

Diagnosing Allergic Contact Dermatitis Through Elimination, Perception, Detection and Deduction

Korbkarn Pongpairoj¹ · Pailin Puangpet² · Supitchaya Thaiwat³ · John P. McFadden⁴

© Springer International Publishing Switzerland 2017

Abstract Several authors have commented upon the skills of detection required in making a diagnosis of allergic contact dermatitis. Here, we emphasise the search for clues in a systematic manner. We describe four stages as part of a systematic method for diagnosing allergic contact dermatitis. Firstly, elimination (or inclusion) of non-allergic diagnoses. Secondly, perception: the pre-patch test diagnosis and the ‘three scenarios’ principle. Thirdly, detection: optimising the sensitivity of the patch test process. Fourthly, deduction: diagnosing allergic contact dermatitis by associating the dermatitis with the allergen exposure. We further compare and contrast the pre-patch test history and examination with the markedly different one (‘micro-history’ and ‘microexamination’) used after patch testing. The importance of knowledge of contact dermatitis literature is emphasised with a review of recent publications. Finally, we also highlight the use of contact allergy profiling as an investigative tool in the diagnosis of allergic contact dermatitis.

Key Points

The four steps to diagnosing allergic contact dermatitis are (i) elimination (or inclusion) of non-dermatitis dermatoses and non-allergic dermatitis, (ii) perception of a pre-patch test diagnosis, (iii) detection of contact allergy by patch testing and (iv) deduction of a diagnosis of allergic contact dermatitis by correlating the exposure to the allergen(s) in terms of dose, time and contiguous aspects with that of the dermatitis.

The pre-patch test history should have a wide scope to check for exposure to a wide range of allergens.

In contrast, once a contact allergy (or allergies) has been identified, the post-patch test history should have a very narrow scope, focusing on exposure to the allergen in question to correlate, in minute detail, the nature of the dermatitis (‘microhistory’ and ‘microexamination’).

Contact allergy ‘profiling’ is an important investigative tool in the diagnosis of allergic contact dermatitis.

✉ Korbkarn Pongpairoj
korbkarnp@hotmail.com

¹ Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Thai Red Cross Society, 1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand

² Institute of Dermatology, Bangkok, Thailand

³ Division of Medicine, Dermatologic Department, Phramongkutklao Hospital, Bangkok, Thailand

⁴ Department of Cutaneous Allergy, St. John’s Institute of Dermatology, Guy’s Hospital, King’s College, London, UK

1 Introduction

The investigation of possible allergic contact dermatitis (ACD) is based upon a systematic search for clues. A striking similarity between the skills of the great fictional detectives such as Sherlock Holmes and those required to diagnose contact dermatitis has been noted by several authors. Goossens [1] comments on the detective skills

involved in assessment of contact dermatitis patients. Belsito [2] remarks on the need for diagnostic clues to solve puzzling clinical presentations. Here, we crystallise this concept further, reviewing how detection skills are utilised in diagnosing ACD. The term ‘Friday Method’ is used as most contact dermatitis clinics have their final reading and assessment on Friday, and can be best summarised as the relentless search for diagnostic clues in a systematic way. The four steps involved are

1. ‘elimination’ (or inclusion) of non-allergic diagnoses;
2. ‘perception’: reviewing the different scenarios of the pre-patch test diagnosis;
3. ‘detection’: maximising the sensitivity of the patch test investigation;
4. ‘deduction’: achieving a diagnosis of ACD by associating the temporospatial nature of the allergen exposure to the temporospatial nature of the dermatitis.

These four specific steps will be discussed within the context of differences between the pre- and post-patch test history and examination in the hands of the clinically experienced patch tester. The concept of ‘contact allergy profiling’ as an investigative tool is also discussed.

2 Diagnosing Allergic Contact Dermatitis: A Simple and Obvious Exercise?

The notion of ACD usually being not only from direct contact but also clinically obvious is a common but misplaced one. The presentation of obvious axillary ACD to fragrance after deodorant use may be a classical but relatively uncommon mode of presentation. For example, only 50% of patients presenting with ACD to hair dye will be aware of this possibility [3]. Only 25% of patients found to be allergic to fragrance give a pre-patch test history of reacting to fragrance/fragranced products (Thaiwat unpublished observation 2016). ACD to other allergens such as preservatives may be even less evident. ACD from direct contact is only one clinical presentation of contact allergy. A recent International Contact Dermatitis Research Group (ICDRG) classification documents 16 different clinical presentations of contact allergy (Table 1) [4].

3 The Pre-Patch Test History and Examination

3.1 Pre-Patch Test History: The Need for a ‘Wide Scope’

There are two components to the pre-patch test history; firstly, regarding the nature of the dermatitis and secondly,

Table 1 Proposed ICDRG classification of the clinical presentation of contact allergy [4]

1. Direct exposure/contact dermatitis
2. Mimicking or exacerbation of pre-existing eczema
3. Multifactorial dermatitis including allergic contact dermatitis (ACD)
4. By proxy
5. Mimicking angioedema
6. Airborne contact dermatitis
7. Photo-induced contact dermatitis
8. Systemic contact dermatitis
9. Non-eczematous contact dermatitis
10. Contact urticaria
11. Protein contact dermatitis
12. Respiratory/mucosal symptoms
13. Oral contact dermatitis
14. Erythroderma/exfoliative dermatitis
15. Minor forms of presentation
16. Extracutaneous manifestations

ICDRG International Contact Dermatitis Research Group

exposure to potential contact allergens. Questions regarding the location and temporal nature of the rash are essential, but ascertaining where the rash originated on the body is important, as an underemphasised characteristic of ACD is its ability to spread [5].

