A Guide to Cutaneous Allergy

Dr David Orton
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The Hillingdon Hospitals NHS Foundation Trust
- Allergy – inappropriate/exaggerated defence reaction to something that is not innately harmful

Type 1 allergy

Type 4 allergy
- not covering immune and non-immune contact urticaria
- not covering urticaria

covering Contact Dermatitis
Contact Dermatitis –

“dermatitis invoked as a result of an exogenous agent”
Allergic contact dermatitis ~20% and Irritant contact dermatitis ~80% differ in the underlying causative mechanism.

In clinical practice, they often co-exist. It is believed that ICD enhances the development of ACD.
Irritant contact dermatitis

- direct toxic injury to the skin
- non-immunological

eg “housewife’s” hands

eg “nappy rash”

eg leg ulcer patients from proteins and in particular tissue repair enzymes in serous exudate
Aetiology of ICD

Factors influencing ICD

Complex interplay of

Individual susceptibility

And environment

- atopy
- Atopic dermatitis
- Skin type
- Race
- Gender
- Care of skin
- Site of contact
Allergic contact dermatitis

prototype Type IV mediated delayed hypersensitivity reaction

2 phases
  - sensitisation
  - elicitation
most contact allergens are highly chemically reactive molecules, with a molecular weight of <1000 Da

being intrinsically too small to act as antigens in their own right (haptens), they must have the ability to penetrate the stratum corneum and bind with epidermal proteins to generate an immune response

generally, the greater the ease with which a chemical reacts with proteins, the greater its skin sensitisation potential
key factor influencing development ACD

- allergen dose / unit area
  individuals sensitised by a high concentration of allergen acquire a greater degree of sensitivity as compared to those sensitised by a low concentration and will be more likely to develop eczema on re-exposure to the allergen
## factors influencing elicitation of ACD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen concentration dose/unit area</td>
<td>Also important in induction</td>
</tr>
<tr>
<td>Individual level of sensitivity</td>
<td>Depends on exposure concentration at induction</td>
</tr>
<tr>
<td>Time of exposure (no. of applications)</td>
<td>Low concentrations require longer exposure periods to elicit a reaction than high concentrations</td>
</tr>
<tr>
<td>Anatomical skin site</td>
<td>Axilla more sensitive than arms etc.</td>
</tr>
<tr>
<td>Occlusion</td>
<td>Facilitates penetration of some allergens, but not others</td>
</tr>
<tr>
<td>Product matrix</td>
<td>Different product types have a different ability to elicit reactions in spite of similar content of allergens</td>
</tr>
<tr>
<td>Combination with irritants or allergens</td>
<td>eg combination of fragrance allergens gives synergistic response, combinations of Ni and irritant gives synergistic response,</td>
</tr>
<tr>
<td>Pre-irritated skin</td>
<td>Pre-irritation of skin with SLS gives stronger responses for allergens</td>
</tr>
<tr>
<td>Abraded skin</td>
<td>Shaving with razors increases risk of FM allergy</td>
</tr>
</tbody>
</table>
What does ACD look like?

- Irritant and Allergic contact dermatitis look similar macroscopically and microscopically.

- Patch testing is the **only** technique available to diagnose allergic contact dermatitis.
Diagnosis of ACD

- clinical history
- knowledge of potential allergens in pts environment
- confirmed by patch testing

have a high level of suspicion; if you don’t patch test you will miss cases of ACD
The greatest abuse of patch testing is failure to use the test.

Jadassohn 1896

Calman 1982
Who should be patch tested?

Any case of dermatitis?
1. When clinical history is suggestive
2. Regional dermatitis
   (i) Hand eczema
   (ii) Facial eczema esp eyelid eczema/periorbital/external ear/lips
   (iii) Leg ulcer, stasis eczema
   (iv) Anogenital
   (v) Photosensitive/Exposed site
   (vi) Foot
   (vi) When distribution is suggestive eg “cut off”

2. Recalcitrant eczema
3. Occupational eczema
4. Drug induced eczema

Having negative patch tests (exclusion) can be just as important
Who should be patch tested?

