 6 weeks after irradiation and mainly along the basement membrane. In contrast, Velthuis et al. (Velthuis et al. 1990) demonstrated that in UV-induced lesions of patients with LE, immunohistochemical changes can be induced similar to those in spontaneously evolved lesions. Furthermore, Nyberg et al. (Nyberg et al. 1998) observed that in experimentally UV-induced lesions of patients with LE, dust-like particles, a specific fine-speckled, epidermosubepidermal direct immunofluorescence staining pattern, can be detected within 2 weeks of UV exposure.

A potential interplay of UV irradiation with specific autoantibodies, particularly anti-Ro/SSA and anti-La/SSB antibodies, has been previously reported, and, in different subtypes of LE, such as SCLE and NLE, photosensitivity has been found to be strongly associated with the presence of such antibodies (for review see Lee and Farris 1999). Results of an early study by LeFeber et al. (LeFeber et al. 1984) indicated that UV irradiation of cultured keratinocytes led to increased immunoglobulin G binding to the cell surface of keratinocytes; several years later, Norris (Norris 1993) noted increased antibody binding as a result of in vivo UV irradiation to human skin. Golan et al. (Golan et al. 1992) independently observed UV-induced binding of antibodies from Ro/SSA-positive sera to a small percentage of cultured keratinocytes. Nevertheless, the strongest evidence supporting the possibility that these antibodies play a role in the pathogenesis of LE comes from patients with NLE (Lee 1993). These infants have maternally acquired anti-Ro/SSA antibodies and develop SCLE-like skin lesions, and because these antibodies are cleared from the infant's circulation several months after birth, the skin lesions resolve spontaneously (Lee et al. 1989). In DLE, the association of skin disease with antibodies is much less clear, and in previous studies, a clear association between the presence of anti-Ro/SSA antibodies and the clinical finding of photosensitivity was not found (Lee and Farris 1999). However, because similar levels of anti-Ro/SSA antibodies are seen in other disorders, such as Sjögren's syndrome, that are not usually associated with specific LE lesions, other factors must be involved in the production of LE inflammation.

In conclusion, photoprovocation tests are an objective tool for evaluating possible photosensitivity in patients with different forms of LE and are even required for diagnosis in some cases. A very important and practically relevant feature of LE photosensitivity, which became evident on routine phototesting, is the delayed and slow UV reactivity in these patients. This conspicuous feature may explain the negligence of many patients with LE as to the negative effects of the sun's radiation on their disease. Therefore, education on photoprotection measures seems to be especially important in this group. Recently, our group demonstrated with the aforementioned test protocol that broadband sunscreens were able to suppress the induction of LE lesions on UV irradiation (Kuhn et al. 2002). Consequent protection against UV light and also other physical and mechanical injuries may be of significant value for the course and prognosis of LE, especially since such injuries may even initiate systemic manifestations of the disease, which was previously limited to the skin. Further steps in the future will consider the pathogenetic mechanisms in LE photosensitivity to develop more specific pharmaceuticals beyond UV filters, such as antioxidants or DNA repair enzymes, which will be able to counteract the detrimental effects of UV irradiation on the disease.

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