The pre-patch history of exposure to potential allergens should have a ‘wide scope’ or extensive and wide anamnesis (Fig. 1) [6]. This is because of the following:

- (a) There are numerous contact allergens in the environment. Even the most basic baseline series contain at least nine groups of contact allergens (i.e. metals, fragrances, dyes, medicaments, plants, preservatives, rubber chemicals, resins and vehicle excipients). In addition, there are also more specialised allergens represented in many different series, such as hair-dressers, dental, medicament, extra cosmetic, plastic/glues series, which may need to be tested for, depending upon the pre-patch test assessment.
- (b) There are at least 14 different specific aspects of everyday life where there is potential for contact allergen exposure (Table 2).
- (c) There are six different routes of exposure to contact allergens (Table 3). Whilst it is easy to remember direct contact and airborne contact, one can easily forget other routes (e.g. ‘by proxy’).

There are therefore many potential different permutations of how an individual can be exposed to contact allergens.

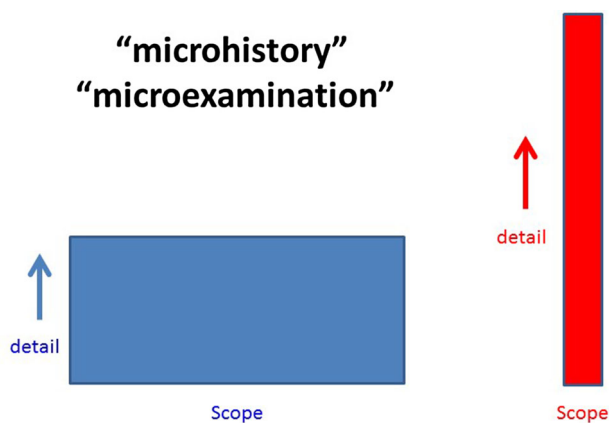


Fig. 1 Pre-patch test ‘scoping’ history and examination versus post-patch test history and examination. The pre-patch test history and examination should have a wide ‘scope’ to screen for potential exposure to multiple allergens from different types of activities (see Table 2) and with different routes of exposure (see Table 3). In contrast, after patch testing, the scope narrows to focus on the potential allergen(s) identified through patch testing so that exposure to specific allergen(s), and the potential association with the dermatitis can be assessed in minute detail (microhistory and microexamination)

Table 2 Aspects of daily life with potential for contact allergen exposure

1. The use of personal care products/cosmetics
2. Cosmetic procedures (e.g. hairstyling/dyeing, nail manicures, waxing)
3. The home environment, including use of household products, furnishings, and home decorating and cleaning
4. The work environment
5. Other environments (e.g. shops, friend’s house)
6. Leisure and sport activities
7. The wearing of clothes, shoes, gloves and hats
8. The use of personal appliances such as spectacles, hearing aids, walking sticks, cutlery, scissors, pens, laptop computers and mobile phones
9. The use of medications, herbal and ‘alternative’ agents
10. The wearing of jewellery and other ornamentation
11. Medical, dental and surgical procedures
12. Travel including car driving, cycling and holiday environment
13. Dietary and mucosal exposure
14. Close physical intimacy
15. Other aspects of daily life

3.2 Pre-Patch Test Examination: Local and Distal Sites

Examination should include both local and distal site examination. Clues may be ascertained from both. For example, a patient presenting with facial rash may show at local site examination bilateral eyelid dermatitis consistent

Table 3 Different routes of exposure to potential contact allergens

Routes of exposure	Examples
Direct exposure	Plaster applied to skin
Airborne exposure	Fragrance, epoxy, parthenium
Hand to face/body	Hand moisturisers, nail varnish
Systemic exposure	Certain fragrance chemicals
By proxy	Partner’s aftershave
Mucosal exposure	Toothpaste, eye drops, dental amalgam

with an airborne exposure, but distally a patchy dermatitis on the neck and upper chest suggestive of nail varnish allergy from hand to neck/body route of exposure and periungual/nail fold dermatitis from direct exposure to nail varnish. In addition, many patients will have pictures of acute exacerbations of their dermatitis stored on their mobile phones, adding a temporal aspect to the physical assessment.

4 The Four Steps in Diagnosing Allergic Contact Dermatitis

4.1 Elimination (or Inclusion) of Non-Allergic Diagnoses

This step is equally as important as the others, as in most contact dermatitis clinics there is a positive patch test rate in only 50–60% of patients tested and, in addition, some patch test reactions are not of current relevance. There are three broad diagnostic groups to consider, the first being non-dermatitis dermatoses such as psoriasis and tinea. Tinea can easily be missed, especially if treatment/steroid modified. At St. John’s, we see four patients with tinea manuum annually that have been referred for patch testing [7].

The second diagnosis to consider is endogenous or reactive dermatitis such as atopic and seborrhoeic dermatitis. ACD often co-exists with endogenous dermatitis, and indeed one clinical presentation of contact allergy is an apparent worsening of an endogenous dermatitis [4].

