What is contact dermatitis?

- Contact with chemical agent
- Split into:
  - Irritant - 80% of reactions
  - Allergic - 20% of reactions
    - Requires prior sensitization
    - Delayed-type IV hypersensitivity reaction
    - Th-1 cytokine response

**Methylisothiazolinone update**

- 2013 CONTACT ALLERGEN OF THE YEAR due to increasing use ALONE
- You know it in MCI/MI (Kathon CG) but now MI is #2 — still increasing!
- Was believed to be a weaker sensitizer than MCI, so a few years ago was introduced alone in products at a much higher level than what is in the MCI/MI mix
- Cosmetic industry use has doubled since 2007
- Unlimited amounts are allowed in industrial products, allowing for occupational exposure
- MCI/MI mix misses approx 40% of MI allergy, likely because of low MI conc. in the mix
- “An EPIDEMIC of sensitivity to methylisothiazolinones”

N. American Contact Dermatitis Group Patch Test Results ‘15-16 (13 centers, 70 allergens) - Dermatitis Nov/Dec, 2018

1. Nickel (18.5%)
2. Methylisothiazolinone (increasing – 13%) ↑ ↑
3. Fragrance Mix I
4. Formaldehyde 2% aq ↑
5. Methylenechloroisothiazolinone/methylisothiazolinone (MCI/MI, Kathon CG) ↑
6. Balsam of Peru/inmotion peroxene
7. Neomycin
8. Bacitracin
9. Formaldehyde 1% aq
10. P. paraphenylenediamine
11. Cobalt chloride
12. Fragrance Mix II
13. Carba mix
14. Lanolin (wool alcohol)
15. Propylene glycol 100% (vehicle) ↑
16. Isopropanyl butylcarbamate
17. Cinnamic aldehyde
18. Quaternium-15 (Dowicil 200)
19. 2-brom-2-nitropropane-1,3-diol (Bronopol)
20. Methyldibromoglutaronitrile/phenoxyethanol (Euxyl K400)
21. Thiuram mix
22. Hydroxyethyl methacrylate (HEMA) ↑ - nail acrylate

**Formaldehyde Releasers**

Quaternium-15 (Dowicil 200)
Imidazolidinyl urea
Diazolidinyl urea (Germall)
DMDM hydantoin
2-brom-2-nitropropane-1,3-diol (Bronopol)
Tris(hydroxymethyl)nitromethane
Take-home points:

- 23% of patients had a relevant allergen outside of the 70-allergen NACDG panel; 14% of these were occupationally related.
- 25% - 40% of allergens detected by NACDG panel would have been missed by T.R.U.E. test.

Textiles: Finishes, dyes, rubber

Textile finishes: Formaldehyde & formaldehyde-releasers
- Wrinkle-free, permanent press, stain/water-resistant, flame-retardant
- Screening test: Fixapret AC (ethylene urea/melamine formaldehyde mix)

Dyes:
- Dye color allergen not related to clothing color
- Most common ACD: Disperse dyes (synthetics) esp azo
  - Disperse blue 106 and 124 – good screening allergens for textile allergy (positive reactions in 80% and 57% of dye-related cases in 2 reports)
  - Para-phenylenediamine — may x-react with azo dyes so was the historical antigen for disperse dyes but disperse blue is better

Formaldehyde & Friends

- Cosmetic and topical agent preservative
  - Everywhere: Textiles, plastics, paper, paints, cosmetics
  - Released as colorless gas
  - Careful reading 1+ reactions; often causes ICD (new data: test at 2% aq)
  - 2-3% allergy rates in Europe, 8-9% in US

Formaldehyde Releasers
- Preservatives which release formaldehyde
  - Quaternium-15 (Dowicil 200)
  -imidazolidinyl urea, diazolidinyl urea (Germain)
  -DMOH hydantoin
  -2-bromo-2-nitropropane-1,3-diol (Bronopol)
  -tris(hydroxymethyl)methylnitromethane

N.B. — These don’t necessarily x-react; imidazolidinyl urea may x-react the least

- p-tert-butylphenol (PTBP) formaldehyde resin - Waterproof glue, often for shoes & leather products (glues down insoles); also dental
  - Allergen is p-tert-butyl, NOT phenol or formaldehyde

A woman has a contact allergy to imidazolidinyl urea and quaternium-15. Which other chemical is she most likely allergic to?
A. parabens
B. thimerosal
C. formaldehyde
D. ethylenediamine
E. cinnamic aldehyde

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Rubber Dermatitis

1) Natural latex rubber, from the tree Hevea brasiliensis, in SE Asia. A leading cause of immunologic contact urticaria, respiratory failure and anaphylaxis, and DTH.
   - DTH to latex may exist more commonly than previously expected, especially in atopics.
   - DTH and IgE reactions can coexist.

