From the Department of Dermatology at Karolinska Hospital,
Karolinska Institute, Stockholm, Sweden

PHOTOSENSITIVE PSORIASIS

EPIDEMIOLOGICAL, CLINICAL AND EXPERIMENTAL STUDIES

Anne-Marie Ros



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INTRODUCTION

LIGHT SENSITIVITY - GENERAL ASPECTS

Photosensitivity is the broad term used to describe adverse reactions to non-ionizing radiation. The radiation region of the ultraviolet spectrum has been subdivided into three bands depending on wavelength: UVA between 400 and 320 nm, UVB between 320 and 290 nm and UVC from 290 to 200 nm. However, wavelengths below 290 nm do not reach the earth's surface because of absorption by ozone in the stratosphere (1).

Both UVA and UVB are erythemogenic and melanogenic, but the amount of UVB energy needed to produce these biological effects is about 1000 times less than for UVA (2). The proportion of UVA from the sun reaching the earth is about 20 times greater than that of UVB (3).

Photosensitivity varies between individuals partly depending on their capacity to acquire a tan. The capacity of the skin to tan in response to ultraviolet radiation (so-called facultative skin colour) is under genetic control. It can be assessed through a careful history of individuals concerning their reactions to sun exposure, and it is possible to classify them by skin type as in Table 1 (4).

Table 1. Sun-reactive skin types based on verbal response regarding first, moderate, unprotected sun exposure

	Skin colour (unexposed skin)	"Sunburn"	"Tan"
Skin type I	White	yes	no
Skin type II	"	yes	minimal
Skin type III	"	yes	yes
Skin type IV	"	no	yes
Skin type V	Brown	no	yes
Skin type VI	Black	no	yes

Thus, photosensitivity in this respect is a question of quantity, so that individuals with skin type I who easily sunburn consider themselves photosensitive. A qualitatively different response to sunlight may give rise to different idiopatic photodermatoses, of which some of the most important are described below.

POLYMORPHOUS LIGHT ERUPTION (PMLE)

PMLE is an acquired photodermatosis of unknown etiology. The term PMLE was first used by Rasch in 1900 (5), and later by Haxthausen in 1918 (6) to describe a group of inflammatory dermatoses caused by sunlight. It may represent more than one disease entity, but this is not known. PMLE is probably a rather common disease, but no thorough prevalence studies have been performed. In one recent study the prevalence was estimated to 11% (7). As documented in several reports (8, 9, 10) PMLE is more common among women. Familial factors are important (11), and a special familial variety is reported among Latin and North American Indians (12). The eruptions may affect individuals of any race or skin colour, from light-skinned Caucasians to blacks with deep pigmentation.

The clinical picture may vary enormously, but is often the same in one individual during subsequent summers. The most common feature is small papules or vesicopapules, followed in frequency by erythema and oedema, prurigo lesions, soft maculonodules, eczema, plaques, urticas, blisters, target lesions and solid nodules (13). The eruption appears primarily on sun exposed areas, and flares of previously involved areas may occur when other parts of the body are exposed. Cheilitis and conjunctivitis may occur as well as chills, headache, fever and nausea (9). The eruption appears after sun exposure with latency varying from 0.5 to several hours or days (9). The disease is chronic with a tendency to recur upon sun exposure (14).

The action spectrum was earlier considered to lie mainly in the UVB range (15), but recently the relative importance of UVA has been documented (16, 17). The diagnosis is often apparent from the history

and the clinical picture. The histopathological features are not specific and may vary depending on the clinical variety. However, a dense perivascular lymphocytic infiltrate is rather common (18, 19).

One way of verifying the diagnosis is to induce PMLE lesions by provocation with UVB and UVA in high doses. High doses of UVA have been advocated as giving a higher frequency of positive reactions than UVB does. In one report a PMLE reaction was provoked in 90% of the patients with UVA, but in none with UVB (20).

A delayed hypersensitivity-immune response has been suggested as a factor in the pathogenesis. The reaction time after sun exposure is usually delayed 24 hours or longer. The eruptions could tally both clinically and histologically with a hypersensitivity reaction. However, several studies of patients with PMLE have shown normal cell-mediated immunity (21, 22), except in two studies where lymphocyte responses to light were abnormal (23, 24). The number of circulating T-lymphocytes was increased, but with normal T-helper/T-suppressor subsets in one study (25). In the same study the dermal cell infiltrate was analysed with monoclonal antibodies after light testing, and a predominance of T-helper cells was observed. However, in another study (26) there was a dominance of T-suppressor/cytotoxic cells in the dermal infiltrate in 4/8 patients with PMLE, while T-helper cells dominated in two and an approximatively equal number of both T-cell subsets was seen in two patients. An increased number of Langerhans cells was observed in the dermal infiltrate. These findings may support the hypothesis of an immunological pathogenesis in PMLE.

SOLAR URTICARIA

In solar urticaria an erythema followed by a weal appears within minutes after sun exposure. Each patient will develop urticaria after exposure to light within a specific range of wavelengths (27). An allergy mechanism has been suggested, as a positive passive transfer test has been observed in some patients (28). The serum factor responsible for this passive transfer has in some cases been consistent

with IgE (29), but complete characterization has hitherto not been done. The diagnosis is usually easily confirmed by history and light testing.

PHOTOCONTACT DERMATITIS

Contact photosensitivity (CPS) describes a reaction caused by an identified chemical applied to the skin and its UV-induced excitation. Traditionally, CPS has been divided into phototoxic and photoallergic reactions. A phototoxic reaction may affect anyone if the concentration of the offending chemical, and the UV dose of the appropriate wavelength, are sufficiently high. A photoallergic reaction requires a sensitization period; the concentration of the chemical, and the UV dose required, are usually low. The exact mechanisms involved in these reactions are unknown.