Finally, there is irritant contact dermatitis. Irritant exposure can occur within the home, work and leisure environments and be additive between them. Both the intensity and duration of exposure to irritants is important in assessing this factor. Irritant contact dermatitis may also be part of a multifactorial dermatitis as it can co-exist with ACD and patients with a history of atopic dermatitis are also prone to developing irritant contact dermatitis [8].

Searching for diagnostic clues can help in this step. As an example, non-pustular psoriasis of the hands may be clinically evident with loosely bilateral areas which are

well defined and contain silvery scale, but sometimes this is not the case. However, there may be a family history, 30% of patients will have classical body plaques and 85% will have plantar psoriasis. Manual workers with non-pustular palmar psoriasis will more likely have involvement of the pressure areas of the hand (thenar, hypothenar, palmar areas, volar aspects of fingers and margin of palmar hand) [9].

4.2 Perception: Pre-Patch Test Diagnosis and the ‘Three Scenarios’ Principle

After an initial consultation and examination in a contact dermatitis clinic, it is common practice to formulate a working ‘pre-patch test’ diagnosis. Amongst other considerations, this is to ensure optimal testing with appropriate patch test series. A ‘three scenarios’ approach can be a useful tool to reach such a working diagnosis.

4.2.1 Scenario 1

The ‘diagnosis certain’ scenario. There is a reasonable certainty of the diagnosis. For example, in a patient presenting with inflammation of the scalp 6 h after hair dye application, a diagnosis of ACD may appear certain. However, irritant contact dermatitis can present in a similar manner—the hair dye process is alkaline which can lead to delayed inflammation; the presence of pre-existing scalp inflammation (e.g. seborrhoeic dermatitis) and exposure to hair dye for a prolonged time can both predispose to an irritant contact dermatitis. The principle is that one should attempt to form a differential diagnosis even when the diagnosis appears to be certain.

4.2.2 Scenario 2

The ‘competing diagnoses’ scenario. If there is a differential diagnosis without there being a single strongly favoured diagnosis, assess each competing diagnosis carefully for the one with the least irregularities. It is possible in this scenario as well that there may be coexisting diagnoses. Airborne ACD and facial seborrhoeic dermatitis may resemble each other but the absence of seborrhoeic eczema at distal sites, especially the scalp, in the presence of significant facial involvement, together with a history of exposure to airborne allergens (e.g. methylisothiazolinone from wet paint) would favour a diagnosis of airborne ACD.

4.2.3 Scenario 3

The ‘diagnosis unclear’ scenario. If at the end of the pre-patch test consultation there is no working diagnosis, there should be a further search for clues in a systematic manner.

- Recheck the history. Sometimes, instead of taking a history chronologically from when the rash started to the present day, it may be worth taking the history in reverse chronology; that is, from the present day and working back in time. When taken this way some patients will remember or emphasise different details.
- Recheck the examination, ensuring that you examine as extensively as possible by examining areas away from the main rash as well as the main site of dermatoses. For example, search for psoriasis of the knees, elbows, scalp and nails in a patient with facial dermatosis.
- Check for the possibility that topical/oral steroids or other immunosuppression could have made a dermatoses or infestation unrecognisable, or ‘incognito’.
- Check for the possibility of ACD ‘by proxy’ which usually presents in a ‘bizarre’ way without clues in the history.
- Think of the ‘mimicking’ diagnoses in dermatology: lupus, mycoses fungoides, syphilis, sarcoidosis and ACD to the hair dye allergen p-phenylenediamine (PPD) can not only be great ‘mimickers’ but also great ‘disguisers’.
- Exclude dermatitis artefacta.
- Perform extensive rather than limited patch test screening.
- Consider further investigations such as biopsy, microbiological and chemical pathology screening.

The principle here is that if the diagnosis is unclear one should keep searching for clues, but in a systematic way.

4.3 Detection: Optimising the Sensitivity of the Patch Test

Patch testing involves a controlled elicitation reaction to a contact allergen. It detects the immunological state of contact allergy [10]. ACD is the elicitation of an eczematous reaction to an allergen in clinical (normal life) conditions. The presence of contact allergy opens the potential for a diagnosis of ACD, but this depends on the next phase of deduction. A negative patch test (assuming no error or false negative reaction occurred) excludes the possibility of ACD.

One way of approaching patch testing is to simply order the baseline series for testing. However, to maximise the sensitivity of patch testing one should be proactive. There are several ways to enhance the sensitivity of patch testing.

1. One should have a low threshold for adding extra series. As an example, the plant series should be added not only for gardeners or people who garden regularly, but also for patients who regularly use cosmetics with multiple plant materials added. Adding a fragrance series of the 26 individual fragrances listed in toiletries

within the EU will increase detection of fragrance allergy by more than 50% compared with testing with the standard series fragrance mixes alone [11].

When a specific allergy is suspected, one can add extra individual allergens to the baseline series to increase sensitivity. For example, if hair dye is suspected, adding in toluenediamine to the standard series, which normally relies only on the response to PPD, will increase diagnosis of hair dye allergy by 15% [12]. A further example is adding amerchol and crude lanolin when lanolin allergy is suspected. Adding compositae mix in addition to the sesquiterpene lactone mix in the standard series will increase detection of compositae allergy by over 20% [13].