“in a particular clinic the incidence of allergic contact dermatitis is determined by the interest the dermatologist takes in allergic contact Dermatitis”

Hjorth and Fregart
standardising the technique

- crude assay
- 70-80% sensitivity/specificity

apply test materials
- for 48hrs
- under occlusion
- upper back
suspected allergens are available commercially or made from pts own materials

Factors influencing test allergen

Bioavailability

- salt of test allergen
- concentration
- vehicle
- occlusivity
- finn chamber size
- exposure time
for ease and convenience
test allergens
amalgamated into test
“batteries” or “series”
<table>
<thead>
<tr>
<th>Allergen (alphabetical order)</th>
<th>Function</th>
<th>patch test</th>
<th>Function</th>
<th>patch test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amerchol L101</td>
<td>Emulsifier</td>
<td>50% (pet)</td>
<td>Propylene glycol</td>
<td>Humectant, 5% (pet)</td>
</tr>
<tr>
<td>Benzophenone 3</td>
<td>Sunscreen</td>
<td>10% (pet)</td>
<td>Quaternium 15</td>
<td>Preservative 1% (pet)</td>
</tr>
<tr>
<td>BHA (butylated hydroxyanisole)</td>
<td>Antioxidant</td>
<td>2% (pet)</td>
<td>BHT (butylated hydroxytoluene)</td>
<td>Antioxidant 2% (pet)</td>
</tr>
<tr>
<td>2-Bromo-2nitropropane-1,3-diol</td>
<td>Preservative</td>
<td>0.5% (pet)</td>
<td>Tea Tree Oil</td>
<td>Essential oil 5% (pet)</td>
</tr>
<tr>
<td>Cetyl/Stearyl alcohol</td>
<td>Emulsifier</td>
<td>20% (pet)</td>
<td>Wool alcohols</td>
<td>emulsion stabilizer, 30% (pet)</td>
</tr>
<tr>
<td>Cocamidopropyl betaine</td>
<td>Surfactant</td>
<td>1% (aq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazolidinyl urea</td>
<td>Preservative</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM DM hydantoin</td>
<td>Preservative</td>
<td>2% (pet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Preservative</td>
<td>1% (aq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fragrance mix 1 &amp; 2</td>
<td>Fragrance</td>
<td>8/14% (pet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxymethyl pentylcyclohexene-carboxaldehyde (Lyral®)</td>
<td>Fragrance</td>
<td>5% (pet)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imidazolidinyl urea</td>
<td>Preservative</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
allergen sequence carefully determined
- indelible marker
- avoid showering/bathing
- avoid exercise
- avoid UV exposure
- avoid topical or systemic steroids
- avoid systemic immunosuppressants
- avoid testing with widespread active eczema
ICDRG standard scoring grades

Table 4. Recording of patch test reactions according to the International Contact Dermatitis Research Group (ICDRG) [36]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>?+</td>
<td>Doubtful reaction; faint erythema only</td>
</tr>
<tr>
<td>+</td>
<td>Weak positive reaction; erythema, infiltration, possibly papules</td>
</tr>
<tr>
<td>++</td>
<td>Strong positive reaction; erythema, infiltration, papules, vesicles</td>
</tr>
<tr>
<td>+++</td>
<td>Extreme positive reaction; intense erythema and infiltration and coalescing vesicles</td>
</tr>
<tr>
<td>-</td>
<td>Negative reaction</td>
</tr>
<tr>
<td>IR</td>
<td>Irritant reactions of different types</td>
</tr>
<tr>
<td>NT</td>
<td>Not tested</td>
</tr>
</tbody>
</table>
atopics particularly prone to non-specific (erythematous) and pustular irritant reactions from test materials
"late" reactions must also be reported to clinic