Clinically, a phototoxic reaction resembles an exaggerated sunburn, while a photoallergic reaction is usually eczematous and may spread to skin areas not primarily involved. The diagnosis is confirmed by photopatch testing. A number of substances have been reported to induce photosensitivity (30). In the following table, those most extensively studied are listed:

Antimicrobial agents, e.g. salicylanilides, fentichlor
Therapeutic agents, e.g. phenothiazines, sulphonamides, 8-methoxypsoralen
Plant derivatives, e.g. furocoumarins
Fragrances, e.g. musk ambrette, 6-methylcoumarin
Tar products
Dyes, e.g. eosin, neutral red
Sunscreens, e.g. para-aminobenzoic acid (PABA)
Animal foodstuffs, e.g. quinoxaline dioxide

Data from the Scandinavian multicentre photopatch study (31) illustrate which chemicals most frequently cause photocontact reactions. Of 1,883 patients with suspected photosensitivity who were photopatch tested,

191 positive photocontact reactions were observed. Of these the most common were to musk ambrette (28%), para-aminobenzoic acid (PABA) (20%), fentichlor (13%), and tetrachlorsalicylanilide (6%).

CHRONIC ACTINIC DERMATITIS

Chronic photosensitivity may be classified into three different categories: persistent light reaction, chronic photosensitive eczema and actinic reticuloid.

In some persons with a photoallergic response to a certain chemical, withdrawal of this chemical does not lead to clearing of the skin. A chronic condition called persistent light reaction may develop. This syndrome was first reported by Wilkinson in 1962 after an epidemic of salicylanilide photoallergy (32). It is now recognized that it may follow both topical and systemic administration of photosensitizers (33). Only very small doses of light give rise to eczematous skin changes on exposed body areas. The explanation for this reaction is still unknown. On light-testing an increased sensitivity to UVB is usually seen and sometimes also to UVA (34).

A condition where photosensitivity appears as a complication of eczema was first described in 1973 and called photosensitive eczema (35). Patients of this category may suffer from atopic, seborrhoeic or contact eczema for a number of years before photosensitivity develops. It has been observed that many patients with photosensitive eczema have positive patch test reactions (without irradiation) to several allergens, often plant derivatives, e.g. lichens, wood mix, balsam of Peru, and fragrances (36, 37). Reactions to other contact allergens, e.g. chromium salts and rubber, are also described among these patients (38, 39).

Some patients deteriorate into a state of actinic reticuloid, first described in 1969 (40). In these patients the skin is red and thickened, initially on exposed areas, but episodes of universal erythroderma are a common feature. This is seen almost exclusively in

elderly men. The histological picture often resembles that in lymphomas, with abnormal lymphocytes and histiocytes in the dermis (40, 41). The abnormal reactivity to radiation is usually observed from below 300 nm to 400 nm and even to longer wavelengths (42).
There are reports of photosensitive eczema as well as persistent light reaction developing into actinic reticuloid (43, 44), which may be looked upon as the most severe form of light sensitivity.

CONTACT DERMATITIS IN RELATION TO PHOTOSENSITIVITY

Not only is contact dermatitis common in the history of patients with photosensitive eczema, as described above, but it is also an important differential diagnosis to photosensitivity. This is especially so with airborne dermatitis, e.g. from Compositae oleoresins (45, 46), where the dermatitis is confined mainly to exposed skin areas, although often accentuated in skin folds, and may be difficult to differentiate from photosensitivity. Furthermore, these patients may also eventually develop photosensitive eczema or even actinic reticuloid (47).

Data from the Scandinavian multicentre photopatch study (31) illustrate that allergic contact reactions are common in patients with suspected photosensitivity. Thus, in 1,883 patients tested, 263 contact allergic reactions were recorded and 191 photocontact reactions. Of the 263 contact allergic reactions, the most common were to balsam of Peru (29%), perfume mix (28,5%), para-aminobenzoic acid (13%), lichen mix (8%), and wood mix (7%). These figures may be compared with the percentage of positive reactions to balsam of Peru (6%) and perfume mix (13%) among all (3,034) positive test reactions in patients patchtested at the Department of Dermatology, Karolinska Hospital 1980-1986.

PSORIASIS

Psoriasis is a common chronic skin disease, which affects about 2% of the population in Sweden (48). The etiology and pathogenesis are still unknown. In recent years many attempts have been made to establish an immunological basis for the pathogenesis of psoriasis. Disturbances in

humoral responses have been reported, e.g. stratum corneum antibodies, increased serum immunoglobulins, anti-globulin serum factors, and circulating immune complexes. In many reports a defective cell-mediated immunity is implied. Thus, in active disease an impaired delayed hypersensitivity is reported. Defective T-lymphocyte function and abnormal distribution of blood T-lymphocyte subpopulations have been observed by some investigators, but these findings are not confirmed by others. The dermal cell infiltrate in psoriasis is composed mainly of T-lymphocytes and macrophages, the T-lymphocytes being largely of T-helper/inducer phenotype. In early psoriasis lesions, T-lymphocytes appear in the epidermis, but there are divergent reports whether these are predominantly T-suppressor/cytotoxic cells (49) or T-helper/inducer cells (50).

It is still unproven whether these events are primary or secondary, as is the case with other hypotheses concerning the pathogenesis of psoriasis. These include abnormalities of arachidonic acid and its products, a defective cyclic nucleotide system, disturbance of protease-antiprotease equilibrum, abnormal polyamine metabolism, disordered neutrophil function, and defective proliferative control in psoriatic epidermis. The literature on the pathogenesis of psoriasis has recently been extensively reviewed (51).

The red, scaly skin lesions of psoriasis are often markedly improved by natural sunlight and artificial ultraviolet radiation. However, it is known that a small percentage of psoriasis patients, on the contrary, seem to worsen after sun exposure or after artificial ultraviolet radiation.

PUVA TREATMENT

PUVA means the administration of psoralens (P) and subsequent long-wave ultraviolet radiation (UVA:320-400 nm). Psoralens are naturally-occurring compounds known as furocoumarins. More than 25 different furocoumarins have been isolated from natural sources but of these only a few have a clinically proven therapeutic effect in psoriasis.

The ones used in clinical practice are 8-methoxypsoralen (8-MOP) and 4, 5',8-trimethylpsoralen (TMP). Their action spectra lie within the UVA range (52). PUVA has been used to treat a variety of diseases according to the following table (53), mainly psoriasis, vitiligo and mycosis fungoides, and is also used in the management of photosensitivity diseases.

