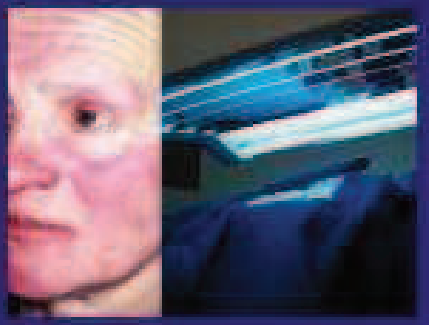
Photoallergy and Photopatch Testing

Edited by
Radoslaw Spiewak



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Institute of Dermatology

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An introduction into patch testing

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The following text is an updated excerpt from the article:
Spiewak R: Patch testing for contact allergy and allergic contact dermatitis. Open Allergy J 2008; 1: 42-51.

Patch test is the generally-accepted method of choice and the "gold standard" in the detection of contact allergy, and in the diagnosis of allergic contact dermatitis. The prevalence of CA is estimated at 26-40% among adults, and 21-36% among children, whereas the lifetime prevalence of ACD is estimated at 10%. These epidemiological data clearly indicate that patch testing should be routinely performed in every allergist's and dermatologist's office. In principle, patch test relies on provoking skin inflammation (eczema) on a very limited skin area (less than 1 cm^2) under controlled conditions. Development of inflammatory reaction at the site of application of a particular hapten is considered as a proof of hypersensitivity, and may also be viewed as reproduction of the disease. Thus, patch test is both a screening test and a provocation test in the target organ skin. Patch testing helps in identification and avoidance of offending haptens, thus in limiting symptoms of the disease. The benefits of patch testing in patients with suspicion of ACD include the reduction of treatment costs and increase in patients' quality of life. The percentage of final diagnoses is higher among patients who had undergone patch testing (88% as compared to 69% among those non-tested). Most notably, the test shortens more than 20 times the time lapse from the first visit to final diagnosis (in average, from 175 down to 8 days).

Indications and contraindications for patch testing

Patch test should be performed in every case of chronic and/or recurrent dermatitis (eczema) or lichenification, whenever a possibility exists that CA may be the cause or a complication of the disease. Thus, beside the suspicion of allergic contact dermatitis, patch tests are also indicated in a variety of inflammatory skin diseases including those regarded as "endogenous": atopic eczema, seborrheic dermatitis, stasis dermatitis, eczema around leg ulcers, irritant contact dermatitis, etc. This is due to the fact that contact hypersensitivity can develop as secondary pathology in the course of other dermatoses - e.g. due to sensitization to topical therapeutics used on long-term basis. The emerging secondary ACD may complicate the course of (or even replace) the primary disease. Contraindications for patch testing include immune deficiencies and immunosuppressive treatment (drugs, sunbathing,

sunbeds). Pregnancy and lactation are conditional contraindications, as there are no data on the safety of the test for mother and child.

Application of patch tests

Certain amounts of suspected haptens are applied on the skin for 2 days (48 h), and the subsequent assessment of skin reaction is done after 2, 3 and 4 days. Additional reading after 7 days may reveal up to 10% positive reactions that were negative on previous checks. Examples of haptens, for which allergic skin reaction may develop later than after 4 days are: neomycin, tixocortol pivalate, and nickel. The test substances are applied onto the skin with the use of specially devised chambers mounted on sticking plaster. If possible, patch tests should be mounted on the patient's back. Upper dorsum is the most convenient site for testing - both for doctor and patient, and most of patch test validation was carried out in this area. Therefore, applying tests in other body areas (e.g. arms, forearms, thighs, abdomen) should be restricted to exceptional situations and should be performed by an experienced doctor as there may be difficulties with interpreting the results.

The most widely used patch test application systems nowadays are: squaric IQ Ultra Chambers made of soft polyethylene foam (Chemotechnique Diagnostics), traditional round aluminium Finn Chambers (Epitest), and "T.R.U.E." Test (Thin-layer Rapid Use Epicutaneous Test). IQ Chambers may be filled immediately before testing, or in advance and then stored in a refrigerator for a few days. However, the concentration of volatile substances (e.g. fragrances) may significantly decrease over time, therefore, the storage time should be kept to minimum. Finn Chambers have to be filled with test substances immediately before application. "T.R.U.E." Test is loaded with haptens already during production. The material, of which the chambers are made may influence the reliability of patch tests: e.g. Finn Chambers are made of aluminium, which may come into (or catalyse) chemical reactions with test substances (e.g. thimerosal or mercury). Therefore, one should choose Finn Chambers, in which aluminium is covered by a polypropylene layer. IQ Ultra Chambers are made of chemically inert polyethylene, which does not react with the haptens and does not sensitize patients. The shape of the test chamber may also influence the final reading: IQ Ultra Chambers and "T.R.U.E." Test are square-shaped, which allows a better discrimination between allergic and irritant reactions. In the allergic reaction, inflammatory infiltrate typically expands beyond the borders of the contact area, which can be seen as "rounding" of the testing areas' corners. In contrast, irritant reaction is typically restricted to the area of contact, so that the shape of the inflamed skin area remains sharp (compare Fig. 1).

Vehicles for test substances

White petrolatum (pet.) and water (aq.) are most frequently used vehicles (solvents) for patch test substances. In some cases, haptens are also dissolved in olive oil, rape oil, acetone, alcohol etc. Typically, 20 µl of petrolatum-based test substances or 30 µl of liquid preparations are loaded into chambers. The accuracy of the volume is one of the factors that determine the test's reproducibility. "T.R.U.E." patches are filled with test substances already during production phase, which ensures the accuracy of hapten dosage. Overall, the sensitivity of patch test is influenced by the choice of application system: Comparative studies have demonstrated that patch test applied with IQ Chamber is more sensitive than "T.R.U.E." Test, which again is slightly more sensitive than patch test with the traditional Finn Chambers.

Selecting haptens for patch testing

Test substances should be chosen accordingly to clinical picture and patient's history, and include haptens suspected of provoking the disease. As in many cases the history does not give clues specific enough for the clear identification of offending haptens, epidemiological situation in a given area or a risk group should also be taken into account. This means that "test series" of haptens should be applied in every patient next to suspect substances indicated by the clinical picture and history. Test series are collections of substances that are the most frequent sensitizers in the population of a given geographical area (e.g. country or continent) or groups of specific exposure (e.g. occupational, lifestyle, certain risk factors). Test series are periodically updated, accordingly to recent epidemiological trends. In Europe, the "European Baseline Series" (EBS, previous name: "European Standard Series") is recommended by the European Society of Contact Dermatitis and European Environmental Contact Dermatitis Research Group as the first choice for testing patients with the suspicion of contact allergy. After last revision in March 2008, the EBS consists of 28 test substances (single haptens or hapten mixes). In Table 1, a comparison of European Baseline Series, North American Series (NAS), the International Standard Series (ISS), and "T.R.U.E." test is given. Although "T.R.U.E." series is not a standard, it is cited here as an "instant" patch test product, which is used by doctors who like to keep their contact allergy diagnostics at basic level. "T.R.U.E." test is a closed system with pre-selected 29 substances only (24 in some countries). There is no possibility of adjusting the list of tested substances to the actual patient's history of exposures and clinical picture of the disease.

Table 1. A comparison of 4 popular patch test series. NAS – North American Series; EBS – European Baseline Series; ISS – International Standard Series; "T.R.U.E."– Thin-layer Rapid Use Epicutaneous Tests

Test substance	NAS	EBS	ISS	"T.R.U.E."
Amerchol L 101	+			
Bacitracin	+			
Myroxylon pereirae (Balsam Peru)	+	+	+	+
Benzocaine	+	+		
Black rubber mix		a		+
Budesonide	+	+	+	
4-tert-Butylphenolformaldehyde resin	+	+	+	+
2-Bromo-2-nitropropane-l,3-diol	+			
Caine mix				+
Carba mix	+	b		+
Quaternium 15	+	+	+	+
Kathon CG	+	+	+	+
4-Chloro-3,5-xylenol	+			
Cinnamic aldehyde	+			
Clioquinol		+		
Cobalt (II) chloride	+	+		+
Cocamidopropylbetaine	+			
Colophonium	+	+	+	+
Compositae mix	+			
Dimethyloldihydroxyethyleneurea	+			
2,5-Diazolidinylurea	+			+
Disperse Blue mix 106/124	+			
DMDM Hydantoin	+			
Epoxy resin	+	+	+	+

Test substance	NAS	EBS	ISS	"T.R.U.E."
Ethyl acrylate	+			
Ethylenediamine dihydrochloride	+	c		+
Ethyleneurea, melamine formaldehyde mix	+			
Formaldehyde	+	+	+	+
Fragrance mix	+	+	+	+
Fragrance mix II	+	+		
Glyceryl monothioglycolate	+			
Glutaraldehyde	+			
Hydrocortisone-17-butyrate	+			
2-Hydroxy-4-methoxybenzophenone	+			
Imidazolidinyl urea	+		+	+
Iodopropynyl butyl carbamate	+			
N-Isopropyl-N-phenyl-4-phenylenediamine	+	+		
Lyral		+		
Mercapto mix	+	+	+	+
2-Mercaptobenzothiazole	+	+	+	+
Primin		+		
Methyldibromoglutaronitrile	+	+	+	
Methyl methacrylate	+			
Mixed dialkyl thiourea	+			
Neomycin sulfate	+	+	+	+
Nickel sulfate	+	+	+	+
Paraben mix	+	+		+
4-Phenylenediamine	+	+	+	+
Potassium dichromate	+	+	+	+
Propylene glycol	+			

Test substance	NAS	EBS	ISS	"T.R.U.E."
Quinoline mix		d		+
Sesquiterpenelactone mix	+	+		
Thiomersal		e		+
Thiuram mix	+	+	+	+
Tixocortol-21-pivalate	+	+	+	+
Toluene sulfonamide formaldehyde resin	+			
Triamcinolone acetonide	+			
Wool alcohols (lanolin)		+	+	+

(a) in 1995, black rubber mix was replaced in EBS by the major sensitizing component of the mix IPPD; (b) Carba mix was withdrawn from EBS in 1988; (c) Ethylenediamine dihydrochloride was withdrawn from EBS in 1995; (d) Quinoline mix was replaced in 1995 by Clioquinol - the major sensitizing component of the mix; (e) Thiomersal is known as a "non-allergen" - a large proportion of population is patch test-positive due to vaccinations with thiomersal-preserved vaccines, however, there are only a few cases of ACD caused by thiomersal.