<table>
<thead>
<tr>
<th>Option</th>
<th>No. of visits</th>
<th>Day 0 Application</th>
<th>Day 2 Removal, reading</th>
<th>Day 3/4 Reading</th>
<th>Day 5/7 Reading</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>Recommended</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>Recommended</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>Highly recommended</td>
</tr>
</tbody>
</table>
it is just as important to ascribe relevance

“current”
“past”
“unknown”

and make the patient understand the meaning of the findings
not possible to have absolute rules to determine relevance. However, based on exposure to a putative allergen, distribution of dermatitis, and effect of elicitation from exposure and improvement by avoidance – allergic reactions may be classified as “possible”, “probable” or “certain” relevance.

The Dermatologist’s skill, experience and curiosity are VITAL factors.
pitfalls of patch testing

- cross reactions (similar structured antigens)
- non specific “irritant” reactions esp. atopics
- false positive reactions
- false negative reactions
compound allergy

- patch test positive (allergic) to formulated products but negative to individual constituents

- irritancy of original formulation

- combination of ingredients forms intermediate allergenic compounds
photoallergic contact dermatitis

- certain substances transformed into allergens only after absorbing UV light
- 2 parallel sets of allergens
- UVA irradiation at 48hrs (5J)
- photoallergic contact dermatitis when positive result on irradiated side ONLY
pitfalls of patch testing

- do not test unknown substances (active sensitisation, necrosis, scarring)
- select correct concentration/vehicle & test control subjects
protein contact dermatitis

Hjorth 1976

- proteins (food, animal products) cause initial urticarial reactions

- after prolonged exposure results in eczematous changes (esp. fingertips)

- cause obscure - possibly an IgE mediated late phase hypersensitivity reaction

- occupations at risk esp. food handlers
- protein contact dermatitis usually to foods in caterers is more common in atopics (with a negative patch test but a positive SPT)
don’t forget why we do patch tests!

- Patients require a clear explanation of their allergies, where the allergen is likely to be encountered and the relevance of any positive test.

- They may need advice on alternative safe products, and in the case of occupational ACD they may require help in creating “low-risk” environments or help with allergen replacement. Others may require advice about gloves or protective clothing.
patch tests

- RELATIVELY SAFE
- CHEAP
- ...BUT DIFFICULT TO INTERPRET
COLOURSAFE

NO PPD  MAIN CAUSE OF  ALLERGIC REACTIONS

NO AMMONIA, NO RESORCINOL & PARABENS FREE

MAXIMUM GREY HAIR COVERAGE

150 ml  5 fl.oz.
INGREDIENTS: COLOUR CREAM: Aqua (Water); Cetearyl Alcohol; Ethoxydiglycol; Phenyltrimethicone; Ethanolamine; Toluene-2,5-diamine sulfate; Stearamide MEA; Ceteareth-60; Betaine; Polyquaternium-6; Isopropyl Myristate; Ethoxydiglycol Oleate; Helianthus annuus (Sunflower) seed oil*; Sesamum indicum (Sesame) seed oil*; Wheat Aminoacids; Soy Aminoacids; Arginine; Serine; Threonine; Parfum (Fragrance); Hexyl Cinnamal; Limonene; Cetrimonium Chloride; Sodium Sulfite; Sodium Ascorbate; Disodium EDTA; 2-Methylresorcinol; 1-Naphtol; 2-Amino-4-hydroxyethylaminoanisole sulfate; 2,6-Diaminopyridine; m-Aminophenol. COLOUR DEVELOPER: Aqua (Water); Hydrogen Peroxide; Cetearyl Alcohol; Tetrasodium EDTA; Etdronic Acid; Sodium Lauryl Sulfate; PEG-75 Lanolin; Simethicone; Phosphoric Acid; Phenacetin. SHAMPOO: Aqua (Water); Sodium Laureth Sulfate; TEA Lauryl Sulfate; Cocamidopropyl Betaine; PEG-7 Glyceryl Cocoate; Glycerin; Sodium Lactate; Aloe barbadensis leaf juice*; Panthenol; Althaea officinalis root extract; Polyquaternium 11; Dipotassium Glycyrrhizate; Polyquaternium 10; Calcium Pantothenate (Vit. B3); Inositol (Vit. B7); Biotin (Vit. H); Retinol (Vit. A); Tocopherol Acetate (Vit. E); Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Arachidonate (Vit. F); Isostearamide MIPA; Benzoic Acid; Propylene Glycol; Glycol Distearate; PEG-55 Propylene Glycol Oleate; Cocamide DEA; Parfum (Fragrance); Citric Acid; Dehydroacetic Acid; Sodium Chloride; Phenoxyethanol; Disodium EDTA. HAIR MASK: Aqua (Water); Cetearyl alcohol; Aloe barbadensis leaf juice*; Cetyl Esters; Glycerin; Juniper communis fruit extract; Behentrimonium Chloride; Panthenol; Cetrimonium Chloride; Parfum (Fragrance); Phenoxyethanol; Benzoic Acid; Dehydroacetic Acid; CI 77891. *Organic farming
my toddler’s Toilet wipes