Table 2. Diseases responsive to psoralen photochemotherapy (PUVA)[1]

Therapy for disease	Prevention of disease
Psoriasis	Polymorphous light eruption
Palmoplantar pustulosis	Hydroa vacciniforme[2]
Mycosis fungoides (stages IA, IB)	Solar urticaria[2]
Vitiligo	Persistent light reaction[2]
Atopic dermatitis	Actinic reticuloid[2]
Generalized lichen planus	Erythropoetic protoporphyria[2]
Urticaria pigmentosa	
Alopecia areata	
Pityriasis lichenoides[2]	
Lymphomatoid papulosis[2]	
Pityriasis rubra pilaris[2]	
Generalized granuloma annulare[2]	

1/ This list includes dermatoses which have been reported to respond to PUVA therapy, but not all of these diseases represent a true indication for this treatment.

2/ Experience limited to small number of patients.

The exact mechanisms by which PUVA causes photosensitivity are presently not known. Two types of reaction seem to be involved. One is an anoxic reaction affecting cellular DNA with the formation of photoadducts, which may act antiproliferatively. The second type is oxygen-dependent, giving rise to reactive oxygen and free radicals, which may damage membranes by lipid peroxidation and induce activation of mediators of the eicosanoid system (prostaglandins, leukotrienes) (54).

PUVA TREATMENT FOR PSORIASIS

The first report on PUVA being effective in the treatment of psoriasis appeared in 1973 when topical administration of psoralens was used (55). Full-scale treatment was reported in 1974 when development of high-energy fluorescent UVA lamps had made it possible to treat psoriasis by oral intake of 8-MOP (56). Since then the effectiveness of this therapy has been documented in numerous reports extensively reviewed (57, 58), but relapses do occur as in other forms of treatment for psoriasis. The mechanisms of PUVA therapy in psoriasis are not fully understood. It is assumed that the effect on DNA replication and cellular proliferation is an important factor. It is also assumed that PUVA may affect immunological abnormalities in psoriasis, and PUVA has also been shown to reduce the chemotactic activity of the psoriasis leucotactic factor (59).

PUVA TREATMENT FOR PHOTOSENSITIVITY DISEASES

The effectiveness of PUVA in prophylactic treatment for PMLE is documented in several reports (60, 61, 62). The UVA dose schedule has to be changed, with reduced doses of UVA exposure compared with treatment of psoriasis. Otherwise provocation of PMLE lesions may occur. PUVA has also been tried in more severe photosensitivity diseases such as persistent light reaction (63, 64) and photosensitive eczema/actinic reticuloid (65, 66). The results are promising, but the initial UVA doses must be extremely low and in some cases combined with oral corticosteroids to prevent exacerbation of the disease (67).

The mechanism by which PUVA therapy produces a protective and therapeutic effect in photosensitive disorders is unknown. Induction of acanthosis, hyperkeratosis and formation of melanin enhances UV absorption in the epidermis. PUVA has also been shown to induce several immunological effects; it interferes with the expression of contact hypersensitivity (68, 69), reduces the number of Langerhans cells in the epidermis (70), and affects skin lymphocytes and circulating lymphocytes (71).

PUVA SIDE EFFECTS

The most common reported acute side effects after PUVA therapy are erythema, pruritus and nausea. Less common side effects which may appear during treatment are vertigo, headache, leg oedema, blistering, and Koebner phenomenon (72). Side effects that have been more seldom reported are: severe skin pain (73), seborrhoeic dermatitis of the face (74), photoallergic reaction to 8-MOP (75), bronchial spasm (76), exacerbation of lupus erythematosus (77), and bullous pemphigoid (78), photo-onycholysis (79), lichenoid dermatitis (80) and drug fever (81).

Concerning long-term side effects, the question of greatest concern is whether there is any increased incidence of skin cancer after PUVA treatment. Many recently reviewed follow-up studies have addressed this question (82). Concerning the incidence of non-melanoma skin cancer, there is a discrepency between American and European follow-up studies. Thus, in American studies a 13-fold increase in squamous cell carcinoma has been reported after PUVA therapy with high cumulative doses (83). However, in European follow-up studies there has not been a higher incidence of non-melanoma skin carcinoma than in a control population (84-88). The reasons for this reported difference in risks are not clear. They could lie partly in different treatment protocols, but also in differences between populations treated. After many PUVA treatments, an increased number of lentigines appear, so called PUVA-lentigines, some of which may show histologically atypical features (89, 90). However, in the follow-up studies no increased incidence of melanoma is reported.

The risk of developing cataract after PUVA treatment has been investigated in several studies, but no definite increased incidence of cataract has yet been observed (91, 92, 93).

PUVA does not seem to be hepatotoxic. Although there are two reported cases of hepatitis occurring in PUVA-treated individuals (94, 95), separate follow-up studies do not give proof of any liver damage caused by long-term PUVA treatment (96, 97).

The above-described studies on side effects after PUVA therapy concern 8-MOP, being the most used psoralen. However, long-term side effects after TMP therapy have also been studied, and no increased risk of carcinoma was apparent (98, 99).

AIMS

to investigate photosensitive psoriasis with regard to

prevalence

clinical aspects

phototest results

immunological characterization of cell infiltrates after phototesting

effect of PUVA treatment,

to study the prevalence of polymorphous light eruption.

PATIENTS AND METHODS

EPIDEMIOLOGICAL SURVEYS (I, V)

Photosensitive psoriasis (I)

A questionnaire was mailed in 1985 to 2,000 of the psoriasis patients who had visited the Department of Dermatology at the Karolinska Hospital during the period 1976-1984 and who were still living in the Department's service area in 1985. Only patients born in even months were selected. Eighty-eight per cent (1,760 individuals) answered the questionnaire. Of the 240 who did not answer four had died, 18 could not be reached by mail and 16 informed the Department that their initial diagnosis had been changed: they did not have psoriasis. Not counting these cases the non-respondents were 202 (10.3%). The mailed questionnaire had two parts. One part contained general questions, while the second part was completed only by individuals who reported a worsening effect from sunlight. For details about the questions, see Paper I. To substantiate the photosensitivity, 80% of the allegedly photosensitive patients (161/201) were interviewed by telephone. In the interviews the nature of photosensitivity was examined in more detail. Any history of polymorphous light eruption was especially questioned, as was a possible history of a Koebner phenomenon, where the patients were asked if psoriasis ever appeared on skin previously injured through scratches, cuts, bruises or burns.