2. Test with patients' own samples. These should include 'leave-on' toiletries, clothing, woods, plastic materials (e.g. spectacle frames) and leaves of plants. Some agents (e.g. wash-off cosmetics, resins) need to be diluted and others (e.g. wood shavings) should be tested with a larger aluminium chamber. As an example, testing with shoe samples increases the sensitivity of detecting shoe contact allergy by up to 20% [14]. Patch testing with patients' own shoes should be performed using pieces of at least 1 cm² and less than 2 mm thick to minimise false negatives and irritant pressure reactions [15].
3. If medicament, fragrance or metal allergy is suspected, deferring the last reading or adding in a further reading at 7 days will increase sensitivity [16–18].

4.4 Deduction: Diagnosing Allergic Contact Dermatitis by Associating the Dermatitis with the Allergen Exposure

4.4.1 Utilising Knowledge of Contact Dermatitis Immunology to Assess Relevance of Exposure

To help identify relevant exposure, some cursory knowledge of the immunology of ACD is utilised. A sensitisation induction reaction occurs at a minimum of 10–21 days after allergen exposure. An elicitation reaction occurs usually within 48 h of allergen exposure [19]. Most clinical cases of ACD reactions occur within 48 h of exposure to the allergen and are, therefore, by definition, elicitation reactions. It therefore follows that most cases of sensitisation to contact allergens are quiet (the sensitisation to PPD from an extremely high dose in temporary beach tattoos being an exception). For an elicitation reaction to occur, this will depend upon the extent of sensitisation that has previously been induced factored with the immunological dose of allergen exposure experienced. ACD reactions therefore occur when either of these increase to a

certain threshold. Levels of sensitisation will increase with repeated exposure to an allergen from a single source (e.g. PPD from intermittent dyeing of hair) or from multiple sources (e.g. exposure to methylisothiazolinone in shampoos, conditioners, moisturisers and wet wipes). Alternatively, the 'immunological dose' may increase from alterations in the nature of exposure. Common examples of increasing the immunological dose are given in Box 1.

Box 1 Common examples of increasing the 'immunological dose' of contact allergen exposure

Changing to a darker hair dye (e.g. blonde to black), which will increase exposure to aromatic amine allergen as much as tenfold [20]

Applying allergen with an agent with irritant/adjuvant properties; for example, fragrance applied with aluminium salts in a deodorant, which are not only astringents used in deodorants but also adjuvants used in vaccines [21]

Applying allergen onto inflamed skin so that 'danger signals' are already present; for example, fragrance in aftershave applied to facial skin with seborrhoeic eczema

Exposure to an allergen for a more prolonged period of time; for example, increasing weekly hours worked in a construction job with subsequent longer exposure to epoxy resin

4.4.2 Microhistory and Microexamination

To diagnose ACD, one needs to causatively associate the temporal and spatial exposure of the contact allergen identified as positive by patch testing with the temporal, morphological aspects and localisation of the dermatitis. Thus, the post-patch test history and examination differs from the pre-patch test history and examination, in some ways being its polar opposite. Instead of having a wide scope in order to explore the full possible range of exposure to potential allergens, the post-patch test history and examination now narrows the scope and focuses on the exposure to the contact allergen(s) identified by patch testing and its relationship to the dermatitis in minute detail.

In a scoping history one may ask 'Do you use perfume spray?' In a 'microhistory', by contrast, one will ask 'How many times a day do you use perfume spray? How much do you use per application? Where on your body do you apply the spray? How long does the spray bottle last for?' To illustrate the large inter-individual variability of personal care product use, Loretz and colleagues [22] reported on the cosmetic uses of 360 American women aged 19–65 years (Table 4). With use of perfume spray, an individual on the 10th percentile will apply once per day whilst the women on the 90th percentile will apply three times per day. When we look at the amount sprayed per

Table 4 The wide interindividual variability in the use and application of various personal care products amongst 360 adult women from the normal general population (2006) [22]

	Spray perfume	Aerosol hairspray	Liquid foundation	Body wash	Shampoo	Solid antiperspirant
Ratio of the number of applications to the number of use days						
Mean	1.67	1.49	1.24	1.37	1.11	1.3
Minimum	1.00	1.00	1.00	1.00	1.00	1.0
10th percentiles	1.00	1.00	1.00	1.00	1.00	1.0
90th percentiles	2.86	2.14	1.86	2.00	1.43	2.0
Maximum	11.64	5.36	2.00	6.36	2.14	4.0
Average amount of the personal care product used per application (g)						
Mean	0.33	2.58	0.54	11.76	11.3	0.61
Minimum	0	0.05	0	0.39	1.10	0
10th percentiles	0.06	0.66	0.08	3.90	4.60	0.14
90th percentiles	0.68	5.33	1.23	22.59	21.1	1.25
Maximum	5.08	14.08	2.65	67.89	58.2	5.55

**Fig. 2** Axillary dermatitis involving axillary vault with apparent spreading from the original site which is characteristic of allergic contact dermatitis

application, the women on the 10th percentile will use 0.06 g per application whilst the women on the 90th percentile will spray 10 times more per application. An individual on the 90th percentile for both number of applications per day and amount used per application, compared with an individual on the 10th percentile for

**Fig. 3** Neck dermatitis from allergic contact dermatitis to the necklace

both, will be exposed to 30 times more fragrance from spray application. In quantitative terms, an affirmative answer to the daily use of spray perfume means little without more details a ‘microhistory’ would give.