INGREDIENTS
Aqua, Aloe Barbadensis Leaf Extract, Glycerin, Polysorbate 20, Disodium Cocoamphodiacetate, Tocopheryl Acetate, Methylchloroisothiazolinone, Methylisothiazolinone, Quaternium-15, Potassium Sorbate, Disodium EDTA, Sodium Chloride, Magnesium Nitrate, Parfum, Citric Acid.
“Ideally every patient with eczema should be patch tested and the importance of this investigation is now universally accepted. The simplicity of the technique belies its many pitfalls, the greatest being to lack the knowledge required to select the correct allergens and to interpret the results.”

Etain Cronin
St John’s Institute of Dermatology
Cosmetic – “any substance or preparation intended for placing in contact with the various external parts of the human body or with the teeth and mucous membranes of the oral cavity with a view exclusively or principally to clean them, perfume them or protect them to keep them in good condition, change their appearance and/or correct body odours”
- cosmetics are NOT stable inert finished products

- undergo degradation, oxidation, photodegradation

- may influence presence of allergens

- stability profiling work not often undertaken
misleading marketing terms - undefined

- “suitable for sensitive skin”
- “hypoallergenic”
- “natural”
- “preservative free”
standardization of procedure

- test allergen conc.
- vehicle of test allergen
- test chamber size
- application time
- number of readings
- scoring of reactions

can ALL influence the result
Difficulties occur in discriminating “weak allergic” from irritant reactions.

Such results need to be handled by supplementary tests such as dose–response tests, serial dilutions and Repeat Open Application Tests.

In the final decision they must also be related to the clinical history.
used to confirm the diagnosis of ACD (sensitivity and specificity ~70-80% operator dependent)
diagnosis of constitutional or ICD made by exclusion
if you don’t test for it you will miss it!

the procedure is EASY
the interpretation is DIFFICULT
to ascribe relevance can be a CHALLENGE
sites of cosmetic reactions

can reach the skin from:

- direct application
- airborne transfer
- direct transfer
- “connubial/consort” dermatitis
tests used in making the diagnosis

- Patch tests
- Photopatch tests
- Repeat Open Application Tests (ROAT)
- Skin prick tests
when is patch testing indicated?