Polymorphous light eruption (V)

A questionnaire was sent to all 412 employees of a Swedish pharmaceutical company situated in Stockholm. The questionnaire had two parts. The first, a screening questionnaire, detailed age, sex, skin type, hair colour, sunbathing habits, use of sun beds for cosmetic purposes, and the use of sunscreens. In the second part, only individuals experiencing PMLE symptoms participated. PMLE was described as a usually itchy papular or papulo-vesicular rash with small or large lesions appearing after sun exposure on exposed parts of the body

and disappearing after days or a week if sun exposure was avoided. Individuals with a rash consistent with this description filled in the second part of the questionnaire, which assessed the natural history of their disease, time of onset each year, clinical lesions, threshold data of response to sunlight, and time for disappearance of symptoms. Other questions asked concerned the presence of a hardening phenomenon, affected skin areas, a family history of the disease and the occurrence of other diseases.

PATIENT SELECTION (II, III, IV)

Among 1,760 psoriasis patients answering a questionnaire concerning light sensitivity (I) 35, who were considered light-sensitive, were willing to participate in light testing (II). Twenty-one were women, 14 were men. Mean age was 52.4 years (34-73). Twenty-one of the patients tested, all of whom had a pathological reaction after UV provocation, were examined by analyzing the biopsies taken from test areas with immunohistochemical technique (III). Of these 11 were women, 10 were men. Mean age was 53.3 years (34-73). Fifteen of the initial 35 phototested patients agreed to participate in a therapeutical trial with PUVA (IV). Eleven were women, four were men. Mean age was 51 years (34-73).

LIGHT SOURCES AND LIGHT TESTING PROCEDURES (II, III, IV)

UVB threshold testing and provocation

Light testing was performed with an Osram high-pressure Xenon arc lamp (XBO 150 W) in a Zeiss microscope lamp housing with a quartz collector to produce a round, bright spot, 1.5 cm in diameter. The distance from the filter holder to the tested skin area was 15 cm. The lamp was equipped with a Schott WG 295 filter. With this equipment the minimal erythema dose (MED), defined as causing barely perceptible redness, was assessed after 24 hours. Three and five times the MED doses were delivered with the Xenon arc lamp and considered as UVB provocation. The UVA doses contained in the UVB doses so given never exceeded

1.2 J/cm^2, which is neglible compared with UVA provocation.

UVA threshold testing and provocation

To test sensitivity to UVA, the Xenon arc lamp described above was also equipped with a 3 mm thick glass filter, excluding wavelengths below 320 nm. A screening UVA dose of 10 J/cm^2 was given and assessed after 24 hours. Where a UVA-induced erythema appeared, the exact UVA threshold dose was established. This was done using a PUVA 500 lamp with Sylvania F15T8 bulbs (Waldmann Werk für Lichttechnik, Schwenningen, Federal Republic of Germany). The lamp was equipped with a glass filter to minimize radiation below 320 nm. It had an emission spectrum mainly between 320 and 400 nm with a peak emission of 365 nm. Unfiltered, this lamp emitted 0.08 mW/cm^2 UVB, which was reduced by the glass filter to 0.009 mW/cm^2 at testing distance. Graded exposures of UVA were given by using a Waldmann skin test apparatus, which can apportion graded doses of UVA below 10 J/cm^2. High doses of UVA were delivered with a UVASUN lamp (Mutzhas Co. Munich, Federal Republic of Germany). This is a high-intensity UVA lamp with an emission spectrum mainly between 340 and 400 nm with a peak emission at 365 nm. Routinely 25, 50 and 75 J/cm^2 were given on 5 cm x 10 cm test areas on the patients' backs. However, in patients with a pathological UVA threshold estimated between 5 and 10 J/cm^2, the UVA provocation doses were lowered to only 25 and 50 J/cm^2, and where the UVA threshold dose was below 5 J/cm^2 the provocation doses were 10, 15 and 25 J/cm^2.

The test areas were examined on days 1, 3, 6, 10, 17, 31 after UVA and UVB provocation, and in some patients even later. Where a pathological reaction was observed, skin biopsies were taken and this was repeated as soon as there was any change in the clinical picture of the test areas, in order to characterize the histological progress of the test reactions provoked.

PUVA treatment was performed with Sylvania F 85 lamps mounted in Waldmann 1000 cabins (Waldmann Werk für Lichttechnik, Schwenningen, Federal Republic of Germany). These lamps have their main emission

spectrum between 320 and 400 nm with a peak emission at 365 nm. However, a very small amount of UVB is emitted (0,6% of the UVA irradiance).

Irradiance measurement

All light intensities from the lamps used in the light testing and their emission spectra were measured with an Optronic Mod. 742 double monochromator HW 1.5 nm spetroradiometer connected to an HP -85 computer. The Xenon arc lamp, when filtered with the Schott WG 295 filter, had a UVC fluence of 0.1 mW/cm^2 and a UVB fluence of 1.8 mW/cm^2, both at 15 cm distance. The UVA fluence was 7.6 mW/cm^2 at 15 cm distance, when the 3 mm glass filter was added. The UVA fluence from the PUVA 500 lamp was 5 mW/cm^2, and the UVA fluence from the UVASUN lamp was 43 mW/cm^2, both at 30 cm distance.All measurements were performed by Ulf Wester, Department of Radiation Physics, Karolinska Institute.

Photopatch testing

Photopatch testing was performed using the PUVA 500 lamp in accordance with the Scandinavian Photodermatology Research Group (SPDRG) protocol & technique recommendations (100). Several sunscreens were added to the standard protocol. The photopatch test reactions were read 24 and 72 hours after irradiation.

IMMUNOHISTOCHEMICAL METHODS WITH MONOCLONAL ANTIBODIES (III)

Twenty-one photosensitive psoriatics were studied, all with pathological reactions after light test provocation with UVB and UVA. The patients were divided into three groups according to the results of phototesting:

1. PMLE reaction and subsequent secondary psoriasis — 7 patients
2. PMLE reaction but no sign of secondary psoriasis — 6 patients
3. Photosensitive psoriasis with no history or sign of preceding PMLE — 8 patients

The test areas were studied in all patients on days 1, 3, 6, 10, 17, 31 after provocation, and in some patients also later. Where a pathological reaction occurred, i.e. PMLE reaction or clinical signs of early psoriasis, a biopsy was taken. New biopsies were taken as soon as there was any change in the clinical picture of the test areas.