Interpretation of patch test results

When a person is sensitized to a given hapten, inflammatory reaction will develop in the exposed area. The intensity of the reaction is scored and recorded according to the rules of the International Contact Dermatitis Research Group (ICDRG), presented in Figure 1. The reading and interpretation of patch results requires training and some experience (Tab. 2). Crucial is doctor's ability to differentiate between specific allergic reactions and irritant ones, which is not always easy. For example, persons tested with 1% cobalt chloride may develop local microscopic bleeding from capillary vessels (*petechiae)* due to the irritant properties of cobalt. Inexperienced investigator might misinterpret such reddish efflorescences as erythema, leading to a false conclusion of cobalt allergy. Similar changes can also be provoked by p-phenylenediamine (PPD), N-Isopropyl-N-phenyl-p-phenylenediamine (IPPD) and certain drugs. While testing with corticosteroids, it must be kept in mind that beside their possible allergizing potential, corticosteroids are inhibitors of allergic inflammatory reaction. Therefore, in case of CA to corticosteroids, positive reactions may be considerably weaker, develop with delay, and sometimes take annular shape (lower concentration, thus lower anti-inflammatory effect at edges of the test area).

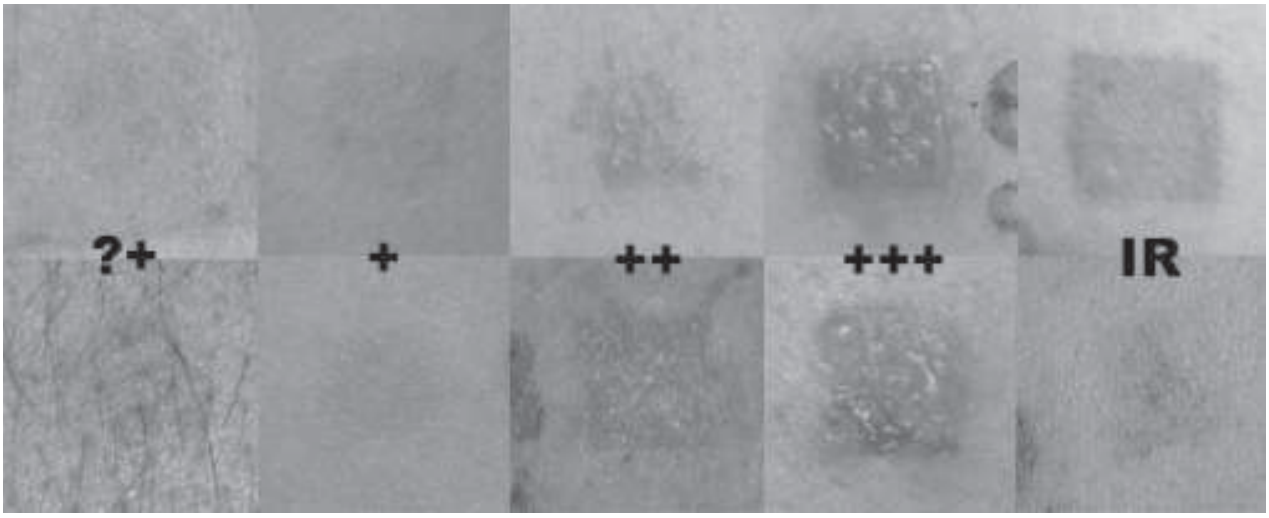

Figure 1. The notation of positive patch test results.
(A colour version of this figure is printed on the back cover of this book)

Table 2. Notation of positive patch test results- compare Fig. 1.

Description	Interpretation	Notation
No skin changes in the tested area	Negative	"-" or "Ø"
Faint, non-palpable erythema	Doubtful reaction; most authors do not consider this kind of reaction as a proof of sensitization	"?" or "?+"
Palpable erythema - moderate edema or infiltrate, papules not present or scarce, vesicles not present	Weak positive reaction	"+"
Strong infiltrate, numerous papules, vesicles present	Strong positive reaction	"++"
Coalescing vesicles, bullae or ulceration	Extreme positive reaction	"+++"
Inflammation sharply limited to the exposed area, lack of infiltrate, small petechiae, pustules, and efflorescences other than papules and vesicles	Irritant reaction; this kind of reactions may cause many problems upon interpretation	"IR"
Not tested		"NT"

Clinical relevance of a positive patch test reaction

A positive result of a patch test is not equivalent with the diagnosis of allergic contact dermatitis. Some persons with positive patch tests will never experience any clinical symptoms after exposure to the hapten. Therefore, the clinical relevance of a positive patch test should be considered in each case. This means answering to the question ”does the positive patch test result really explain the patient’s symptoms?”. In such assessment, the COADEX classification may be very helpful (Table 3). At this stage, it should also be clarified, whether the sensitizing hapten originates from occupational sources or not. In many cases, this is important from legal point of view.

Table 3. The COADEX system for assessing the clinical relevance of positive patch test reactions (a modification)

Code	Meaning
C (current)	Current relevance: The patient has been exposed to the hapten prior to the current episode of dermatitis, improvement of the disease after cessation of exposure
O (old)	Old or past relevance: Past episodes of dermatitis from exposure to the hapten
A (active sensitization)	Actively sensitized: Patient presents with a sensitization (late[a]) reaction
D (doubtful)	Relevance difficult to assess, no traceable relationship between positive test and the disease
E (exposed)	History of previous exposures that did not cause dermatitis
X (cross-reaction)	The positive test is due to cross-reaction with another hapten that is really of clinical relevance

[a]Active sensitization during patch testing is extremely rare and most of late patch test reactions will fall into another categories of relevance.

Patch testing in children

A recent study from our group has demonstrated that every second child with eczema is diagnosed with contact allergy, whereas in every third such child the final diagnosis is allergic contact dermatitis. Nowadays, most authors suggest patch testing children exactly the same way as adults, although some suggest halving concentrations of certain test substances (nickel sulfate, formaldehyde, mercaptobenzothiazole, mercapto mix, para-

phenylenediamine, thiuram) when testing children under 5 years old.

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An introduction into photopatch testing

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In photoallergic contact dermatitis (PACD), an additional factor required for the development of skin symptoms is the light, typically ultraviolet (UV) light. Following photoactivation, precursors are converted into offending haptens. Diagnosis of PACD requires respective modifications of patch tests: 1) applying double sets of test substances, and 2) irradiating one of these sets with an appropriate dose of UV. The application of photopatchs test in patients with suspicion of photocontact dermatitis is presented on the example of the following case (Figures 1-4).

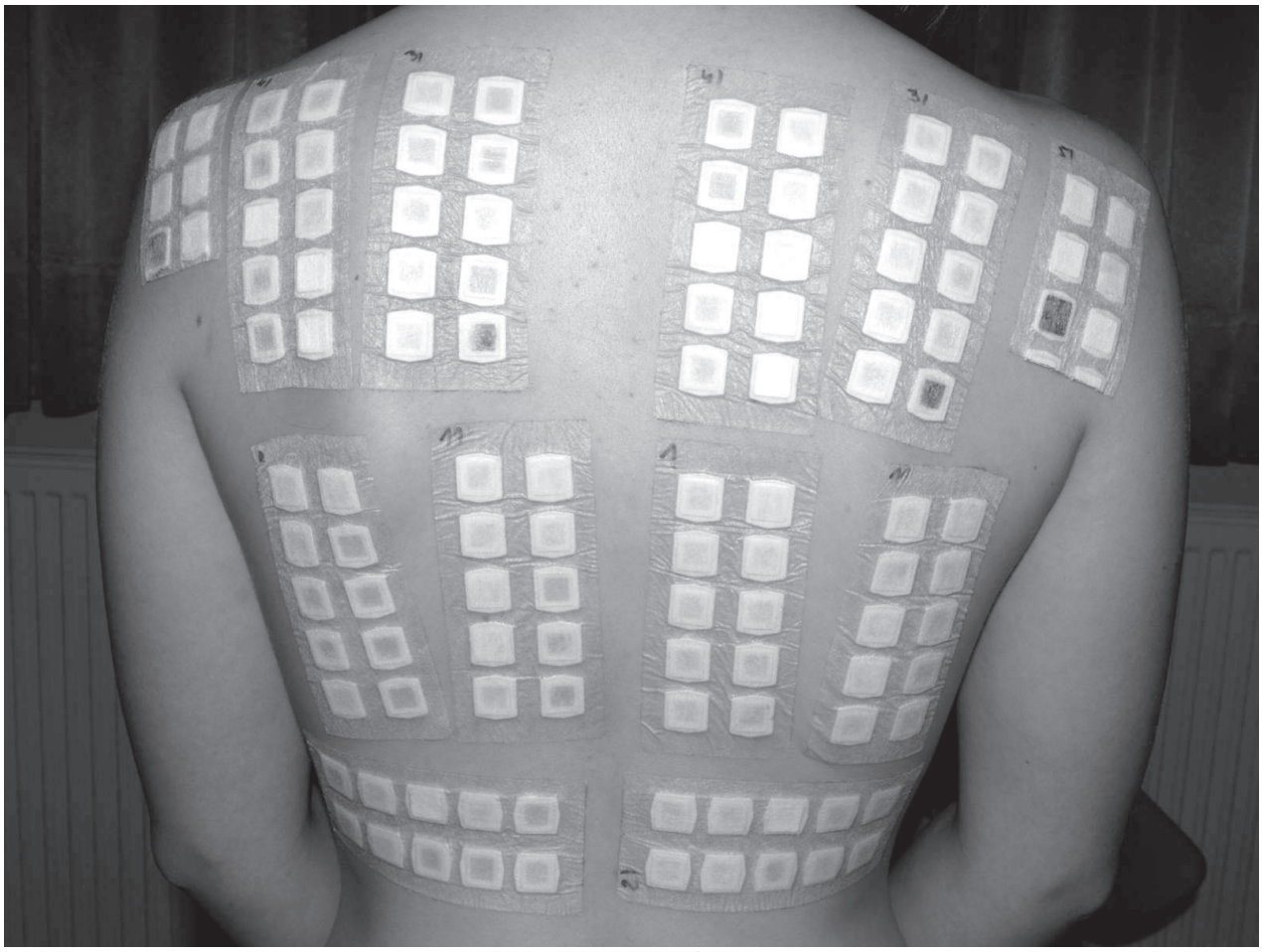

Figure 1. This 22 years-old patient complained of "sun allergy". She noticed that she can tolerate the sunlight when taking no medicines. Our extensive photoallergy series (Table 1) was supplemented with 7 drugs and a sunscreen that she admitted to use at the time of the occurrence of her symptoms.

