

Psoralen photoallergy caused by plant contact

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A case of acquired photocontact allergy to furocoumarins in plants is reported. Photopatch testing was performed with four psoralens [8-methoxypsoralen (8-MOP), 5-methoxypsoralen (5-MOP), trimethylpsoralen (TMP) and imperatorin (IMP)]. The use of serial dilutions of the test compounds made it possible to differentiate between photoallergic and phototoxic reactions. 8-MOP gave a positive eczematous test reaction down to a concentration of 0.0001 %. The reactions to 5-MOP and IMP also were positive, while that to TMP was negative. Histopathological examination of a biopsy specimen from a positive test site showed changes consistent with photoallergic contact dermatitis.

The multiple reactions could be explained on the basis of multiple sensitization, but cross reactions cannot be ruled out.

Key words: Photoallergy – photopatch testing – plant dermatitis – psoralens.

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Furocoumarins (psoralens) are well-known phototoxic agents. This effect is manifested clinically as, e.g. phytophotodermatitis (for review see Pathak 1974) and has also been utilized in the treatment of vitiligo and psoriasis.

Photoallergic reactions to furocoumarins have been reported (Sidi & Bourgeois-Gavardin 1953, Fulton & Willis 1968) but seem to be very rare. This is perhaps due partly to difficulties in differentiating between these two types of reactions.

A case of photocontact allergy to psoralens acquired from contact with plants recently seen at our Department was investigated by phototesting.

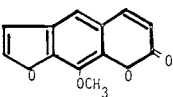
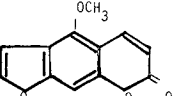
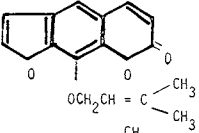
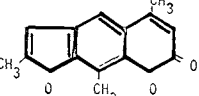
Case Report

The patient was a 56-year-old sales manager with no history of skin diseases. Since

1953 he has visited the Department of Dermatology, Malmö General Hospital, on nine occasions because of a phytophotodermatitis. On each occasion it was mainly the hands, forearms, feet and face that were affected. In 1963 the attack was so severe that the patient required treatment with systemic corticosteroids for 2 weeks. In 1968 he spent 10 days in the hospital because of photodermatitis acquired after picking garden parsley. On that occasion itching was noted for the first time. New episodes occurred in 1970 and 1971 while on holiday in Spain, and in 1972. The last attack occurred in August 1976, when he complained of severe itching and had scattered papulo-vesicular lesions on the hands, forearms and feet.

The dermatitis usually reached a maximum within the first 24 h after contact with the plants. The causative agents hith-

Table 1. Chemical structure of the four psoralens tested

Name	Abbreviation	Chemical structure
Xanthotoxin ¹	8-MOP	
Bergapten ²	5-MOP	
Imperatorin ²	IMP	
Trimethylpsoralen ²	TMP	

¹ Paul B. Elder Co., Bryan, USA.

² Kindly supplied by AB Draco, Lund, Sweden.

erto incriminated are parsnip (*Pastinaca sativa*), giant hogweed (*Heracleum mantegazzianum*) and garden parsley (*Petroselinum sativum*).

Material and Methods

Thin-layer chromatography: The chemical structures of the test compounds are given in Table 1. The purity of the four test compounds was studied by thin-layer chromatography. Silica gel plates (DC-Fertigplatten, Kiesegel F254, Merck, Darmstadt, German Federal Republic) were used. The substances were applied in ethanol solution and the plates were run for 1 h in toluene:ethyl acetate:acetic acid 5:4:1. The plates were inspected in 254 and 360 nm UV irradiation.

Photopatch testing was done with an ethanol extract of garden parsley and with

the four pure psoralens, three naturally occurring (8-MOP, 5-MOP and IMP) and one synthetic compound (TMP). The test substances were dissolved in ethanol and a series of dilutions was prepared. 8-MOP and TMP were tested down to a concentration of 0.000001 %; 5-MOP and IMP were tested at 0.1 % only. The test solutions were applied in duplicate to the back of the patient under occlusion with the Finn chamber technique (Pirilä 1975) and left there for 2 h. One set of tests was then removed, and the test sites were cleaned with ethanol and immediately irradiated with long-wave ultraviolet light (UVA) from a 150 W xenon arc lamp (Osram XBO) equipped with a Schott BG38 filter and a windowglass filter. The output in the UVA-range was approximately 30 mW/cm sec (as measured with an optometer UDT-40X from United Detector Technology). The dose delivered to each site was 1.8 J/cm². After irradiation the test area was covered with opaque aluminumized paper. The phototest and the ordinary patch test were read after 48 h and the result was graded according to the following scale:

– = negative, + = slight erythema, ++ = strong erythema and infiltration, +++ = strong erythema, infiltration and vesicles. A test was also performed with UVA-irradiation only. The test dose was 18 J/cm².