- a suggestive *pattern* of dermatitis
- in the context of *occupational/leisure* exposure to recognised sensitisers
- treatment “resistant” cases of dermatitis
- a history of reactivity to a sensitiser

- having negative patch tests (exclusion) can be just as important!
Patterns of dermatitis where patch testing might be indicated with possible suspect allergens included in parenthesis

- Facial dermatitis including eyelid dermatitis (cosmetic allergens – fragrance, chemicals/biocides, medicaments)
- Chronic otitis externa (ear medicament allergens)
- Cheilitis (Cosmetic allergens, flavourings)
- Flexures (Cosmetic allergens, textile dyes)
- Hands (Cosmetic allergens, rubber chemicals, plant allergens)
- Anogenital (Medicament and cosmetic allergens)
- Feet (Footwear allergens inc. chromate, rubber chemicals)
- Photosensitive dermatitis (Sunscreen chemicals, cosmetic allergens)
- Airborne dermatitis (Volatile cosmetic allergens inc. fragrance chemicals, volatile occupational allergens inc. epoxy resin, plant allergens).
patch testing

- used to confirm the diagnosis of ACD
  (sensitivity and specificity ~70-80% operator dependent)
- diagnosis of constitutional or ICD made by exclusion

- if you don’t test for it you will miss it!

the procedure is EASY
the interpretation is DIFFICULT
to ascribe relevance can be a CHALLENGE
diagnosis

- occlusive patch testing
- photopatch testing
- repeat open application tests (ROATs)
occlusive patch testing

- test allergens at recommended concentrations in recommended vehicles
- keep updating patch test batteries
- test products “as is” wherever appropriate and use control subjects
- obtain manufacturing grade constituents if analytical grade materials negative
Repeat Open Application Tests (ROATs)

- useful when patch tests with suspected allergens/products are negative or where relevance is in doubt

- mimics normal exposure
main culprits for cosmetic allergy

- fragrance chemicals (30-45% of all cosmetic reactions)
- preservatives
Contact urticaria and protein contact dermatitis to chapatti flour

Dr Emily Davies and Dr David Orton
Amersham Hospital
CHAPATTI FLOUR IN WATER
Protein contact dermatitis to food proteins

- Chronic eczema
- Urticarial/vesicular exacerbations
- Burning and stinging in eczematous skin within minutes of handling allergen
- Combined type I and IV mediated allergic reaction to proteins
- -ve patch tests; +ve prick or scratch/patch tests
Type I hypersensitivity