Table 1. Photoallergy series used in the patient

Parsol 1789	4-Aminobenzoic acid (PABA)
Homosalate	2-Ethylhexyl-4-dimethylaminobenzoate
Parsol 5000	Benzophenone-10
Benzophenone-3 (Oxybenzone)	Mexoryl SX
Parsol MCX	Triclocarban
Novantisol	Promethazine hydrochloride
Benzophenone 4 (Sulisobenzone)	3,4,5-Tribromo-salicylanilide
Drometrizole trisiloxane (Mexoryl XL)	Chlorpromazine hydrochloride
Octocrylene	6-Methyl coumarine
Octyl salicylate	Bithionol
Octyl triazone	Fentichlor
Isoamyl-p-methoxycinnamate	(+)-Usnic acid
Tinosorb S	Atranorin
Tinosorb M	Wood mix
Uvinul A Plus	Evernic acid
Neoheliopan AP	Balsam Peru *(Myroxylon pereirae)*
Uvasorb HEB	3,3',4',5-Tetrachloro salicylanilide
Polysilicone-15	Hexachlorophene
Ketoprofen	Chlorhexidine digluconate
Etofenamate	Triclosan
Piroxicam	Diphenhydramine hydrochloride
Diclofenac	Perfume mix
Ibuprofen	

Table 2. Patient's own drugs/cosmetics supplementing the above series

Mercilon (desogestrel+ethinylestradiol)	Duac gel (benzoyl peroxide + clindamycin)
Diane-35 (cyproterone+ethinylestradiol)	Tetralysal (lymecycline)
Voltaren Emulgel 1% (diclofenac)	Bioderma Photoderm Kid 50+
Olfen (diclofenac)	

A digression

The patient – a medical student – has used regularly or occasionally a dozen of drugs, including contraceptives, painkillers and acne therapeutics. This does not seem an exception, as uncontrolled consumption of therapeutics (OTC and Rx) seems quite frequent among young people in Poland. In a recent survey of 105 Public Health students in Krakow, 100% admitted to using OTC, 98% to using Rx drugs, and 39% have had drugs with them while answering the questionnaire. As many as 30% of surveyed students have experienced at least 1 episode of adverse drug reaction ever in life [1]*. In another study of 205 Polish students, we have found that 5 (2.4%) reported on episodes of photosensitivity related to internal, and 2 (1%) - to external drugs* [2]*. Together with the popularity of suntanning among young people, this seems a serious, though unrecognised, threat to public health.*

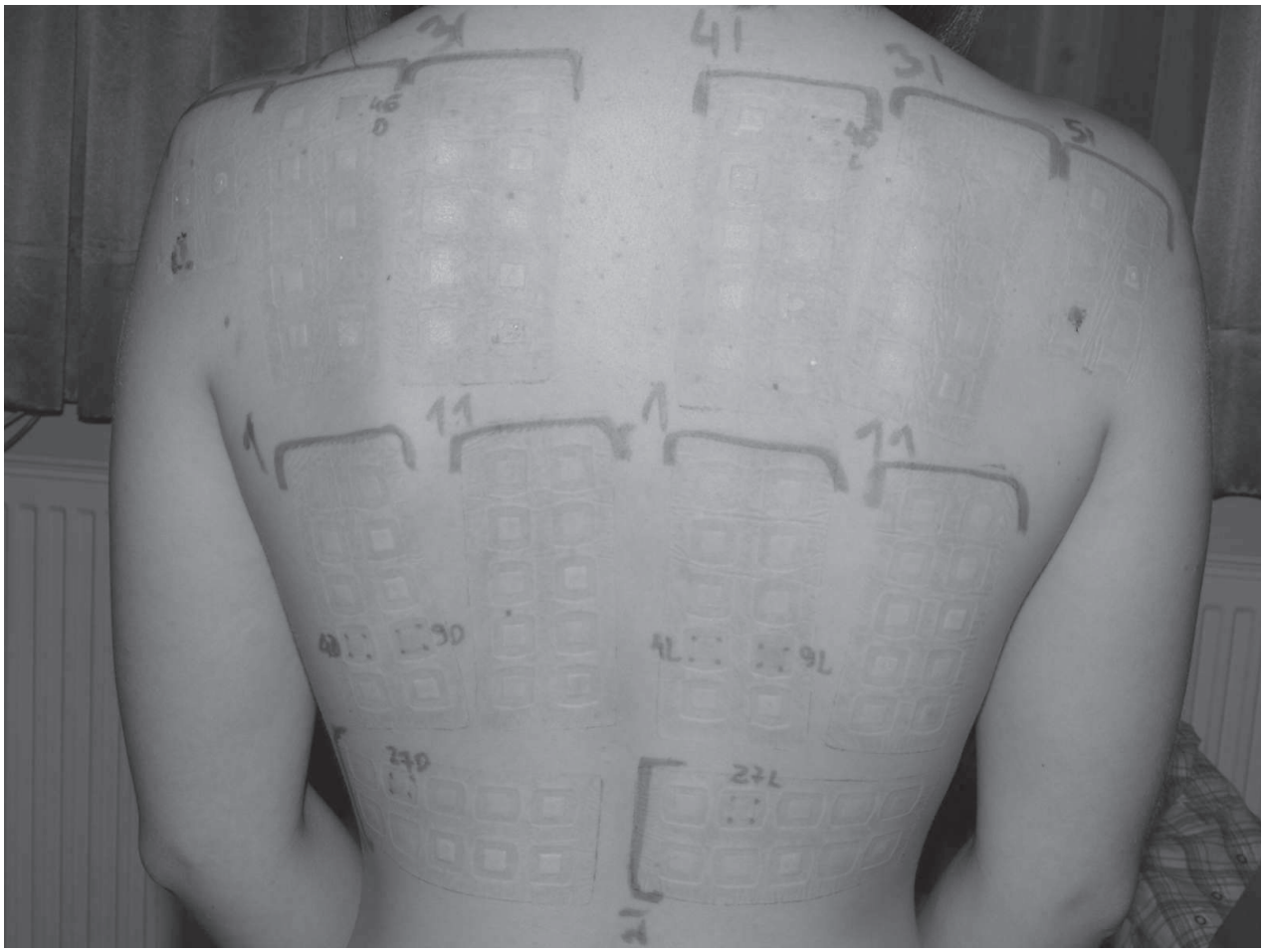

Figure 2. The same patient as in the previous photograph, Day 3 (48 h after application of the tests): Immediately after removing the test chambers, a few positive reactions are already visible before the irradiation ("classical" contact allergy).

In photopatch testing, the test substances (haptens) are applied in two identical sets. The next step is irradiation of one of these sets. Typically, UVA (wavelength 320-400 nm) is used; in rare cases UVB (290-320 nm) may be necessary for the initiation of the photoallergic reaction. The typical UVA dose used is 5 J/cm^2. In patients with suspected or confirmed extreme photosensitivity, 50% of minimal erythema dose (½ MED) should be used. In the case presented here, MED for UVA was greater than 5 J/cm^2, therefore, the standard dose was used. While interpreting the results, reactions on the irradiated side are compared with reactions on the not exposed side [3].