The patient was also tested with pre-irradiated solutions of 8-MOP. These were obtained by irradiating ethanol solutions of 8-MOP, 0.1 % and 1.0 % respectively, for 2 h with the filtered xenon arc lamp previously described. The dose delivered was approximately 216 J/cm². The irradiated solutions were then applied as ordinary patch tests under occlusion for 48 h with no further irradiation. The tests were read 72 h after application.

As controls, five healthy volunteers were tested with the same test battery.

Histopathology: The positive test reaction

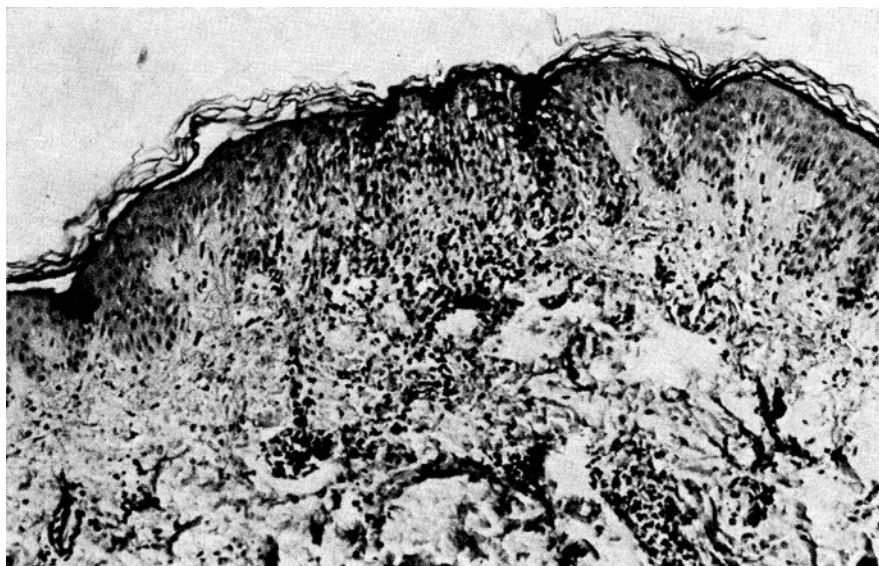


Fig. 1. Skin biopsy specimen from positive test reaction to 8-MOP 0.0001 %. Perivascular lymphocytic and histiocytic infiltrate extending up in the epidermis, where spongiosis is evident. HTX $\times$ 133.

to 8-MOP 0.0001 % was biopsied after 48 h and prepared for histopathology.

Results

Thin-layer chromatography. All four compounds yielded single spots on the plates when inspected in UV irradiation.

Photoepicutaneous testing. The patient reacted to 8-MOP and UVA down to a con-

centration of 0.0001 % (Table 2). The response was clinically of the eczematous type with papules, and at higher concentrations even with vesicles, but no bullae. The control subjects reacted to a concentration of 0.1 % with only barely perceptible erythema with no infiltration. Tests with pre-irradiated 8-MOP were negative. The tests with 5-MOP and IMP and extract of parsley were strongly positive in the patient, negative in the controls. The tests with TMP, on

Table 2. Results of photopatch tests with four psoralens in decreasing concentrations in patient (P) and controls (C). —negative; + slight erythema; ++ strong erythema and infiltration; +++ strong erythema, infiltration and vesicles. NT = not tested

Concentration %	8-MOP		5-MOP		IMP		TMP	
	P	C	P	C	P	C	P	C
0.1	+++	+	+++	—	+++	—	NT	NT
0.01	+++	—					+	+
0.001	+++	—					—	—
0.0001	++	—					—	—
0.00001	—	—					—	—
0.000001	—	—					—	—

the other hand, produced identical responses in the patient and in the controls. At a concentration of 0.01 % all reacted with a slight erythema without infiltration. This was considered a phototoxic type of response. The reactions to all non-irradiated test substances were negative in the patient as well as in the controls, as was the test with UVA only.

Histopathology. The biopsy specimen from the site of the positive test reaction to 0.0001 % 8-MOP showed perivascular lymphocytic and histiocytic infiltrate, spreading into the epidermis where spongiosis was evident (Fig. 1).