Controls

A. PMLE patients with no psoriasis, but with a proved PMLE reaction after sunlight, phototesting or sun bed exposure — 8 patients
B. Normal healthy Caucasians with no history of skin disease or light sensitivity — 5 individuals

Immunoperoxidase technique

A two-stage monoclonal antibody/peroxidase conjugated rabbit antimouse Ig staining system with 3-amino-9-ethyl carbazole (AEC) as reagent was used. Frozen sections of 6 um thickness were dried, fixed in acetone, dried and stained. Sections were first incubated with normal swine serum before incubation with the mouse monoclonal antibody in a previously determined concentration. After washing, incubation with the peroxidase conjugated rabbit antimouse Ig was done (Dakopatts, Copenhagen, Denmark). Staining was achieved by incubation in a freshly prepared acetate buffered solution containing 3-amino-9-ethylcarbazole (Sigma Chemical Co., St Louis, MO, USA), dimethylformamide (Kebo, BHH Chemicals Ltd, Poole, England), and hydrogen peroxide.

Counterstaining was done with Mayer's haematoxylin and the sections were mounted with glycerol-gelatine. Control sections were prepared and run in parallel except for the monoclonal antibody. Also, tonsils from tonsillectomy patients were used as positive controls.

Identification of cell types

Details of the monoclonal antibodies used are given in Paper III

(Table 2). All slides were judged independently by two assessors. Enumeration of positively stained cells in the infiltrate was semiquantitative, and they were grouped according to the following scheme: less than 25%, between 25 and 50%, 50 to 75%, and more than 75% staining.

PUVA TREATMENT (IV)

Fifteen light-tested patients with a history of photosensitive psoriasis were willing to be treated. In twelve, treatment was started with trimethylpsoralen, TMP, (Trisoralen, Elder USA) 30 mg two hours before UVA exposure. Three patients were given 8-methoxypsoralen, 8-MOP (Puvamet, Draco Co., Sweden) in a dose of 0.6 mg/kg bodyweight. The therapy was started in early spring and continued until June. The initial UVA dose was low, 0.15 J/cm^2. It was increased by 0.25 J/cm^2 each time up to 3 J/cm^2, then by 0.5 J/cm^2 up to 5 J/cm^2 and thereafter by 1 J/cm^2 per session up to maximum dose achieved, which varied from 3 to 20 J/cm^2. Treatments were given twice a week. If side effects appeared, i.e. pruritus, erythema or exacerbation of preexisting lesions, the UVA dose was lowered to the previous dose a few times before an increment was tried again.

STATISTICAL METHODS (I)

Differences between mean values were tested with Student's t test. Associations between variables were estimated with Pearson's product moment correlation coefficients.

Multivariate analysis was performed using stepwise logistic regression according to the SAS program (101). In this analysis the predictor with the defined most significant association to the dependent variable, photosensitivity, was chosen first. In the next step, the variable was chosen which together with the first variable was most significant. This stepwise regression analysis was continued until all variables within 0.1% level of significance had been displayed.

The prevalence of photosensitive patients was estimated as follows: Define N_0 as the number of non-photosensitive patients. Define N_1 as the number of patients who answered that their psoriasis "always" worsened from sun exposure and N_2 as the number of patients who

answered "sometimes". Let n_1 and n_2 be the corresponding numbers of sampled patients who were telephone-interviewed. Let P_1 and P_2 correspond to the fraction of the samples eventually characterized as photosensitive patients.

$N_1P_1 + N_2P_2$ is an estimate of the total number of photosensitive patients. This number is divided by $N_0 + N_1 + N_2$ and an estimate of the relative frequency (prevalence) of photosensitivity is obtained as:

$$(N_1P_1 + N_2P_2)/(N_0 + N_1 + N_2)$$

The standard error of this estimate is given as:

$$\sqrt{\frac{N_1^2P_1(1-P_1)/(n_1-1) + N_2^2P_2(1-P_2)/(n_2-1)}{(N_0 + N_1 + N_2)^2}}$$

In Paper I (Table I, columns A and B) the relative frequency of photosensitive patients with a certain attribute has been estimated by weighting the frequencies in the two groups, taking into account the sampling fraction in the telephone interviews.

The odds ratios in the same table were significance-analyzed in the following way: Let q_1 symbolize the fraction of patients with e.g. pruritus within the group who originally answered "always worsened by sun" and who according to the telephone interviews were photosensitive. Let q_2 denote the same fraction in the corresponding group answering "sometimes worsened by sun". Let Q symbolize the relative frequency of patients with e.g. pruritus among non-photosensitive patients. The relative frequency, F, is estimated as:

$$F = \frac{N_1P_1q_1 + N_2P_2q_2}{N_1P_1 + N_2P_2}$$

and its standard error is approximated as:

$$SE\ (F) = \sqrt{\frac{\frac{N_1^2P_1^2q_1(1-q_1)}{n_1P_1-1} + \frac{N_2^2P_2^2q_2(1-q_2)}{n_2P_2-1}}{(N_1P_1 + N_2P_2)^2}}$$

The odds ratio given in the last column in Table I is estimated as:

$$OR = \frac{F}{1-F} \cdot \frac{1-Q}{Q}$$

The significance of the odds ratio is analyzed by the approximately standardized normally distributed critical ratio, Z.

$$Z = \frac{F - Q}{\sqrt{Q^* (1-Q^*)\left(\frac{1}{N_0} + \frac{N_1^2 P_1^2 (n_1 P_1 - 1) + N_2^2 P_2^2 (n_2 P_2 - 1)}{(N_1 P_1 + N_2 P_2)^2}\right)}}$$

where $$Q^* = \frac{N_1 P_1 q_1 + N_2 P_2 q_2 + N_0 Q}{N_1 P_1 + N_2 P_2 + N_0}$$

RESULTS

CLINICAL DATA (I, II, V)

Photosensitive psoriasis (I, II)

In the survey of 2,000 psoriasis patients (I) 88% replied, and of these 4.4% answered that their psoriasis always worsened following sun exposure, and 7.3% that this was sometimes so. After telephone interviews with an 80% sample of these 201 allegedly photosensitive patients, half of them were considered non-photosensitive. Thus, an estimated prevalence of 5.5% photosensitivity was obtained regarding this hospital material. The prevalence of photosensitivity seems to increase with age (I, Figure 1). Age at appearance of photosensitivity in relation to age at psoriasis debut can be seen in I, Figure 2, which illustrates that the patients had psoriasis first and photosensitivity appeared years later in many. Forty-three per cent of the light-sensitive psoriatics had a history of polymorphous light eruption with secondary exacerbation of psoriasis lesions. For details of symptoms of photosensitivity, see I.