Rubber Dermatitis

2) Synthetic rubber.
Many types of chemicals used in manufacturing:
   - Vulcanization accelerators enhance raw rubber polymerization
   - Thiurams, carbamates, thioureas, diphenylguanidine, mercaptobenzothiazoles
   - Antioxidants slow environmental degradation
   - Paraphenylenediamine
   - Activators
   - Retarders
   - Reinforcing agents
   - Fillers
   - Pigments
   - Processing aids
   - Blowing agents

Rubber Dermatitis: Learn the root word

- 5/36 T.R.U.E. test allergens are dedicated to rubber:
  1. Mercaptobenzothiazole and
  2. Mercapto mix (3 benzothiazole derivatives) – vulcanization accelerators
     - N-cyclohexyl-2-benzothiazyl sulfenamide, di-2-benzothiazyl disulfide, morpholino-2-benzothiazyl sulfenamide
  3. Thiuram mix – 4 vulcanization accelerators (all with methylthiuram in name)
     - Tetramethylthiuram disulfide (TMTD)
     - Tetramethylthiuram monosulfide (TMTM)
     - Tetramethylthiuram disulfide (TETD)
  4. Carba mix – 3 stabilizers/vulcanization accelerators
     - Diphenylguanidine and the 2 "carbamates"
     - Zinc dibutyldithiocarbamate & zinc diethylthiocarbamate
  5. Black rubber mix – 3 antioxidants (N-phenyl paraphenylenediamine in name)
     - Prevents drying/cracking of grey/black rubber products
     - Avoid hair dyes with para-Phenylenediamine

For testing purposes, connect the allergen to the most likely sensitizer:

Thiuram
Mercaptobenzothiazole

Rubber Dermatitis

- Mercaptobenzothiazole is #1 cause of ACD from shoes
- Also causes ACD from rubber gloves

- Thiuram is #1 cause of ACD from gloves; #2 from shoes
- Also in disinfectant, germicide, insecticide (flea powder!), adhesives, soap/shampoo
- Wear vinyl gloves
- Antabuse (disulfiram) contains thiuram; can cause a generalized dermatitis in thiuram-sensitive patients

For testing purposes, connect the allergen to the most likely sensitizer:

Thiuram
Mercaptobenzothiazole
Rubber Dermatitis

- Monobenzyl ether of hydroquinone
  - Preservative (rubber antioxidant, among many other uses)
- Mixed dialkyl thioureas
  - Vulcanization of rubber, especially neoprene
  - If all other patch testing to rubber is negative, consider this
  - Mouse pads, Spans, rubber grips in gym, among others
  - The mixed dialkyl thioureas are a mixture of the two more common thioureas (diethylthiourea & dibutylthiourea)
- Rubber gloves: Thiuram and carbamates
- Shoes, industrial materials, and tires: Mercaptans and paraphenylenediamine
- Neoprene rubber in medical and sporting goods: Thioureas

Shoes

- Rubber – Group of allergens which is the #1 cause of shoe ACD
  - Mercaptobenzothiazole (#1), thiuram (#2), monobenzoyl ether of hydroquinone, mixed dialkyl thioureas, dithiodimorpholine (DTDM)
- Leather tanning
  - Potassium dichromate
  - Formaldehyde (white leather)
- Adhesives
  - p-tert-butylphenol (BTBP) formaldehyde resin
  - Colophony resin
- Foam padding (polyurethane): Diisocyanates
- Metals: Cobalt; nickel
- Dyes

Chromate allergy

- Chromium salt
- Used in:
  - Tanned leather (gloves & shoes) – potassium dichromate
  - Wet cement, mortar (#1 ACD for construction workers)
  - Green pigment: Paints, dyes, tattoos, cosmetics
  - Foods high in chromium may exacerbate chromate dermatitis
- Allergy to shiny material? Think nickel/cobalt, not chrome.

COBALT!

- 2016 contact allergen of the year (why?)
  - 7% of NACDG patients tested positive
  - Fallacy: Don’t have to have nickel co-sensitization
  - Darker (silver) metal jewelry = cobalt
  - Leather products, implanted devices
  - Rare sensitivity to B12 oral/injected

Alkyl glucosides – 2017 Contact Allergen of the Year!