Discussion

Photoallergy to furocumarins is certainly rare, and the present case seems to be the first recorded where the sensitivity was acquired from contact with plants. In previously reported cases the sensitization occurred during therapeutic procedures. In the five cases reported by Sidi & Bourgeois-Gavardin (1953) a psoralen extract containing both 8-MOP and IMP was used in the treatment of vitiligo. All five patients reacted initially to 8-MOP only, but one patient subsequently became photosensitized also to IMP during continued treatment with this compound. The report gives no details of the test procedure.

Fulton & Willis (1968) found three cases of photoallergy to 8-MOP in a group of 20 volunteers participating in a chronic light exposure study during which a 1 % 8-MOP solution was painted on the back three times a week. These patients were tested also with pre-irradiated solutions of 8-MOP and showed positive dark test reactions to these solutions. This implies that photoallergy to 8-MOP is in fact ordinary contact allergy to some photoproduct of the substance, as has been shown for other compounds, e.g. halogenated salicylanilides

(Willis & Kligman 1968). Our results do not lend support to such an assumption, since tests with pre-irradiated solutions produced no reactions.

The clinical pictures of toxic and allergic photodermatitis differ, but it may not be easy to differentiate between the two conditions in practice. Itching is a predominant symptom of the allergic dermatitis, but not of toxic dermatitis. Also the inflammatory reaction tends to reach its peak earlier in a photoallergic dermatitis than in a furocumarin-induced phytophotodermatitis, where a maximum is often not reached before 48 to 72 h (Breit & Kligman 1969, Jung 1976). This difficulty in distinguishing between toxic and allergic photoreactions can to some extent be overcome by phototesting with a series of dilutions of the compound. Elicitation of toxic reactions requires a higher concentration of the compound, or more UV-energy, than allergic ones (Epstein 1972). This has been shown experimentally to hold for various photosensitizing compounds (Mizuno & Ohno 1976). This is also illustrated by the observation that a thousand-fold dilution of the minimum phototoxic dose in normals will still elicit an eczematous response in the patient. All non-irradiated control tests were negative in the patient and thereby ruled out ordinary contact allergy. A general sensitivity to UVA could also be excluded as the test with UVA alone produced no response.

Histopathological examination may be helpful in distinguishing toxic from allergic photoreactions. Photocontact allergy is essentially identical with allergic contact dermatitis (Epstein 1972), while phototoxic reactions produce epidermal damage with necrosis, oedema and only few infiltrating cells (Epstein 1974). However, biopsy specimens from clinical lesions are often inconclusive, but such a specimen from a positive photopatch test can be diagnostic (Epstein

1968). In our case the histopathological picture argued strongly for photoallergy.

The psoralens vary in phototoxic sensitizing potency. Of the three natural compounds, 8-MOP is the strongest after topical application, followed by 5-MOP, while IMP showed no activity whatsoever (Musajo 1955). Such application of the synthetic compound, TMP, however, produces the strongest effects of all four agents (Toda et al. 1974). Given systemically, both TMP and IMP are phototoxic, though less so than 8-MOP and 5-MOP (Ljunggren & Möller, in preparation). There is obviously no close correlation between phototoxic potency and photoallergic sensitizing capacity.

All three naturally occurring psoralens tested occur in plants with which the patient came into contact. TMP has been isolated from celery infected with pink rot disease (Scheel et al. 1963), but there are no reports of its isolation from the plant species relevant in the present case, and it has not been included in extensive studies of the furocumarin content of plants (Pathak et al. 1962, Beyrich 1966). *Pastinaca sativa* contains all three psoralens (Beyrich 1966), *Petroselinum sativum* and the *Heracleum* species only 5-MOP (Pathak et al. 1962). It is thus not possible to say whether the patient had become sensitized to each of the psoralens by contact, or whether some of the positive tests were due to cross reactions. The synthetic compound, TMP, with which the patients has probably never been in contact, was negative, and there is obviously no obligatory cross reaction pattern between TMP and the other compounds. This might have some practical consequences for the clinical use of psoralens. TMP should perhaps be preferred for topical therapy in order not to exclude future systemic treatment with 8-MOP in case of photoallergy.

It is possible that plant-induced photoallergy to psoralens is apt to be overlooked because the dermatitis is assumed to be

phototoxic, and because the latter type of reaction is the more frequent one. Photopatch testing with furocumarins seems indicated in atypical cases of phytophotodermatitis. The test should be performed with serial dilutions of the compound and it should include controls.

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