Comparison between the 81 considered after the telephone-interviews to be definitely photosensitive and the 1,510 non-photosensitive patients concerning background factors and symptoms showed a statistically significant ($p \leq 0.001$) overrepresentation in the photosensitive group of skin type I, psoriasis affecting hands, heredity for photosensitivity and high age (I, Tables I and II). Those considered non-photosensitive after the telephone interviews were not included in this comparison.

Thirty-five of the photosensitive patients were willing to be investigated in more detail (II). All 35 had long-standing psoriasis and had observed a photosensitivity for 2-40 years (mean 11.4 years). Exacerbation of psoriasis from sun exposure was observed mostly on the back of the hands and forearms, followed in frequency by the legs, face, chest and back. Abrupt appearance of the light sensitivity was seen in 13/35

and a distinct overexposure prior to onset was reported by eight. A hardening phenomenon was noticed by 11. Symptoms of light sensitivity usually appeared in May, but the time of appearance varied from March to July. The most common subjective complaint after sun exposure was pruritus (26/35). Skin type distribution was normal in this group with no overrepresentation of skin types I or II. Eighteen of these patients (about 50%) had a history of PMLE with secondary psoriasis lesions.

Photopatch testing showed no photoallergic reactions and there was no history or sign of drug photosensitivity. Other photosensitivity disorders were excluded following appropriate laboratory tests, including antinuclear antibodies (ANA), anti-Ro antibodies, urinary porphyrin and erythrocyte protoporphyrin measurements.

Polymorphous light eruption (PMLE) (V)

In the survey of 412 individuals aged 18-65 years (mean 40,2), 96.4% answered a questionnaire regarding prevalence and symptoms of PMLE. The women numbered 263 (66%) and the men 134 (34%). Eighty-three individuals (21%), of whom 89% were women, had symptoms consistent with a diagnosis of PMLE. There were no significant differences between men and women in the PMLE group concerning any of the answers regarding symptoms or background factors. Within the material there were 9/134 men (6.7%) with PMLE symptoms and 74/263 women (28%) with PMLE symptoms. If this overrepresentation of females in the surveyed group is adjusted (presuming an equal sex distribution), the prevalence of PMLE will be 17.4%. The percentage of women with PMLE in such a population would be 80%, but was in our survey 89% because of the overrepresentation of women in the surveyed group.

Among individuals with PMLE, duration of their disease ranged from one to 53 years (mean 14). A positive family history of PMLE was common (46%). Considerable doses of sunlight were required to trigger eruptions: 42% of these individuals judged their threshold doses to be from 30 minutes to two hours of sun exposure, and 45% over two hours. In 72%, the eruptions disappeared within six days if sun was avoided.

Only 3% had consulted a physician for their PMLE. A hardening phenomenon occurred in 84%. Many in the PMLE group enjoyed sunbathing (70%). A fair complexion was common in the PMLE group, 40% having skin type I or II, while 22% of individuals with no light sensitivity had skin type I or II.

The mild symptoms of PMLE in the surveyed group may be illustrated by comparing their symptoms with those of patients who had consulted a physician for their PMLE, as described in a Finnish study (9). Their tolerance to light was considerably lower than in those with PMLE in our survey. For this comparison see V, Tables 2 and 3. However, since there were so few men with PMLE in our group, all figures in the tables will be somewhat uncertain if men and women are weighted equally.

LIGHT TEST RESULTS WITH UVA AND UVB IN PHOTOSENSITIVE PSORIASIS (II, III)

Clinical and histopathological responses (II)

The results in 35 patients after light testing with UVB and UVA provocation are summarized in II, Table 3. Two reaction patterns were observed.

A. In 18/35 patients with a history of PMLE and secondary psoriasis, a PMLE reaction was provoked in 12/18 with high-dose UVA and in four with UVB. Three of the latter also reacted to UVA. The PMLE reaction was usually papular except in four patients who initially developed erythematous, oedematous eruptions and in one patient who exhibited haemorrhagic maculae. Psoriasis followed the PMLE reaction after provocation; in six patients after UVA and in three after UVB, two of the latter reacting also after UVA. The psoriasis lesions appeared 17 to 23 days (59 days in one patient) after provocation, and were documented by histopathological examination.

B. 17/35 patients had a history of light-sensitive psoriasis without any evidence of preceding PMLE. Psoriasis was provoked with UVB in

nine and with UVA in five. These five all reacted to UVB as well. Psoriasis lesions were fully developed 17 to 48 days after provocation, as documented by histological examination.

The UVA dose necessary to evoke the positive reactions in these patients (groups A and B) was 3 x 75 J/m^2 in one case, 2 x 75 J/cm^2 in one, 75 J/cm^2 in three, 50 J/cm^2 in seven, 25 J/cm^2 in four and 10 J/cm^2 in one. Four patients (all with PMLE reactions) had to be retested on the forearm to elicit a positive reaction, while the back was non-reactive.

Histological examination

Patients who developed psoriasis lesions after light testing did so both clinically and histologically. The histopathological features thus tallied with the findings in psoriasis (102 a), i.e. elongation of the rete ridges with thickening in their lower portion, elongation and oedema of the papillae, relative thinning of the suprapapillary portions of the stratum malpighii, hypogranulosis, parakeratosis, and presence of Munro microabscesses. However, not all these features were present in all patients concurrently.

In the patients with a PMLE reaction after light testing, all had a patchy lymphocytic infiltrate in the dermis. In most patients the epidermal changes comprised features of epidermitis. It should, however, be noted that the histopathological picture in PMLE is nonspecific and depends on the clinical variety (102 b). All skin biopsies were examined by Björn Lagerholm, M.D., Department of Dermatology, Karolinska Hospital.