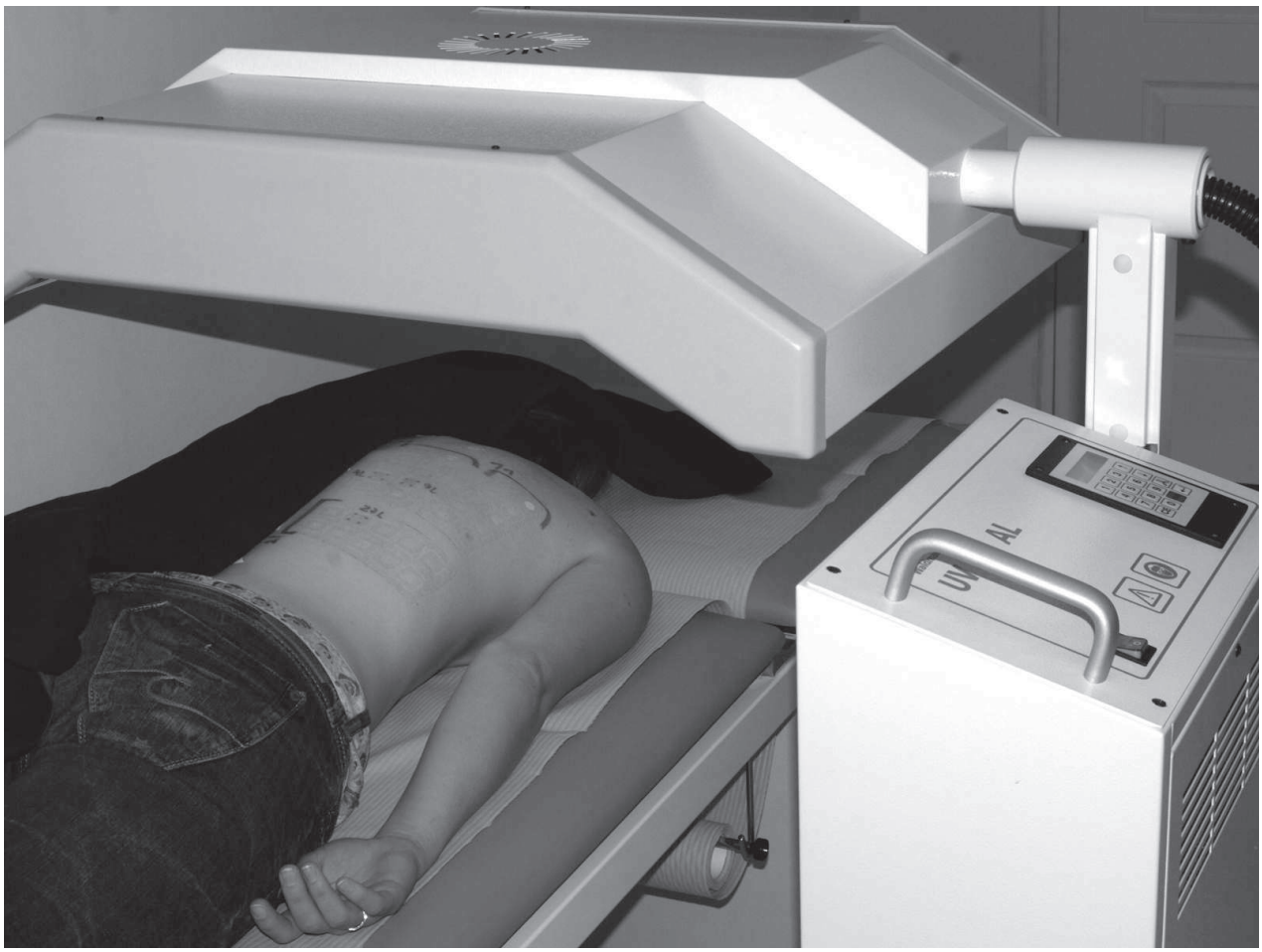

Figure 3. The same patient as in the previous photograph, a few minutes later: One set of patch test substances is exposed to an appropriate dose of UV, while the other one is covered tightly with paper towels and a thick black cloth to prevent accidental irradiation.

A positive test reaction on the irradiated side with negative result on the non-irradiated one confirms photoallergy, while positive results on both sides point on "classical" contact allergy (Tab. 3).

Table 3. Interpretation of photopatch test results

Non-irradiated	Irradiated	Conclusion
□	□	No confirmation of allergy
□	■	Photocontact allergy
■	■	"Classical" contact allergy

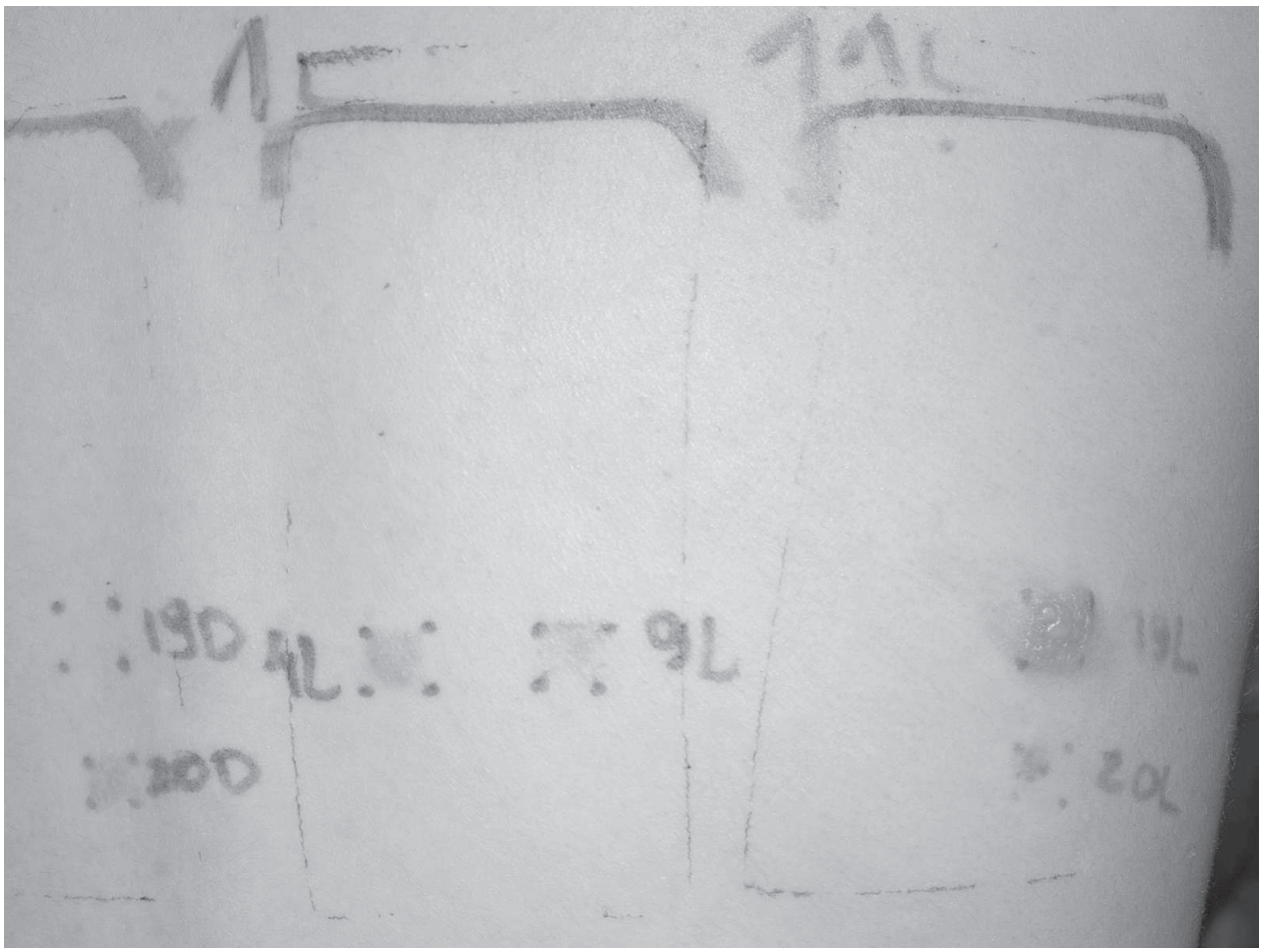

Figure 4. Forty-eight hours after UVA irratiation, an extreme positive reaction with erythema, infiltration, papules and coalescing vesicles (an ICDRG "+++" reaction) develops to a hapten on the irradiated side only (position 19L) with no visible reaction to the same hapten on the non-irradiated side (19D). This pattern suggests a photoallergic reaction to ketoprofen (compare Table 3). In contrast, in both position 20D and 20L, a moderate infiltration with erythema (ICDRG "+") is observed. Equal expression on both irradiated and non-irradiated sides suggests a "classical" contact allergy (compare Tab. 3).

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The influence of light on the skin barrier

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The outermost layer of the skin, the stratum corneum, primarily mediates permeability barrier function. The formation of corneocytes is considered to be result of finely regulated differentiation process. During terminal differentiation process structural change of the keratinocyte is associated with the sequential formation of differentiation marker protein: keratin 5 and 14 present in stratum basale, keratin 1 and 10 in the stratum spinosum and late differentiation marker proteins: filaggrin, loricrin and involucrin in the granular layer. Granular layer is composed of secretory cells producing polar lipids and lipid converting enzymes. Polar lipids are packed into lamellar bodies and secreted into the intercellular space to be converted by enzymes to form non polar lipid structures. The stratum corneum lipid matrix constitutes of ceramides, fatty acids and cholesterol. Small amounts of cholesterol esters and cholesterol sulfates are also present in the stratum corneum and both play a critical role in proper structural organization of the lipids, low pH, lipids crystallization, desquamation process and therefore, in normal barrier function [1].

Solar ultraviolet radiation (UV) is a major environmental factor that dramatically alters the homeostasis of the skin by affecting the survival, proliferation and differentiation of various cutaneous cell types. The horny layer of the epidermis reflecting and/or absorbing about 90% of UVB and 50% of UVA radiation. However, the rest of UV radiation can penetrate into the deeper layers of the epidermis induces DNA damage and apoptosis in epidermal cells, including those in the germinative basal layer. The epidermis contains several major solar UV radiation absorbing endogenous chromophores including DNA, urocanic acid, lipids, melanins and their precursors and metabolites. Melanin plays an important role in protecting the skin against UV radiation and levels of melanin correlate inversely with amounts of DNA damage induced by UV radiation. Epidermal melanocytes synthesize two main types of melanin: eumelanin and pheomelanin. Melanin, particularly eumelanin, represents the major photoprotective mechanism in the skin. Melanin limits the extent of UV penetration through the epidermal layers, and scavenges reactive oxygen radicals that may lead to oxidative DNA damage [2]. Skin pigmentation is accomplished by production of melanin in specialized membrane-bound organelles termed melanosomes and by transfer of these organelles from melanocytes to surrounding keratinocytes.

Urocanic acid (UCA), present in the upper layer of epidermis, is a metabolite of filaggrin. UCA is a major UV-absorbing chromophore in the upper epidermis and has been suggested to act as one of the initiators of UV-induced immunosuppression. Especially, cis-UCA, the isomer from UCA that is formed upon UV exposure, has been shown to impair some cellular immune responses [3]. UV radiation induces pyrimidine dimers in DNA, which are recognized and repaired by a number of unique cellular surveillance systems. The most direct biochemical mechanism responding to this kind of genotoxicity involves direct photoreversal by the enzyme endonuclease. UV-light induces DNA damage in human epidermal keratinocyte triggering p53 activation, and subsequent apoptosis involving distinct cell layers which reduced the carcinogenic effects of sunlight [4].