Likewise, a ‘microexamination’ may reveal more clues than an examination. An examination (Fig. 2) may reveal axillary dermatitis. A microexamination will reveal axillary dermatitis going into the vault with apparent spread from the original site, characteristic of ACD. A distal examination may reveal further clues; for example, dermatitis from ACD to airborne fragrance on the eyelids or from direct contact on the hands and neck. Another case examination (Fig. 3) reveals neck dermatitis. A microexamination reveals patchy lichenified eczema with pigment change, indicative of chronicity, correlating with skin contact to the patient’s favourite necklace. Distal examination such as dermatitis consistent with jean button dermatitis and wrist bracelet dermatitis gives further clues towards a diagnosis of ACD to nickel.

5 Knowledge of Contact Dermatitis Literature

Acquiring a working knowledge of contact dermatitis literature is a key requirement in optimising practice. Journals such as *American Journal of Clinical Dermatology*, *Contact Dermatitis*, *Dermatitis* and the *Journal of the American Academy of Dermatology* should be routinely reviewed to assure that one is kept up to date with recent advances. We have broadly divided the literature into the following subheadings, with examples from recent papers given.

5.1 Classical Papers and Reviews

An original report on shoe dermatitis, delineating the six patterns of dermatitis (dorsa of feet and toes, sides of feet, heel area, anterior part of soles and toes, strap and buckle area and sole area) is still relevant today [14]. A more recent review assesses the diversity of potential shoe allergens [15]. For example, tanning agents which are potential allergens include not only chromate but also formaldehyde, 2-*n*-octyl-4-isothiazolin-3-one and vegetable tanning agents such as quebracho, bark, myrobalan, mimosa, and chestnut extracts. The authors of this review also comment on plasticisers benzoyl peroxide and butyl phthalate as potential shoe allergens.

5.2 Patch Test Technique

A recent comprehensive guideline for diagnostic patch testing [10] has recommended that occlusion time should stay at 48 h. They also recommended that there should be at least two readings at two of 2, 3, 4 and around 7 days. They also review the suitability of patients' substances. 'Leave-on' cosmetic products can usually be tested 'as is', rinse-off products such as shower gels tested at $\sim$ 10% aqueous. Water-based metal-working fluids should be diluted 5% aqueous and oil-based at 50% in olive oil. Solid materials (paper, textile, rubber, metal, wood dust) can usually be tested as they are. Plants can usually be tested 'as is' provided that the botanical identity is known.

5.3 Epidemiological/Incidence Studies

The most important recent change in the incidence of ACD has been the 'epidemic' of contact allergy to the cosmetic and household preservative methylisothiazolinone [23]. A decision to allow methylisothiazolinone as a single agent preservative in cosmetics at 100 ppm in 'leave-on' and 15 ppm in 'wash-off' cosmetics was followed by a sharp rise in allergy to this agent. Patch test rates of allergy to isothiazolinones rose from 2–4% up to 15.3%. High rates

have been reported in America, Europe, Australia and Asia with a rate of 40% in one Bangkok clinic. Allergic reactions are usually eczematous and most common on the head and neck in females over 40 years old. Pseudolymphomatoid, pseudoangioedematous and lichen planus-like reactions have also been reported. Recently used water-based wall paint is an important source of airborne methylisothiazolinone and can elicit severe dermatitis reactions.

Oxidised limonene and linalool are emerging as important fragrance allergens. Of 4731 sequential patients in a UK multicentre study, 5.0% had contact allergy to limonene, a citrus-derived fragrance allergen tested at 0.3% pet. concentration, and 5.9% had contact allergy to linalool, a lavender-derived fragrance allergen tested at 1.0% pet. concentration [24]. A similar study from Spain found 5.1 and 4.9% of patch test patients were allergic to limonene and linalool, respectively [25]. Oxidised limonene and linalool are not contained within the screening Fragrance Mixes 1 and 2, nor the natural fragrance screening agent *Myroxylon Pereirae* and should now be tested as single fragrance agents within a baseline series. Unfortunately for allergic individuals, limonene and linalool are the commonest fragrance agents used in toiletries, estimated as being in 49 and 66% of personal care products [26]. However, whether a contact dermatitis reaction occurs will depend upon the amount of oxidised agent present.

Studies assessing the prevalence of contact allergy within a normal population, rather than data extracted from patch test clinics, are rare. Therefore, the recent undertaking of studies relating to this area by the European Dermato-Epidemiological Network (EDEN) project represents an exciting insight into the burden of contact allergy within the normal population. A study from this group reports a positive patch test rate of 3.3% from patch test patients to the hair dye screening agent *p*-phenylenediamine (1% pet.) and a rate of 1.3% within the normal population in Holland [27].

5.4 Case Reports

Just as lawyers need to know case law and precedents, knowledge of case literature is extremely important in the practice of contact dermatitis. Case reports could be related to new allergens, established allergens which are presenting in a novel way, or reinforcing known presentations of established contact allergens.