Immunological analysis (III)

The dermal infiltrate after light provocation consisted mainly of leu-4 positive cells (PAN-T) with a dominance of leu-3 positive cells (T-helper/inducer phenotype) and less staining of leu-2 positive cells (T-suppressor/cytotoxic phenotype), except in a few cases where leu-2

positive cells were more abundant. This pattern was seen in all patient groups including the control group of non-psoriatic PMLE patients. Exocytosis with mainly leu-2 positive cells in the epidermis was seen in 12 patients after psoriasis had developed. OKT-6 positive cells (Langerhans) in the dermis were sparse, except in individual patients in all groups where a considerable number of positive cells were observed. Leu-M1 positive cells in the dermis (monocytes, granulocytes) were also sparse, but increased in most patients after psoriasis had developed. No B1 positive cells (B-lymphocytes) were seen and only single leu-7 positive cells (NK).

The only significant differences in the reaction pattern between the different clinical groups were the increased number of leu-M1 positive cells in the dermis and the exocytosis of leu-2 positive cells after psoriasis had developed. Concerning the dermal staining with leu-4, leu-3, leu-2 and OKT-6, the proportion of these markers did not change during the development of the lesions in the different patient groups, either from early PMLE lesions or from late lesions where psoriasis had developed. The results are summarized in III (Table 3).

The clinical picture of these patients and the time course for the development of pathological reactions after provocation is described in more detail on pages 29-30.

PUVA TREATMENT FOR PHOTOSENSITIVE PSORIASIS (IV)

Of 15 patients with photosensitive psoriasis treated, 12 showed good to excellent results with regard to prevention of their summer exacerbation of psoriatic lesions. The results are summerized in IV (Table).

Ten of the patients had PMLE with secondary psoriasis. All were treated with TMP, five showing an excellent response to the therapy and four a good response. One patient became worse during therapy. In seven of the ten patients who had positive light test reactions following provocation before therapy, new provocations were performed after therapy in the same manner as before. Only one patient showed a PMLE reaction.

This was weak, and healed without the subsequent psoriasis reaction that had occured before therapy.

In five patients with photosensitive psoriasis without PMLE, the result was excellent in three cases, two treated with 8-MOP and one with TMP. No effect was achieved in one patient treated with TMP, and one in whom both 8-MOP and TMP were tried became worse on both treatment trials. In these five patients, light provocation before therapy were positive in two, and provocation after therapy were negative in both.

DISCUSSION

Psoriatics who consider themselves photosensitive may do so for various reasons. Absence of expected improvement in psoriasis lesions after sun exposure is sometimes interpreted as meaning that sunlight has a worsening influence. The tendency to sunburn and associated problems in skin types I and II is by some psoriatics confused with actual worsening of psoriasis lesions. PMLE with no relation to psoriasis lesions may occur. Secondary psoriasis lesions may supervene in the PMLE lesions. Finally, psoriasis lesions slowly worsen after sun exposure in some psoriatics although they have no history of PMLE. In this study we have concentrated on the last two groups, i.e. where psoriasis lesions actually worsen following sun exposure.

In earlier reports on photosensitive psoriasis, emphasis has been laid on a fair complexion and a tendency to sunburn (103, 104). Observations have been published regarding disorders concomitant with photosensitivity, such as lupus erythematosus, hypocomplementaemia, vitiligo or porphyria (105).

In the survey of 2,000 psoriatics (I) the prevalence of photosensitivity was estimated to 5.5%. This was with regard to worsening of psoriasis lesions following sun exposure, in a hospital material. Patients with other manifestations of photosensitivity, e.g. fair skin types, PMLE and psoriasis which did not worsen after sun exposure, were not included. This is probably one reason why our prevalence figure is so low. Other investigators have found considerably higher figures concerning prevalence of photosensitivity in psoriatics, varying between 14% and 24% (106-110). However, in these studies photosensitivity was only one question among many, and was not analysed in detail.

Forty-three per cent of the patients in our study reporting a worsening effect of sunlight had a history of PMLE with secondary psoriasis in the PMLE lesions. However, some psoriatics had a history of PMLE, but had never noticed that psoriasis lesions appeared as a sequela. This was the case with 35% of those reporting photosensitivity, and these

were all excluded, as they did not fulfil the criterion of psoriasis lesions worsening after sun exposure. The reason for this difference in reaction pattern is unknown. If the tendency to develop psoriasis secondary to PMLE is a manifestation of a Koebner phenomenon in these cases, it could support the idea that there are groups of psoriatics who are Koebner-positive and others who are Koebner-negative (111, 112).

Since we found such a high prevalence of PMLE in our photosensitive psoriatics, we initiated a study to find out the prevalence of PMLE in a normal population (V). This resulted in a surprisingly high figure of around 17%. It should be emphasized that the population surveyed consisted of individuals with indoor occupations, aged 18-65 years, and with females over-represented. Before adjustment for this female over-representation the prevalence was even higher (21%). The accuracy of the PMLE diagnosis may be questioned, as it was established entirely on the basis of the history. In PMLE the symptoms are often very characteristic and easily described, and even when examining the patient there is no certain way of verifying the diagnosis unless the patient exhibits acute lesions. Therefore, the diagnosis in clinical practice is often established with regard to the symptoms as described by the patient. The accuracy of the diagnosis in the survey was confirmed by a randomized telephone interview with 20 of the 83 individuals who stated that they had PMLE. All these 20 cases reported clinical symptoms typical of PMLE, such as itchy, often papular rash on exposed skin, appearing after sun exposure and disappearing after a few days or a week of sun avoidance. The main differential diagnoses were a fair complexion (skin types I and II), solar urticaria, lupus erythematosus, and intake of drugs known to induce light sensitivity, and such cases were excluded on the basis of their history.

The conclusions are that PMLE is a common disease, especially in its mild forms, and that people with minor symptoms probably seldom seek medical advice. Only 3% of those with PMLE answering our survey had visited a physician for their PMLE. The prevalence of PMLE has in one other report been estimated to around 11% (7). But apart from this survey no other prevalence studies on PMLE are reported. With this high

prevalence of PMLE in mind it is not surprising that psoriasis patients may also have PMLE.