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The influence of light on the skin immune system

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The results of numerous in vitro and in vivo studies, performed for over 30 years, indicate that ultraviolet radiation (UVR) has the ability to modulate skin immunity. UVR suppresses contact hypersensitivity response what results from functional impairment of the contact between antigen presenting cells and T lymphocytes. Photoproducts formation, generation of hapten-specific T regulatory cells as well UV-mediated release of various cytokines such as IL-1, IL-6, IL-10 and TNF-α from the epidermal cells also take part in the development of photoimmunosuppression. Because of the evident link between excessive exposure to UVR and photoaging and development of nonmelanoma skin cancers, it is obligatory for clinicians, especially dermatologists to spread the knowledge on suppressive effects of UVR. In the lecture molecular basis of UVR influence on human immunity will be discussed.

Photodermatoses – skin diseases induced by light: An overview

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The photodermatoses form a group of conditions induced or aggravated by sunlight. Essentially these are subdivided into the idiopathic (possibly immunologically mediated) conditions, namely, polymorphic light eruption, actinic prurigo, solar urticaria, juvenile spring eruption, hydroa vacciniforme and chronic actinic dermatitis. Drug and chemical induced photosensitivity is subdivided into photoallergy and phototoxicity. Other diagnostic groups include the porphyrias, the genophotodermatoses and the photoaggravated disorders. It is undoubtedly the case that polymorphic light eruption is the commonest of the photosensitivity disorders. This condition, which arises particularly in young women, can persist for the majority of life. Essentially when a patient has one of the idiopathic photodermatoses, they are restricted to the natural history of that disease and its management.

Other photodermatoses are, in comparison, relatively uncommon. Photocontact dermatitis, whether due to photoallergy or phototoxicity is an important diagnosis to make. To label an individual as an endogenous photodermatosis when identification of an allergen an enable preventative medicine, is an unsatisfactory outcome of a visit to the clinic. Key photodermatology investigations are phototesting, including provocation testing, photopatch testing, porphyrin and lupus analysis. The genophotodermatoses require careful laboratory cell mutation studies to define whether a disorder is due to an abnormal helicase or DNA repair function.

Having obtained the diagnosis, the natural history, prognosis and therapeutic options come into play. Each condition has its own particular therapeutic aspects. While milder forms can be managed with simple photoprotective regimes, the more severe quality of life disabling conditions may need our most potent immune suppressive therapies. During this lecture, individual diagnoses and their investigative findings will be discussed.

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Pathomechanisms of phototoxic dermatitis

Radoslaw Spiewak

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A young lady applied herbal mask of common rue *(Ruta graveolens)* onto her face. After that, she took a nap on a balcony in the full sun. An hour later, she woke up with a burning sensation, erythema and oedema of the skin. A few hours later, painful erythema and oedema developed. Subsequently, she developed a bullous reaction, which became superinfected in the following days. After treatment of the secondary infection, the inflammation resolved within 5 days, however, postinflammatory hiperpigmentation persisted over 1 year of follow-up.

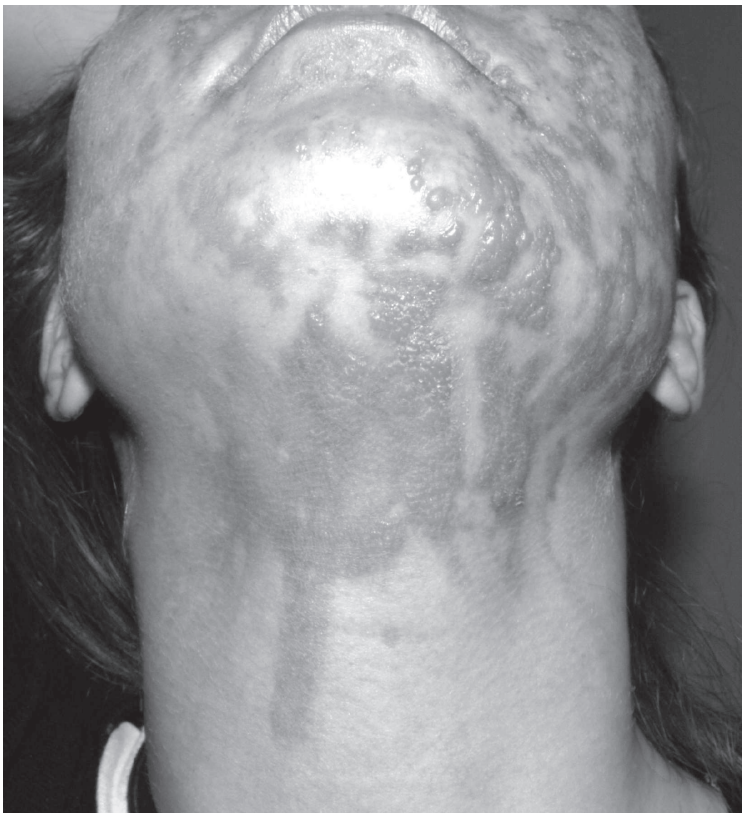

Figure 1. Phototoxic reaction to *Ruta graveolens*

This short clinical history demonstrates typical features of a phototoxic reaction:

- the reaction develops after applying a substance with phototoxic activity.

Common rue contains 5-methoxypsoralen and 8-methoxypsoralen, which are potent phototosensitising agents [1],
- the second factor necessary for provoking the skin reaction is the subsequent exposure to sunlight (in case of psoralens, UVA is the active range of the sunlight),
- the reaction develops within hours (no involvement of time-consuming processes of immunological recognition by antigen-specific lymphocytes),
- phototoxic reactions occur also upon first exposure to phototoxic agent (no sensitization phase is necessary),
- in many cases, the reaction resolves with leaving postinflammatory hiperpigmentation.

What is a phototoxic reaction?

The terms "phototoxic reaction" and "phototoxicity" refer to an inflammatory reaction of the skin, resulting from a direct cellular damage produced by the photochemical reaction initiated by photoactive chemicals (photosensitizers) and the active spectrum of radiation on the skin. The activation spectrum of such photochemicals expands from the UVB to the UVA range [2], however, in a vast majority of patients UVA is the causative factor [3].

There are three elements essential for a phototoxic reaction:
- the radiant energy,
- the chemical,
- the skin (substrate) [2].

Molecules capable of absorbing energy carried by the light are referred to as chromophores. Photobiologic responses induced by reactions initiated by such molecules include sunburn and photosensitivity to chemicals and drugs. There are 2 main pathways of phototoxicity:

- the reactive oxygen species (ROS) pathway,
- the reactive nitrogen species (RNS) pathway.

The most common clinical manifestation of phototoxicity is an exaggerated sunburn-like response in exposed areas. In many cases, this inflammatory reaction is followed by localized hyperpigmentation [4]. In contrast to "classical" sunburn, skin inflammation in the phototoxic reactions is provoked by UV doses that normally are well tolerated by the skin [3]. In contrast to photoallergy, no individual- or photosensitizer-specific predisposition is prerequisite for phototoxic reaction. This means that phototoxicity will occur already upon the first exposure in most persons of the same skin type, as long as both the threshold concentration of the photosentising chemical and the threshold dose of radiation have been reached.

In contrast to photoallergy, no mechanisms of adaptive immunity (specific antibodies or lymphocytes) seem to be involved into phototoxic reaction.

However, an involvement of innate immunity mechanisms was suggested, such as activation of complement [5], proteases [6], and prostaglandin secretion [7].

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Pathomechanisms of photoallergic dermatitis

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The inflammatory skin disease - photoallergic contact dermatitis (PACD), is a clinical expression of specific immune reactions that takes place in the skin, however, also extracutaneous structures (e.g. lymph nodes, circulating and resident lymphocytes) are involved at some stages of the reaction.

The initiation of the disease symptoms requires an interaction of three substantial elements:

- pre-existing contact hypersensitivity to a given photohapten in the exposed individual,
- exposure of the skin to the offending photohapten (via direct contact or blood-borne),
- subsequent exposure to the light with the wavelength capable of interacting with the photohapten (in most cases, UVA is the active spectrum).

Contact allergy (synonym: contact hypersensitivity) is defined as body's readiness to develop an inflammatory reaction against a specific low molecular weight substance (hapten) upon skin contact [1]. By analogy, photocontact allergy (PCA) can be defined as readiness to develop inflammatory response to a photohapten present in the skin upon subsequent exposure to light. The light supplies energy necessary for the conversion of precursors (prohaptens or prehaptens) into the actual sensitizing photohaptens, or for the initiation of binding between hapten and endogenous carrier protein (photobinding) into a full antigen. The term "photocontact allergy" refers to an altered reactivity of the immune system to a given substance, which is not a disease as such. Certain proportion of people with PCA will never develop clinical symptoms [1].

The aetiology of photoallergic reactions remains unknown: We still don't know, why one individual develops a hypersensitivity to a given photohapten, whereas most people tolerate it. It seems that this process is determined by an intricate interplay of multiple factors, including:

- individual susceptibility (large populations are continuously exposed to numerous photohaptens and light, but only a fraction will develop photoallergy),
- intrinsic properties of a photohapten (there is a relatively low number of substances that are the most frequent causes of photoallergy; an important role is ascribed to the chemical's ability to form photobonds - photosensitised chemical bonds with body's proteins; another important

intrinsic property of a hapten is its irritant potency and ability to trigger so-called "danger signals" in the skin),
- environmental and microenvironmental influences, which may play an important role as co-factors in the breach of immune tolerance to the photohapten that results in the development of PCA, e.g. co-existing infections, inflammation, substances with adjuvant properties.

The natural history of contact allergy (and most probably also of photocontact allergy) can be divided into 2 phases:
- induction phase, in which the hypersensitivity to a given (photo)hapten – photocontact allergy – is developed,
- elicitation phase, following the hapten (or photohapten and light) exposure in a sensitised person.