5.4.1 Case Reports of New Allergens

There is steady production of new contact allergens reported in the literature. Examples of recent case reports include the following:

- Ethylhexylglycerin is a newly introduced agent used for its surfactant, skin-conditioning, emollient and antimicrobial properties in a wide variety of cosmetics. A series of 13 cases were reported from Belgium [28]. The face was most commonly involved (11/13 cases) followed by axilla, neck, abdomen and hands. Sources of exposure included day creams, deodorants, tinted moisturiser, anti-aging cream and sunscreen. This report serves to remind that even though some agents, such as ethylhexylglycerin, are reported as non-sensitisers or weak sensitisers in animals, they can still cause multiple cases of ACD with human exposure.
- Tosylamide formaldehyde resin is the traditional allergen found in nail varnish. However, over the past decade a new nail varnish resin, phthalic anhydride/trimellitic anhydride/glycols copolymer, has been characterised as a contact allergen. The distribution of dermatitis in a series of four cases reported with this contact allergy (periorbital and fingertip eczema, perioral and lip eczema, face and fingers, fingers) illustrates the diverse presentations of ACD to nail varnish [29].
- A 46-year-old patient with scalp seborrhoeic dermatitis was advised to use a new anti-dandruff shampoo. One day after using it, she developed intense pruritus of the scalp, which she attributed to her seborrhoeic dermatitis. Two days later she used it again, and immediately developed erythema on the forehead and around the nose, with mild oedema. Patch testing to the individual ingredients of the shampoo revealed a +++ to distearyl phthalic acid amide, tested at 3%. This agent is used as an emulsifier in various toiletries and pharmaceutical preparations [30].
- A 39-year-old woman presented with a history of facial eczema for several years [31]. The lesions had occurred after a skin cosmetic cream. Subsequent patch testing found a +++ reaction to glyceryl caprylate at a concentration of 5% pet. Glyceryl caprylate is manufactured from natural oils such as coconut oil. It is used as a skin conditioning agent in some cosmetics, having antimicrobial and moisturising properties.
- A 51-year-old non-atopic male presented with a bilateral temporal oozing dermatitis, which had been complicated by two episodes of cellulitis around the ears [32]. Patch testing showed a ++ reaction to shave samples of his black spectacle frames. Data sheet information of the plastic used revealed that <25% of the material was the plasticiser triethylene glycol bis (2-ethylhexanoate). Although commercially not available for patch testing, the agent was extracted from the spectacle frame material by high-performance liquid chromatography and the patient reacted to this on patch testing. Triethylene glycol bis (2-ethylhexanoate) is a plasticiser which contains two acyl groups that can be

attacked by a nucleophile and thus may act as a hapten, being able to generate a protein–hapten complex in contact with the skin.

5.4.2 Case Reports of Established Contact Allergens Presenting in Novel Ways

The following case reports provide recent examples of established contact allergens presenting in novel ways:

- Methylisothiazolinone is an established contact allergen found in toiletries, household goods and wet wall paint. However, recent case reports report novel presentations of ACD to methylisothiazolinone [33, 34]. A 48-year-old man presented with a facial dermatitis suspected of being ACD to spectacle frame. He had a ++ patch test reaction to shavings of the spectacle frame and ++ to methylisothiazolinone. Gas chromatography and mass spectrometry found concentrations of methylisothiazolinone of 12 ppm in both the surface plastic and the inner plastic of the spectacle frames, showing that the methylisothiazolinone was not an external contaminant but part of the plastic, even though it was not labelled on the plastic data sheet [33]. A 38-year-old female presented with face and hand dermatitis which she suspected was due to an allergic reaction to a ‘natural’ sponge [34]. Patch testing showed a ++ reaction to methylisothiazolinone and gas chromatography/mass spectrometry analysis revealed that methylisothiazolinone was present in the sponge at a concentration of 387 ppm, which was almost four times the permissible concentration allowed for methylisothiazolinone in ‘leave-on’ products at that time. The authors noted that the sponge had been marketed as ‘100% natural’ and that it had not been disclosed that the sponge contained methylisothiazolinone. These papers serve to highlight the occult nature of some exposure to preservative and that ingredient labelling does not always fulfil the obligation of being complete.
- A 39-year-old male with atopic dermatitis presented with extensive dermatitis poorly responding to therapy [35]. The dermatitis was particularly severe on the arms and thighs. Patch testing showed marked positive reactions to multiple azo/clothing dyes, including red, orange, blue and black. Wearing white underclothing to protect from his coloured work clothes resulted in marked improvement of his dermatitis. This case report illustrates that clothing dye ACD may not only present as a classical flexural rash but also as an extensive truncal dermatitis or as an endogenous truncal dermatitis which is poorly responding to therapy.

- A 3-year-old atopic boy developed widespread dermatitis a day after his mother had used an insect-repellant wet wipe. Patch test revealed a + to the single fragrance chemical hydroxycitronellal. Although this was not included in the ingredient labelling, gas chromatography and mass spectrometry revealed its presence. This case illustrates that insect-repellant agents are often fragranced and can cause ACD to fragrance [36].

In addition to reading contact dermatitis literature, national and international meetings dedicated to contact dermatitis are also essential ways to keep informed.

6 Contact Allergy Profiling

‘Contact allergy profiling’ can be used as an important investigative tool in the diagnosis of ACD. For each standard contact allergen, one can use case literature and clinical experience to compile a profile of the allergen with respect to the potential sources of exposure, different routes of exposure and various manifestations of contact allergy to the specific agent. For example, profiling fragrance (Table 5) reveals a very wide range of potential exposures from different aspects of daily life, routes of exposure and multiple forms of clinical presentation. In contrast, the allergy profile of the hair dye chemical PPD (Table 6) shows a much more limited exposure profile from daily life and routes of exposure. However, known clinical manifestations of contact allergy to PPD are even more numerous than that of contact allergy to fragrance allergen.