Type IV hypersensitivity

Conclusion

- Important diagnosis
- Relevant occupational/domestic setting
- Large impact on quality of life
<table>
<thead>
<tr>
<th>Water and its additives</th>
<th>(Salts and oxides of calcium, magnesium, and iron)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cleansers</td>
<td>Soaps, detergents, “waterless cleansers,” and additives (sand, silica)</td>
</tr>
<tr>
<td></td>
<td>Detergents, surface-active agents, sulfonated oils, wetting agents, emulsifiers, enzymes</td>
</tr>
<tr>
<td>Industrial cleaning agents</td>
<td></td>
</tr>
<tr>
<td>Alkalis</td>
<td>Soap, soda, ammonia, potassium and sodium hydroxides, cement, lime, sodium silicate, trisodium phosphate, and various amines</td>
</tr>
<tr>
<td>Acids</td>
<td>Severe irritancy (caustic): sulfuric, hydrochloric, nitric, chromic, and hydrofluoric acids</td>
</tr>
<tr>
<td></td>
<td>Moderate irritancy: acetic, oxalic, and salicylic acids</td>
</tr>
<tr>
<td>Oils</td>
<td>Cutting oils with various additives (water, emulsifiers, antioxidants, anticorrosive agents, preservatives, dyes and perfumes)</td>
</tr>
<tr>
<td></td>
<td>Lubricating and spindle oils</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>White spirit, benzene, toluene, trichloroethylene, perchloroethylene, methylene chloride, chlorobenzene</td>
</tr>
<tr>
<td></td>
<td>Methanol, ethanol, isopropanol, propylene glycol</td>
</tr>
<tr>
<td></td>
<td>Ethyl acetate, acetone, methyl ethyl ketone, ethylene glycol monomethyl ether, nitroethane, turpentine, carbon disulfide</td>
</tr>
<tr>
<td></td>
<td>Thinners (mixtures of alcohols, ketones, and toluene)</td>
</tr>
<tr>
<td>Oxidizing agents</td>
<td>Hydrogen peroxide, benzoyl peroxide, cyclohexanone peroxide, sodium hypochlorite</td>
</tr>
<tr>
<td>Reducing agents</td>
<td>Phenols, hydrazines, aldehydes, thioglycolates</td>
</tr>
<tr>
<td>Plants</td>
<td>Citrus peel and juice, flower bulbs, garlic, onion, pineapple, pelargonium, iris, cucumbers, buttercups, asparagus, mustard, barley, chicory, corn</td>
</tr>
<tr>
<td></td>
<td>Various plants of the spurge family (Euphorbiaceae), Brassicaceae family (Cruciferae) and Ranunculaceae family (for further details see [1])</td>
</tr>
<tr>
<td>Animal products</td>
<td>Pancreatic enzymes, bodily secretions</td>
</tr>
<tr>
<td>Miscellaneous irritants</td>
<td>Alkyl tin compounds and penta-, tetra-, and trichlorophenols (wood preservatives)</td>
</tr>
<tr>
<td></td>
<td>Bromine (in gasoline, agricultural chemicals, paper industry, flame retardant)</td>
</tr>
<tr>
<td></td>
<td>Methylchloroisothiazolinone and methylisothiazolinone (irritant at high concentrations during production or misuse)</td>
</tr>
<tr>
<td></td>
<td>Components of plastic processing (formaldehyde, phenol, cresol, styrene, di-isocyanates, acrylic monomers, diallyl phthalate, aliphatic and aromatic amines, epichlorohydrin)</td>
</tr>
<tr>
<td></td>
<td>Metal polishes</td>
</tr>
<tr>
<td></td>
<td>Fertilizers</td>
</tr>
<tr>
<td></td>
<td>Propionic acid (preservative in animal feed)</td>
</tr>
<tr>
<td></td>
<td>Rust-preventive products</td>
</tr>
<tr>
<td></td>
<td>Paint removers (alkyl bromide)</td>
</tr>
<tr>
<td></td>
<td>Acrolein, crotonaldehyde, ethylene oxide, mercuric salts, zinc chloride, chlorine</td>
</tr>
</tbody>
</table>
Causes of false-positive reactions

1. Too high a test concentration for that particular patient
2. Impure or contaminated test preparation
3. The vehicle is irritant (especially solvents and sometimes petrolatum)
4. Excess of test preparation applied
5. The test substance, usually as crystals, is unevenly dispersed in the vehicle
6. Influence from adjacent test reactions (see above “Sequence of Allergens”)
7. Current or recent dermatitis at test site
8. Current dermatitis at distant skin sites
9. Pressure effects of tapes, mechanical irritation of solid test materials, furniture and garments (brassiere)
10. Adhesive tape reactions
11. The patch itself has caused the reactions
12. Artifacts
angry back or multiple allergic responses
- Mitchell - “angry back syndrome” - false positive patch test reactions not reproducible when repeated separately

- non-reproducibility blamed on the presence of other strong positive tests/or inflamed skin elsewhere

- “excited skin syndrome” may be a more appropriate term
Causes of false-negative reactions

1. Insufficient penetration of the allergen
   a. Too low a test concentration for that particular patient
   b. The test substance is not released from the vehicle or retained by the filter paper
   c. Insufficient amount (dose) of test preparation applied; patch test concentration lower than declared [99]
   d. Insufficient occlusion
   e. Duration of contact too brief – the test strip has fallen off or slipped
   f. The test was not applied to the recommended site – the upper back
2. Failure to perform delayed readings; e.g., neomycin and corticosteroids are known to give delayed reactions (see Table 3)
3. The test site has been treated with corticosteroids or irradiated with UV or Grenz rays
4. Systemic treatment with corticosteroids or immunomodulators
5. Allergen is not in active form, insufficiently oxidized (oil of turpentine, rosin compounds, d-limonene) or degraded
6. Compound allergy
most ICD results from repetitive cumulative exposure to insult