In the induction phase, usually numerous exposures to a hapten are necessary to induce contact allergy [2,3], depending on the hapten's sensitizing potency [4,5]. This altered reactivity may be acquired months or years before the first clinical contact allergic reaction takes place. A similar pattern could also be true for photocontact allergy, although the picture seems more complex due the involvement of the light into these processes: UV-induced damage of the skin may enhance penetration of photohaptens and leads to infammatory reaction that might have an adjuvant effect during the development of hypersensitivity. On the other hand, in everyday circumstances, photoallergy develops under influence of sunlight, which consists not only of UVA, but also of UVB, which is a potent immunosuppressive agent. An impairment of the induction of contact hypersensitivity (CH) to haptens applied to UVB-exposed skin was demonstrated in both animal and human experiments. It has been suggested that these immunosuppressive effects of UVB are primarily mediated by tumour necrosis factor-alpha (TNF-α) [6,7].

Haptens are low molecular weight chemicals too small to be recognised by the adaptive immune system. However, they can bind to endogenous proteins of the body, causing changes in their spatial conformation. This leads to a recognition of resultant molecules as "non-self" and to initiation of immune response. Such complexes are caught and processed by the Langerhans cells (LC) – dendritic cells resident in epidermis, which belong to "professional" antigen presenting cells. While processing the antigens, LC undergo activation and maturation and migrate along lymph vessels to local lymph nodes. During maturation/migration of LC, lipophilic antigens are transported (endocytosis) into the cell. After processing, antigenic epitopes are presented in the context of major histocompatibility complex I (MHC-I), similar to intracellular (e.g. viral) antigens. Hydrophilic antigens are presented in the context of MHC-II, similar to extracellular (e.g. bacterial) antigens. In the lymph node, LC present the antigens to thousands of lymphocytes passing

through the lymph node. This process is random, yet effective due to a very high turn-over of lymphocytes. If there exist naïve T lymphocytes with T-cell receptors (TCR) capable of specific recognition of the presented antigen, these will eventually encounter the LC, recognise the antigen, and start activation and proliferation into antigen-specific effector cells. Depending on the type of antigen and the context, in which the antigen is presented (MHC-I or MHC-II), respectively CD8(+) or CD4(+) lymphocytes will recognise the antigen and proliferate. This phenotype determines further immune reactions, correspondingly to the secretory profile and cytotoxic properties of respective T cell types, which may be Tc1, Th1, Tc2, Th2, possibly also NKT1, NKT2. In the lymph node, antigen-specific lymphocytes are also assigned to the respective target organ (the skin in the case of PACD). During this process, the cells acquire organ-specific "homing antigens", e.g. the cutaneous lymphocyte antigen (CLA). It seems that also chemokine receptors may play role as determinants of the target organ. This "addressing" of the lymphocytes is probably determined rather by soluble factors present in the lymph draining into the lymph node, than the type and origin of the antigen presenting cell itself [8]. After maturation, specific effector lymphocytes migrate to the skin site of the initial hapten penetration and may initiate an inflammatory response there. Some of the effector lymphocytes will turn into long-lived effector memory T cells that will circulate in the body as a part of immune surveillance. Some will reside in the skin, especially in the site of previous hapten exposure (local immune memory). These circulating and resident antigen-specific effector memory lymphocytes are the physical substrate of (photo)contact hypersensitivity.

Subsequent exposures to the offending photohapten and light will result in a cascade of processes referred to as elicitation of photoallergic contact dermatitis. The elicitation phase takes a significantly faster and more violent course. At this stage, the involvement of professional antigen presenting cells is no longer prerequisite. Sufficient for the initiation of the immune response is antigen presentation by keratinocytes (KC), which constitutively express MHC-I, moreover, they can also express MHC-II in a range of skin conditions. Notably, tumour necrosis factor alpha (TNF-α) – a potent stimulator of MHC-II expression on KC, is released in large amounts upon UVB irradiation, which may play an important role in the elicitation of photoallergic contact dermatitis [9].

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The epidemiology of photoallergy

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Photoallergy is investigated by photopatch testing, but due to the multiple steps involved, methodology can vary greatly. Over the past 3 decades, groups have attempted to standardise photopatch testing methodology within different European countries. Recently, a European consensus methodology has been published to further aid standardisation and facilitate accurate comparison of results between centres [1]. The precise incidence of photoallergy is not known. Results from a U.K.-wide multicentre study of organic sunscreen filters demonstrated a frequency of 4% for photocontact allergy alone and 5% for contact allergy alone. This study also emphasised the importance of testing the patients own products [2].

Presently, a European multicentre photopatch test study is underway to determine the frequency of photoallergy to 19 organic sunscreen filters and 5 topical nonsteroidal anti-inflammatory drugs (NSAIDs). In preparation for this, a pilot study was conducted in one U.K. centre investigating the irritant potential of the 19 sunscreen filters used in the present Europe-wide study. This demonstrated that 18 filters could be used at concentration of 10% for photopatch testing and one, benzophenone-4, should be used at a concentration of 2%, due to its higher irritant potential.

An interim analysis of the results of the present European study has shown that 2 NSAIDs, ketoprofen and etofenamate, appear to produce a high frequency of photoallergy. Although leading to fewer reactions than these 2 NSAIDs, the organic sunscreens octocrylene and benzophenone-3 appear to cause more photoallergic reactions than other sunscreens. The importance of testing the patients' own products is again evident, with high numbers of reactions to proprietary preparations. Similar to previous studies, the number of reactions showing photoaugmentation and photoinhibition of contact allergy remains low. However, contact allergy alone to agents remains important in numerical and clinical terms.

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History of photopatch testing

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Photoallergic reactions were observed for the first time after the introduction of sufonamides in the 1930s. Somewhat later, phenothiazines gained interest as photosensitizers. In order to accomplish a correct diagnosis and to detect the causative agent first attempts to perform photopatch testing were undertaken in the late 1930s. Stephen Epstein was the first researcher, who described in detail the methodology of photopatch testing in 1939. In Germany, K.S. Schulz performed extensive studies employing photopatch testing in order to evaluate the photosensitivity to phenothiazines. During the years 1962 to 1970, halogenated salicylanilides were identified as the cause of widespread outbreaks of photoallergy. The photosensitivity was traced down to the use of deodorant soaps and cosmetics containing salicylanilides as antimicrobial agents. Since then, the photopatch test has been adopted in clinical dermatology as the gold standard of investigation to identify photoallergens. However, until the early 1980s, photopatch testing was not standardized. The procedure varied between dermatology centres, among different countries and internationally, as has been shown by a worldwide survey.

The first attempt to standardize the method was initiated by the Scandinavian Photodermatitis Research Group (SPDRG) in 1982. Stimulated by the result of the above mentioned international survey, and following the example of the SPDRG, 45 dermatology hospitals in Germany, Austria, and Switzerland formed in 1984 a Photopatch Test Group in order to perform an epidemiological study on photoallergens, and also to finally standardize the procedure. The first report of this large group appeared after 5 years, and the final results after 12 years. In both test periods, nonsteroidal anti-inflammatory drugs, disinfectants, and phenothiazines were the leading photoallergens in the central European region. Sunscreens were the most frequent photoallergens relevant to the investigated clinical picture. By using computer assisted reaction-pattern analysis, substance specific reaction patterns could be distinguished. Test modifications after the first period led to a remarkably improved specificity of the procedure.

Following this example, a multicentre photopatch study group was established in the U.K. with similar aims. Here, sunscreens were detected as the most frequent photoallergens, not only causing photosensitivity but also contact sensitivity. Large photopatch test studies were also reported from New York (monocentre study), and Italy (multicentre study). These efforts led finally to the initiation of a European Photopatch Test study group. The participants are currently investigating photosensitivity caused by photoallergens throughout Europe, following a consensus methodology.

Photopatch tests: consensus methodology, present standard procedures

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The European Taskforce for Photopatch Testing, an initiative of the European Society for PhotoDermatology and the European Society of Contact Dermatitis, published in 2004 a consensus methodology on photopatch testing. This is an important step in standardization. The test procedure, for general purposes, will be explained.

The light source, patch test materials, allergens, application period and the reading method are standardized. As light source is chosen a broad-spectrum fluorescent PUVA lamp. The allergens, placed preferable in Finn chambers, are applied in duplicate to the upper back and covered with opaque material. After 24 or 48 hours the materials are removed and one site is irradiated with 5 J/cm^2, the non-irradiate site is again covered with opaque material after the first reading. The standard photopatch test series consists in organic sunscreens and NSAIDs. Readings are performed direct after removal of the allergens and again after the irradiation. The next readings are preferably 48 hours and 72 or 96 hours post-irradiation.

The reading of patch tests is always a two-step procedure. First step: scoring of the reaction without any interpretation of the nature of the reaction. Second step: interpretation of the nature of the reaction. The scoring of the reactions is according the standard ICDRG scoring system for patch tests: ranging from ?+ through +++. The interpretation of the photopatch test may be difficult. Regarded as a positive photopatch test is a reaction (> ?+) at the irradiated site and negative at the non-irradiated control site. Positive reactions at both sites are not regarded as positive photopatch tests but as positive contact reactions, which can be aggravated at the irradiated site by the UV-light. The relevance of a positive reaction depends on the possible exposition to the allergen in combination with UV, dermatitis in the correct topographically area and there should be a time correlation.

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Selected slides

Please note: to ensure the unified look of the book, the slides were adjusted, therefore, they appear slightly different from those displayed during the lecture.