7 Clinical Experience

Stressing the importance of clinical experience may have become a cliché, but perhaps there is some evidence to support such a claim. Performance psychologists argue that most performers have practiced for 1000 h per year for 10 years before optimising their sport, musical or professional discipline (aggregate 10,000 h) [37]. However, this ‘practice’ needs to be purposeful (i.e. sustained, focussed and developmental). If this rule applies to analytical medical skills, and one were undertaking three patch test clinics per week, then approximately 20 years would be needed to accumulate 10,000 h of clinical experience to optimise skill set performance. Purposeful experience, however, requires interactions with colleagues and regular attendance at group meetings to discuss cases. Involvement with at least 200 cases per year has been recommended to

Table 5 A profile of allergic contact dermatitis to fragrance from case literature and clinical experience

<i>Examples of potential exposure from aspects of daily life</i>
Personal care products—70% are fragranced
Cosmetic procedures
Home environment and other environments: air fresheners, scented candles, partner, sprays for bedding
Occupational—toilet room sprays; catering: cinnamon, spice, citrus; healthcare: scented soap; beautician
Leisure: gardening (scented plants)
Sports: increased deodorant use
Travel: room and bed spray, hotel toiletries, car air freshener, insect repellent
Clothing: fragrance-sprayed clothes
Medicaments: fragranced topical medicaments, suppositories
Dental procedures: eugenol
Dietary and mucosal (e.g. citral, cinnamal, geraniol, Balsam of Peru chemicals)
Sexual intercourse (by proxy)
<i>Routes of potential exposure</i>
Direct contact
Airborne
Hand to face/neck/chest
Mucosal
Systemic
By proxy
<i>Various known clinical manifestations of contact allergy to fragrance</i>
Major forms of presentation
Direct exposure
Airborne ACD
Mimicking/exacerbating endogenous dermatitis
Multifactorial dermatitis
Minor forms of presentation
By proxy ACD
Non-eczematous contact dermatitis
Pustular contact dermatitis
Granulomatous contact dermatitis
Contact urticaria
Respiratory/mucosal symptoms
Oral contact dermatitis
Known cross-reactions
NSAID (e.g. ketoprofen)
Sunscreen (octocrylene)
Epoxy resin

maintain competence (<http://www.bad.org.uk/shared/get-file.ashx?itemtype=document&id=1618>). Membership of societies such as the American Contact Dermatitis Society and European Society of Contact Dermatitis may also be beneficial.

Table 6 A profile of allergic contact dermatitis to *p*-phenylenediamine from case literature and clinical experience*Examples of potential exposure from aspects of daily life*

Cosmetic procedures: hair dyeing, eyelash and eyebrow tinting

Occupational: hairdressers

Travel: temporary 'henna' beach tattoo

Clothes, shoes (rare)

N.B. may cross-react to azo dyes (clothing), black rubber (occupational, travel, leisure, home) caines (medicaments)

Routes of potential exposure

Direct exposure

By proxy

Various known clinical manifestations of contact allergy to p-phenylenediamine

Major forms of presentation:

Direct contact

Exacerbation of endogenous eczema

By proxy contact dermatitis

Mimicking angioedema

Minor forms of presentation:

Non-eczematous forms of contact dermatitis:

Lichenoid

Pigmented

Depigmented

Pseudolymphomatoid

Purpuric

Erythema multiforme-like

Neutrophilic and eosinophilic dermatoses

Contact urticaria

Other reported forms of presentation:

Primary sensitisation (henna beach tattoo)

Bullous

Prurigo nodularis-like

Lichen simplex chronicus

Reported cross-reactions:

Other aromatic amine hair dyes (e.g. toluenediamine)

Azo/disperse dyes

Black rubber

Benzocaine

Some epoxy hardeners

involves elimination/inclusion of non-allergic dermatological diagnoses. Step 2 involves perception—entertaining the different scenarios in a pre-patch test diagnosis. Step 3 involves detection of contact allergy, utilising the patch test process to increase its sensitivity. Step 4 involves deduction in order to diagnose ACD. The post-patch test 'microhistory' and 'microexamination' should focus in minute detail on the association of exposure to allergen(s) identified by patch testing to the presenting dermatitis to be able to diagnose ACD. Clinical experience and knowledge of contact dermatitis case literature are essential tools in the practice of contact dermatitis.

Acknowledgements The authors would like to thank David A. Basketter for his valuable comments.

Compliance with Ethical Standards

Funding No funding was received for the preparation of this review.

Conflict of interest Korbkarn Pongpairaj, Pailin Puangpet, Supitchaya Thaiwat and John McFadden have no conflicts of interest.