In Paper II, in which 35 photosensitive psoriatics were light-tested, it was possible to verify that PMLE with secondary psoriasis was one cause of photosensitivity in these patients. Thus, of 35 patients with a history of worsening of psoriasis after sun exposure, 18 had a history of PMLE. A PMLE reaction could be induced by light provocation in 13 of them, and in seven this developed further into psoriasis. The PMLE reaction was easier to induce with high doses of UVA than with UVB, which agrees with the findings of other investigators (16, 17, 20).

Seventeen of the 35 photosensitive psoriatics tested had no history or sign of PMLE. Nine of them developed psoriasis successively in the test areas. All nine reacted after UVB and five after UVA as well. Thus, in this patient group it was easier to induce psoriasis lesions with UVB than with UVA.

The way by which psoriasis appears in the test areas may possibly be a Koebner phenomenon. However, there was no correlation between patients with positive phototest results and those with negative results concerning a possible history of Koebner reactions. If Koebner reactions can explain how psoriasis develops in these cases, skin type distribution should show a higher frequency of types I and II, yet skin type distribution among our 35 tested patients was normal for the Stockholm area (113). It should, however, be added that there was probably a certain selection in the patients who were light tested, as skin type distribution in all photosensitive psoriatics answering the survey (I) showed a significant ($p \leq 0.001$) increase of skin type I compared to psoriatics without photosensitivity. But in the survey it could also be seen that the patients had psoriasis first, and that photosensitivity appeared years later in many. This would not be the case if skin type alone could explain the photosensitivity.

The hands are a common location of psoriasis in photosensitive psoriatics. In the survey (I) this, together with heredity for

photosensitivity, skin type I and high age, was one of the variables that explained most in predicting photosensitivity in psoriatics. Among the 35 patients phototested, 71% reported that their hands, and also their arms, flared after sun exposure.

To get further insight into the problem of how psoriasis develops after sun exposure, the cells infiltrating the skin after light provocation were subjected to immunological analysis. The special features observed after psoriasis had developed clinically and histologically were that cells with T-suppressor/cytotoxic phenotype infiltrated the epidermis, and that many leu-M1 positive cells (monocytes, granulocytes) were present in the dermal infiltrate. T-helper/inducer cells dominated in the dermal infiltrate in nearly all patients after light provocation before and after psoriasis had developed, in the PMLE patients who never developed secondary psoriasis after provocation, and in the control group of non-psoriatic PMLE patients. Thus, the dominance of cells with T-helper/inducer phenotype seems to be a common feature in several disease patterns when lymphocytes are recruited into the skin. It may be a reflection of the proportion of lymphocyte subpopulations in the blood (114).

The question of which cells predominate in the epidermis of early psoriasis is controversial. Some investigators have observed, as we did, mainly cells with T-suppressor/cytotoxic phenotype in the epidermis of early psoriasis (49); others have found mainly cells with T-helper/inducer phenotype there (50). Whether these cells are involved in a primary or a secondary immunological event in the pathogenesis of psoriasis is still unknown. Our findings do not permit any substantial conclusion as to the role of T lymphocytes in photosensitive psoriasis.

Many recent studies concern the efficacy of PUVA treatment for various photosensitive diseases, and the results have been promising (60-67). The mechanisms may be the induction of epidermal hyperplasia and melanocyte stimulation, but probably also influences on immunocompetent cells and factors (68-71).

To assess the prophylactic effect of PUVA in patients with light-sensitive psoriasis (IV), trimethylpsoralen (TMP) was chosen for several reasons: for some years we have used oral TMP in PUVA therapy for PMLE with satisfying results (unpublished data). Oral TMP photochemotherapy has a well-documented pigment stimulation capacity, for example in the treatment of vitiligo, and has less phototoxic effect than 8-MOP (115). TMP was therefore expected to give fewer problems of exacerbation and flare-up reactions. However, TMP was not expected to heal existing psoriasis lesions (116).

Of 13 photosensitive psoriatics, ten showed a good to excellent result of PUVA therapy with TMP as a prophylactic means of preventing exacerbation of psoriasis lesions following sun exposure. However, all these patients had minor psoriatic lesions before therapy and these healed only in two, confirming that TMP given orally has slight or no therapeutic effect for psoriasis. Since so few patients were treated with 8-MOP, no definite conclusions as to the efficacy of this treatment may be drawn. The effect of 8-MOP photochemotherapy in photosensitive psoriasis warrants further studies.

PRINCIPAL FINDINGS

Photosensitive psoriasis, i.e. psoriasis lesions worsened after sun exposure, is rare. An estimated prevalence of 5.5% was found in a survey among 2,000 psoriasis patients.

Photosensitive psoriatics have a statistically significant ($p \leq 0.001$) higher frequency of skin type I, heredity for photosensitivity, high age, and psoriasis affecting hands, compared to non-photosensitive psoriatics.

The reaction patterns of photosensitive psoriatics may be divided into two major groups. About half have a history of polymorphous light eruption (PMLE) after sun exposure, with secondary psoriasis lesions appearing, and the other half slowly develop psoriasis lesions after sun exposure, but without preceding PMLE. Psoriasis in patients with skin type I or II as the distinguishing feature, or in those presenting PMLE, is not considered photosensitive unless exacerbated by light exposure.

PMLE with subsequent psoriasis was provoked most easily with UVA, and psoriasis with no preceding PMLE most easily with UVB.

Immunohistochemical investigation with monoclonal antibodies after provocation with UVA and UVB revealed no differences between photosensitive psoriatics with or without PMLE, and controls, concerning the proportion of dermal Langerhans cells or cells with T-helper/inducer and T-suppressor/cytotoxic phenotype. After psoriasis had developed, cells with T-suppressor/cytotoxic phenotype were seen in the epidermis and an increased number of monocytes/granulocytes in the dermis.

PUVA therapy with oral trimethylpsoralen and UVA exposure was effective treatment for photosensitive psoriasis with regard to prevention of summer worsening of psoriasis lesions.

PMLE is a common disorder. In a survey of 412 individuals 21% had a history of PMLE. After correction for the female overrepresentation the prevalence of PMLE was esitmated to 17.4% in the group surveyed.

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