Current photopatch test method

Uniform method, like for allergic contact dermatitis, for photo-allergic (systemic) dermatitis

accepted by:

European Society for Photodermatology (ESPD)

and

European Society of Contact Dermatitis (ESCD)

Photopatch test method

For general purposes:

- preferable only minimal variations

(comparability of results / publications)

For questionable points:

- research

Photopatch test method

- Light source, energy dose
- Patch test materials
- Allergens
- Application period
- Readings
  - Grading
  - Interpretation

Irradiation

- UVA source: PUVA fluorescent lamps
  broad-spectrum
- 5 J/cm2 (or 50% MED)

Patch test materials

- Finn chambers on Scanpore tape
- UV opaque covering material

Photoallergens

Working Party (ESPD - ESCD)

- Selection of allergens
- Evaluation of allergens

Continuous process

Standard photopatch test series

Standard photopatch test series

- Organic sunscreens
- Topical NSAIDs

Patients own products

European photopatch test series

Sunscreen agents (INCI)	conc.	CAS no.
Octyl methoxycinnamate	10%	5466-77-3
Benzophenone-3	10%	131-57-7
Octyl dimethyl PABA	10%	21245-02-3
PABA	10%	150-13-0
Butyl methoxydibenzoylmethane	10%	70356-09-1
4-Methylbenzylidene camphor	10%	36861-47-9
Benzophenone-4	10%	4065-45-6
Isoamyl p-methoxycinnamate	10%	71617-10-2
Phenylbenzimidazole sulfonic acid	10%	27503-81-7

European photopatch test series

Non-steroidal anti-inflammatory agents	conc.
Naproxen	5%
Ibuprofen	5%
Diclofenac	5%
Ketoprofen	2.5%

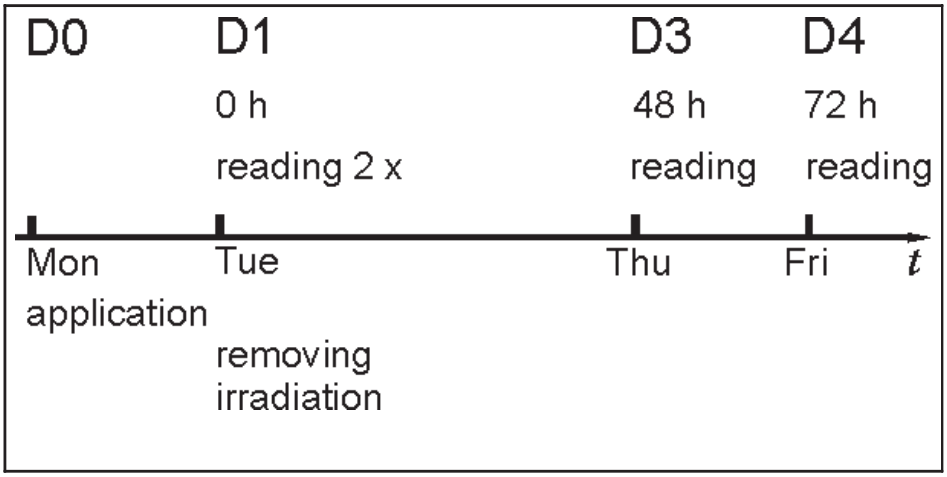
Hermal–Trolab Patch Test Allergens, Reinbek, Germany
Chemotechnique Diagnostics Vellinge, Sweden

Application

- Upper back skin
- Duplicate sets
- Application period 24 or 48 h
- After which both are removed (D1 or D2)
- 1 set is covered with UV opaque material
- Other set is irradiated

Timing of readings

- Pre-irradiation
- Immediately post-irradiation
- 48 h post-irradiation (D3 or D4)
- 72 and 96 h desirable (D4/5 or D5/6)



Readings

Reading is a 2-step procedure:

- Scoring: according to the ICDRG scoring system
- Interpretation: is the reaction positive or negative or perhaps false positive?

ICDRG scoring system

?+ (doubtful):	faint erythema
+ (weak):	erythema, infiltration, possible papules
++ (strong):	erythema, infiltration, papules, vesicles
+++ (extreme):	erythema, infiltration, coalescing vesicles/bulla

Interpretation

Positive reaction:

- control site negative
- photopatch test site positive

False positive photopatch test:

weak irritant/allergic reaction + subclinical UVA effect ⇔ photoaggravation

Relevance

[Clinical aspect of (photo-)dermatitis, positive photopatch test reaction]

- Exposure to photo-allergen
- Exposure to UV-light
- Dermatitis on exposed sites
- Time relation

COADEX

C = current relevance
O = old relevance
A = actively sensitized
D = do not know relevance, cross-reaction
EX = positive reaction:
- exposure history, no dermatitis
- no-exposure history

Therapeutic options for photoallergy

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In brief, therapy of photoallergic diseases consists of the avoidance of the causative substance and the avoidance of sun exposure. Thus, the first step of therapy of photoallergy consists in an accurate diagnosis by identifying the culprit agent so that it can be avoided. Also, avoidance of sunlight is important, by using sunscreens and/or wearing hat and long-sleeved dress made of UV-absorbing textiles. If the photoallergic reaction has already occurred, symptomatic treatment using topical steroids or systemic antihistamines can be used. Also topical calcineurin inhibitors (pimecrolimus, tacrolimus) have been used successfully. On the other hand, topical antihistamines should be avoided as they may cause photoallergic reactions themselves. Desensitization is rarely successful, but can be tried in some cases of very mandatory drugs.

In chronic photosensitive disorders that may result in actinic dermatitis, therapy becomes more challenging. Here, sometimes immunosuppressive agents such as cyclosporine A or azathioprine can be tried. There are also reports that UVB or PUVA-therapy might be useful.

Treatment options for solar urticaria include non-sedating antihistamines such as fexofenadine and cetirizine; other options include absorbent sunscreens, restriction of UV radiation at the relevant wavelength, maintenance of the non-responsive state with natural or artificial light exposure and, in very rare cases, plasmapheresis.

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Photoallergic contact dermatitis to terbinafine

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A 60-year old male patient started oral terbinafine therapy for his onychmycosis in the first days of a sunny autumn. On Day 6 of the therapy, he first noticed a moderately itching skin rash on his forehead and dorsal aspects of hands. The rash aggravated on the following day, after spending approx. 1 h in midday sun. Suspecting a causal connection between his skin problems and the newly-started terbinafine, the patient discontinued the drug on Day 8. The progression of dermatitis continued. Finally, erythema, oedema and scaling covered the face, décolleté and dorsal neck with sparing of shaded areas and scalp. The patient showed for examination on Day 12, after orbital swelling appeared overnight. After introduction of local mometasone, oral prednisone and fexofenadine, all skin symptoms significantly improved overnight. On Day 14, there were no more symptoms, and the therapy was discontinued.

Photopatch tests were carried out with an extensive series of photoallergens (cosmetic ingredients, sunscreens, drugs), as well as with all medications that the patient was receiving at the time of the above-described episode: terbinafine, metizol, tolperisone, lansoprazole, perindopril, trimetazidine, bisoprolol. The only observed positive reaction was to terbinafine: According to the ICDRG scale, the reaction was (+) after 72 hours of application to the skin (24 h after irradiation of the site with 5 J/cm^2 UVA) and (++) after 96 hours (48 h after irradiation). The test reaction to terbinafine alone (no irradiation) remained negative, thus indicating on "pure" photoallergic reaction. Based on the positive photopatch test result, delayed onset and progression of the disease after discontinuation of the drug, the final diagnosis is photoallergic contact dermatitis to oral terbinafine.

Terbinafine is capable of inducing a wide array of cutaneous adverse drug reactions, ranging from toxic epidermal necrolysis to drug-induced cutaneous lupus erythematosus and psoriasis. To the author's best knowledge, there were no published reports of photoallergy to oral terbinafine.

When to suspect a photoallergic reaction?

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Photoallergic contact dermatitis is thought to occur when an exogenous agent combines with a carrier molecule within the skin in the presence of light, to create an antigenic complex. Currently, the best method of investigating photoallergy in humans is photopatch testing. Sunscreens and topical nonsteroidal anti-inflammatory drugs (NSAIDs) are currently the commonest photoallergens.

Indications for photopatch testing include:
1) Any photo-exposed site dermatitis
2) Precipitation or aggravation of a dermatosis by sunlight
3) History of sunscreen reaction
4) History of topical NSAID reaction
5) Deterioration of photosensitivity in a pre-existing photodermatosis (e.g. Polmorphic Light Eruption - PLE, Chronic Actinic Dermatitis - CAD, lupus).

Contraindications include:
1) Extreme photosensitivity
2) Age less than 5 years
3) History of anaphylaxis to agent
4) Xeroderma pigmentosum.

Patients should be aware that there are benefits and disadvantages to having photopatch tests performed and it is their choice on whether to proceed with the investigation.

Benefits include:
- The patient becomes aware of contact and photocontact allergens they should avoid
- Testing is a relatively non-invasive procedure
- Negative results are still useful in the differential diagnosis
- Results aid research.

Disadvantages include:
- Time needed (3-5 days)
- Expenses/travel involved
- No washing of test area
- Keeping the test area out of the sun
- Angry back / worsening of pre-existing dermatitis

- Florid positive reactions
- Exposure and sensitisation to agents to which they may not otherwise have come into contact with.

To perform photopatch testing, the clinician should have as a minimum, a radiation source, test agent(s) and a method of recording results. Due to the multiple steps involved in photopatch testing, there have been differing methodologies over recent years. However, a European consensus methodology now exists to allow better comparison between centres. For photopatch testing photosensitive patients, a dose 50% that of the UVA MED or the dose below the MED has been suggested.

Reference

Bruynzeel DP, et al. Photopatch testing: a consensus methodology for Europe. J Eur Acad Dermatol Venereol 2004; 18: 679-682.

Occupational photocontact allergy produced by carprofen

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A 42-year old had an 18-month history of recurrent episodes of facial dermatitis that she attributed to working with Rimadyl® (a non-steroidal anti-inflammatory drug [NSAID], carprofen, used in veterinary medicine). By the time she attended the dermatology clinic this problem had caused her to resign from her work in a pharmaceutical factory. Patch testing and photopatch testing showed photoallergy to carprofen.

The same year, a 47-year old was admitted with erythrodermic dermatitis. Chronic actinic dermatitis was considered, amongst other possible diagnoses, but excluded by normal phototesting and patch testing. Later, it became evident that remissions of dermatitis, which tended to affect exposed sites more than covered sites, coincided with periods off work. She was a secretary in the same factory that the first patient had worked in. At first, her dermatitis remained undiagnosed; subsequent investigation included patch testing and photopatch testing to carprofen, which revealed both contact allergy and photoallergy. Although her exposure was indirect these results did appear relevant and her skin only completely cleared once she got a new job.

There are limited reports of patch testing and photopatch testing to this chemical so we tested controls. We stopped this after one of three controls developed active photoallergic sensitisation. After occupational health input to the factory, several members of staff there were referred of whom a further 3 were found to have carprofen photoallergy.