References

- Goossens A. Art and science of patch testing. *Indian J Dermatol Venereol Leprol.* 2007;73(5):289–91.
- Belsito DV. A Sherlockian approach to contact dermatitis. *Dermatol Clin.* 1999;17(3):705–13.
- Ho SG, et al. Analysis of para-phenylenediamine allergic patients in relation to strength of patch test reaction. *Br J Dermatol.* 2005;153(2):364–7.
- Pongpairaj K, et al. Proposed ICDRG classification of the clinical presentation of contact allergy. *Dermatitis.* 2016;27(5):248–58.
- Streit M. and Braathen LR. Contact dermatitis: clinics and pathology. *Acta Odontol Scand.* 2001;59(5):309–14.
- Goossens A. Minimizing the risks of missing a contact allergy. *Dermatology.* 2001;202(2):186–9.
- Smith HR, et al. Association between tinea manuum and male manual workers. *Contact Dermat.* 2000;42(1):45.
- Gittler JK, et al. Atopic dermatitis results in intrinsic barrier and immune abnormalities: implications for contact dermatitis. *J Allergy Clin Immunol.* 2013;131(2):300–13.
- Kumar B, et al. Palmoplantar lesions in psoriasis: a study of 3065 patients. *Acta Derm Venereol.* 2002;82(3):192–5.
- Johansen JD, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermat.* 2015;73(4):195–221.
- Vejanurug P, et al. Fragrance allergy could be missed without patch testing with 26 individual fragrance allergens. *Contact Dermat.* 2016;74(4):230–5.
- Basketter DA. and English J. Cross-reactions among hair dye allergens. *Cutan Ocul Toxicol.* 2009;28(3):104–6.
- Bong JL, et al. Diluted compositae mix versus sesquiterpene lactone mix as a screening agent for compositae dermatitis: a multicentre study. *Contact Dermat.* 2001;45(1):26–8.
- Calnan CD. and Sarkany I. Studies in contact dermatitis IX Shoe dermatitis. *Trans St Johns Hosp Dermatol Soc.* 1959;43:8–26.
- Matthys E, et al. Shoe allergic contact dermatitis. *Dermatitis.* 2014;25(4):163–71.

8 Summary

The 'Friday' method for diagnosing ACD relies on skills used in other fields of detection. The pre-patch test history and examination should include a wide scope to include questioning on the different aspects of daily life with potential for exposure to contact allergens. Examination should include both a local and distal aspect in respect to the anatomical location of the presenting rash. Step 1

16. Isaksson M. and Bruze M. Late patch-test reactions to budesonide need not be a sign of sensitization induced by the test procedure. *Am J Contact Dermat.* 2003;14(3):154–6.
17. Davis MD, et al. Delayed patch test reading after 5 days: the Mayo Clinic experience. *J Am Acad Dermatol.* 2008;59(2):225–33.
18. Higgins E. and Collins P. The relevance of 7-day patch test reading. *Dermatitis.* 2013;24(5):237–40.
19. Friedmann PS. The relationships between exposure dose and response in induction and elicitation of contact hypersensitivity in humans. *Br J Dermatol.* 2007;157(6):1093–102.
20. Kock M, et al. Continuous usage of a hair dye product containing 2-methoxymethyl-*para*-phenylenediamine by hair-dye-allergic individuals. *Br J Dermatol.* 2016;174(5):1042–50.
21. Powell BS, et al. Polyionic vaccine adjuvants: another look at aluminum salts and polyelectrolytes. *Clin Exp Vaccine Res.* 2015;4(1):23–45.
22. Loretz L, et al. Exposure data for personal care products: hair-spray, spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. *Food Chem Toxicol.* 2006;44(12):2008–18.
23. Latheef F. and Wilkinson SM. Methylisothiazolinone outbreak in the European Union. *Curr Opin Allergy Clin Immunol.* 2015;15(5):461–6.
24. Audrain H, et al. Allergy to oxidized limonene and linalool is frequent in the UK. *Br J Dermatol.* 2014;171(2):292–7.
25. Deza G, et al. Contact sensitization to limonene and linalool hydroperoxides in Spain: a GEIDAC* prospective study. *Contact Dermat.* 2017;76(2):74–80.
26. Buckley DA. Fragrance ingredient labelling in products on sale in the UK. *Br J Dermatol.* 2007;157(2):295–300.
27. Vogel TA, et al. *p*-Phenylenediamine exposure in real life—a case-control study on sensitization rate, mode and elicitation reactions in the northern Netherlands. *Contact Dermat.* 2015;72(6):355–61.
28. Aerts O, et al. Ethylhexylglycerin: a low-risk, but highly relevant, sensitizer in ‘hypo-allergenic’ cosmetics. *Contact Dermat.* 2016;74(5):281–8.
29. Gach JE, et al. A series of four cases of allergic contact dermatitis to phthalic anhydride/trimellitic anhydride/glycols copolymer in nail varnish. *Contact Dermat.* 2005;53(1):63–4.
30. Carballada F, et al. Distearyl phthalic acid amide, a new contact allergen. *Contact Dermat.* 2014;71(5):310–2.
31. Herbert VG, et al. Glyceryl (mono)caprylate—a new contact allergen. *Contact Dermat.* 2013;69(6):383–5.
32. Andersen KE, et al. Triethylene glycol bis(2-ethylhexanoate)—a new contact allergen identified in a spectacle frame. *Contact Dermat.* 2014;70(2):112–6.
33. El-Houri RB, et al. Methylisothiazolinone in a designer spectacle frame—a surprising finding. *Contact Dermat.* 2016;75(5):310–2.
34. Madsen JT, et al. Undisclosed presence of methylisothiazolinone in ‘100% natural’ Konjac(R) sponge. *Contact Dermat.* 2016;75(5):308–9.
35. Mohamoud AA. and Andersen F. Allergic contact dermatitis caused by textile dyes mimicking atopic dermatitis. *Contact Dermat.* 2017;76(2):119–20.
36. Corazza M, et al. Allergic contact dermatitis caused by insect repellent wipes. *Contact Dermat.* 2016;74(5):295–6.
37. Ericsson KA. and Lehmann AC. Expert and exceptional performance: evidence of maximal adaptation to task constraints. *Annu Rev Psychol.* 1996;47:273–305.