This NSAID appears to be a potent photoallergen with sensitisation possible after limited exposure. It remains in use in veterinary medicine and therefore photopatch testing should be considered in pet owners who present with an exposed site dermatitis.

Reference

Kerr AC, et al. Occupational carprofen photoallergic contact dermatitis. Br J Dermatol 2008; 159: 1303-1308.

Patient's and doctor's safety during photopatch testing: Possible risks and precautions

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Cutaneous adverse drug reactions including photoallergy and phototoxicity are a frequent problem in clinical medicine. Skin tests including photopatch tests with drugs can be helpful in determining the cause of adverse reaction. To obtain a reliable result, one must use an adequate concentration of a drug, but in most cases there is no standardization and a dose is established based on doctor's experience. Another aspect is to use an adequate dose of UVB and UVA, however in some cases it also should be modified, depending on the patient's skin phototype. At last one must remember that in some cases both false positive and false negative results can be obtained, thus interpreting must be very careful. The patient must be aware that performing skin tests may give no answer to his problem. These and other aspects of photopatch tests will be discussed during the lecture.

Managing photopatch test results: How should we interpret these?

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When reviewing the photopatch test literature, there is no doubt that a number of problems emerge. Probably the most obvious of these is the difference in methodologies used and published by different groups. It was in recognition of this that a consensus methodology for Europe was produced and published [1].

Other problems that have significantly bedevilled the literature and in no small way have been responsible for the underuse of photopatch testing, are the presence of false-negative and -positive photopatch test results. When using the consensus methodology in a multicentre photopatch test study group in the UK [2], photoaugmentation and photoinhibition was encouraged to be recorded as part of the standard photopatch test technique. In addition, crescendo and decrescendo patterns illustrating photoallergy and phototoxicity (irritancy) [3] are important when deciding the mechanism. Finally, when obtaining a true positive reaction, a decision is required as to the relevance of the readings. One such system that is in routine use within the European Multicentre Study currently underway is COADEX (C = current relevance; O = old or past relevance; A = actively sensitised; D = do not know; and EX = no history of exposure) [1].

With careful interpretation, the photopatch test technique provides essential management information. Too often we have patients with a suspected photodermatoses who have not had photopatch testing conducting with the consequences of a misdiagnosis. Both contact and photodermatology investigational clinics should make good use of this investigation which currently is underused. Why should this be? To some extent the addition of an extra parameter, i.e., ultraviolet A, has resulted in this investigation falling between two stools. Careful evaluation of the results is essential as part of restoring the confidence in this underemployed technique.

References

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Photocontact allergic and phototoxic studies of chlorproethazine

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Neuriplege® cream was available as a non-prescription medication in France as a muscle relaxant, until its removal from the market in January 2007. The active ingredient is chlorproethazine (CPE), a derivative of the phenothiazine chlorpromazine. We investigated the photocontact allergic and phototoxic potential of Neuriplege® cream and CPE by means of an in-vitro phototoxic study and volunteer photopatch testing.

The in-vitro phototoxicity study was performed in HaCaT keratinocytes using the neutral red dye phototoxic assay, which showed clear evidence of phototoxicity. The concentration of CPE required to reduce dye uptake by 50% was 0.9 μg/ml in the presence of 5 J/cm^2 UVA light and 11.9 μg/ml without UVA light exposure. Therefore, a one hour incubation of keratinocytes with CPE was approximately 13 times as toxic to the cells in the presence of UVA light compared to incubation with the drug alone.

Of 2 healthy volunteers photopatch tested to Neuriplege® cream, one developed a phototoxic reaction. These 2 volunteers were then photopatch tested to Neuriplege® and CPE with 7 additional healthy volunteers. Both of the initial study volunteers revealed a photocontact allergic reaction to the Neuriplege® as is upon re-exposure and one also reacted to 10% CPE in white soft petrolatum (WSP). Of the 7 volunteers not previously exposed to Neuriplege as is, 5 developed phototoxic reactions, with similar but less pronounced phototoxic reactions seen when 10% CPE was used.

These studies demonstrate the strong phototoxic and photocontact allergic sensitisation potential of CPE in Neuriplege® cream. Its previous availability to consumers within the European Union means many have been sensitised.

Reference

Kerr AC, et al. Photocontact allergic and phototoxic studies of chlorproethazine. Photoderm Photoimmunol Photomed 2008; 24: 11-15.

Differential diagnosis of photoallergic skin diseases

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A vast variety of dermatoses must be taken into consideration in order to encompass the differential diagnosis of photoallergy (PA). Inflammatory skin diseases occurring on sun exposed sites are to be considered and differentiated by the clinical picture, history, histology, and phototesting. Classical photoallergic dermatitis is characterized by a pruritic eczematous reaction on sun exposed body areas. Photopatch testing is decisive to detect the culprit photoallergen. Systemic photoprovocative testing may be employed, when a photosensitive drug is suspected to induce the reaction.

Primary and secondary photodermatoses must be ruled out. Polymorphic light eruption (PLE) is characterized by plaques, papules and vesicles, but not classical eczema. Furthermore, PLE occurs only in certain exposed sites and rarely in all sites, unlike PA. Also, PLE tends to ameliorate during the summertime and photopatch testing is negative. Other primary photodermatoses present different clinical pictures: In solar urticaria (SU) urticarial plaques develop within minutes after sun exposure and vanish after cessation of the irradiation in a short period of time. Phototesting leads here quickly to the correct diagnosis. Hydroa vacciniforme occurs in children, while PA does not, and the clinical picture is characterized by a vesicular reaction followed by the development of scars. Actinic prurigo occurs at any age, starting in childhood. It is characterised by a very pruritic reaction, undistinguishable from classical prurigo. Photopatch test is negative. Chronic actinic dermatitis affects mostly old men, sometimes starting with a classical PA. The eczema may generalize and affect also covered body regions. In later stages lichenification is a hallmark of this immensely torturing disease.

The main differential diagnosis in the group of secondary photodermatoses is photoprovoked atopic dermatitis, since here one encounters also an eczematous reaction in sun exposed areas. Here, history and also other characteristic clinical and laboratory signs of atopy lead to the correct diagnosis. Many patients of this group start with a classical atopic dermatitis and develop the photosensitivity only in later stages. Other secondary dermatoses, which can easily be differentiated by history, clinical picture, histology, and phototesting include lupus erythematosus, erythropoetic protoporphyria, dermatomyositis and rosacea. Airborne contact dermatitis (ABCD) may be undistinguishable from PA. Here, history, photopatch test and patch test including plant allergens, will enable the correct diagnosis.

Photosensitivity induced by quinidine sulfate: Experimental reproduction of skin lesions

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A case of quinidine sulfate-induced photodermatitis is presented. The photosensitivity reaction to quinidine sulfate was reproducible in the photopatch test and after oral intake subsequent to UVA irradiation. Eczematous dermatitis was provoked by intradermal injection of in vitro UVA-irradiated quinidine sulfate only in the presence of the patient's serum. Clinical picture and histology suggest an allergic reaction.

The photobinding of quinidine sulfate to a potential carrier protein in skin or serum seems to be of crucial importance to this type of photodermatitis. Quinidine sulfate is frequently used as antiarrhythmic drug. Its potential as photosensitizer should be carefully considered.

Photoallergy Meeting and Photopatch Test Course
Krakow, Poland, 18-19 September 2009

Photoallergy to Neotri and a cross reaction to Teneretic: Detection by systemic photoprovocation

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A patient is presented, who suffered for three years of increasing photosensitivity with chronic eczematous lesions in sun-exposed areas. He had taken one tablet Neotri (xipamide, triamterene) daily for 6 years. After discontinuation of the drug photopatch testing and phototesting failed to reveal pathological reactions. Eczematous lesions, however, were induced in test areas upon systemic photochallenge with Neotri. One year later, the antihypertensive medication was changed to Teneretic (atenolol, chlortalidone) and the eczematous photosensitive reaction recurred.

Since both xipamide and chlortalidone have a chlorsulfamoyl-substituted aromatic ring in common, it seems that a photoallergic cross-reaction has occurred.

Photoallergic and phototoxic disorders of the ethnic skin

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In comparison to the Caucasian skin type, the Afro-American skin type - or skin type IV - is much less sensitive to sunburn. However, also the ethnic skin is able to tan and can even get sunburned if not continuously sun-exposed. In addition, also a large variety of photosensitive disorders are common in Africans, such as cutaneous LE, drug-induced eruptions and some forms of atopic dermatitis. Vitiligo is a common disease leading to easier sunburn and also socio-psychological problems. In addition, several hereditary pigmentary disorders are quite frequent due to consanguinity among various tribes. Xeroderma pigmentosum, and especially oculo-cutaneous albinism lead to heavily increased susceptibility against sun, premature skin ageing, as well as early and often invalidating squamous skin cell carcinomas. Besides these medical problems, albinos often face severe social problems, ranging from being excluded from society up to being killed for their fair skin, which is said to have aphrodisiac effects according to some archaic beliefs. Finally, hypoalimentation may lead to nutrition disorders with associated photosensitivity: Pellagra and pellagroid are quite common in some regions depending on seasonal changes of staple food supply.

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Annex

European Society of Contact Dermatitis

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The purpose of the ESCD is to promote interest, stimulate research, and disseminate information on all aspects of contact dermatitis and other environmental and occupational skin diseases.

To this end the ESCD arranges congresses covering its entire field every other year and supports symposia or conferences confined to themes of special interest.

"Contact Dermatitis" is the main journal of the ESCD for publication of clinical and scientific reports. The society also issues a periodic Newsletter for the benefit of the members.

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The Institute of Dermatology Ltd. in Krakow (Cracow), Poland, is an independent organisation founded to promote modern, evidence-based dermatology. Our mission is to achieve better health and quality of life of people suffering from skin diseases, as well as to prevent skin diseases before they arise. Our strategy for achieving this goal includes research & development, as well as education of doctors, other specialist active in the field of skin health (beauty therapists, hairdressers), and patients. Institute's priority activities include:

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