- A group of several compounds including decyl, lauryl, cetearyl, and coco glucosides
- Surfactants
- Low irritancy and allergenicity profiles
- “Eco-friendly”
- Personal care products
- Small but steady rise in allergy rates
- Decyl glucoside is an allergen in sunscreens
- Cross-reaction is common
Cosmetics

• #1 cause of ACD in cosmetics: Fragrance
  • Balsam of Peru (50%), Fragrance mix I and II (75%)

• #2 cause of ACD in cosmetics: Preservatives (including)
  • Formaldehyde releasers
  • Non-formaldehyde preservatives:
    • Kathon CG (MCI/MI, methylchloroisothiazoline/methylisothiazolinone)
    • Parabens – “the parabens paradox” – ACD only in inflamed skin
    • Benzyl alcohol
      • Antifungal, hearing aids, non-immunologic urticaria
    • Glutaraldehyde (glutaral)
      • Instrument cold-sterilization (medical i.e. endoscopy/dental)
      • Tissue fixative
      • Xray developer
      • Biocide in cosmetic products
      • Goes thru rubber gloves
    • Thimerosal

Fragrance allergy: Balsam of Peru

• Resin from South American tree (Myroxylon/Toluifera pereirae)
  • Dark brown viscous fluid from wounding the tree – releases “granulation tissue”

• Cosmetics, perfumes

• Think: Vanilla and cinnamon
  • 2/3 is comprised of the volatile oil cinnamal, which contains:
    • Vanilline/benzyl cinnamate, cinnamic acid & aldehyde, benzyl alcohol, vanillin, and eugenol

• Avoid balsam-related substances:
  • Eugenol/isoeugenol (component of essential oils from cloves and cinnamon)
  • Foods: Tomatoes, citrus fruit peel, spices, chocolate
  • Colophony
  • Benzoin, benzyl alcohol

• Can also cause allergic contact photodermatitis

Fragrance allergy: Fragrance Mix

• 2007 Allergen of the Year

• Your mother’s fragrance: Fragrance Mix I (1977)
  • Evernia prunastri (oak moss) – masculine odor
  • Eugenol (cloves)
  • Isoeugenol
  • Cinnamon
  • Cinnamic alcohol (very common, also in Balsam of Peru)
  • Hydroxycitronellal
  • Geraniol
  • Amyl cinnamal

• New in 2005: Fragrance Mix II (2005)
  • Citronellol
  • Hexyl cinnamal
  • Citral
  • Coumarin
  • Farnesol
  • Hydroxyisohexyl 3-cyclohexene carboxaldehyde [lyral] 2.5%

This patient recently developed this allergic contact dermatitis to fragrance. You will patch test him but in the meantime tell him to avoid:

• Chamomile
• Primin
• Abietic acid
• Benzocaine
• Cinnamon

Patients allergic to fragrances also may need to avoid certain spices like cinnamon.
Nails

- **Nail polish & some nail hardeners/base coat**: Contain a film-forming resin to increase adhesion of the nitrocellulose film
  - Toluene sulfonamide-formaldehyde (tosylamide/formaldehyde) resin is used most commonly
  - Substitute a polyester (“hypo-allergenic”) resin instead

- **Artificial (acrylic) nails**: Cyanooacrylate, methyl methacrylate, ethyl acrylate, nickel
  - Methyl methacrylate – peripheral neuropathy in addition to ACD
  - Acrylates: 2012 Contact allergen of the year
  - Have been reports of systemic contact dermatitis to acrylate

- **Epoxy resins** - Glues, nail lacquers, artificial nails, paints, adhesives
  - Most common epoxy monomer is bisphenol A/epichlorohydrin

Propylene glycol

- 2018 contact allergen of the year!
- 2-3% of allergy cases
- Ubiquitous
- Skin care products and cosmetics, coated pills, food coloring, flavorings (i.e. vanilla extract), topical medications

Systemic cross-reactivity

**Para-phenylenediamine (PPDA)**
- HCTZ
- Procainamide
- **Para-aminobenzoic acid (PABA)**
  - PABA isomers (anesthetics, ie benzocaine)
  - PPDA is derived from PABA
  - Amyl dimethyl PABA (padimate A)
  - Octyl dimethyl PABA (padimate O)
- **Parabens** (ester of para-hydroxybenzoic acid)
- Para-aminosalicylic acid
- Sulfonamides (bactrim)
- Sulfonylureas (glyburide)
- Azo and aniline dyes

**Ethylendiamene**
- Hydroxyzine
- Theophylline
- Aminophylline
  - EDTA – controversial
- Mycolog - historical
- Antazoline
- Promethazine
- Piperazines
  - Preservative in medicated creams, esp. antifungals, among other uses

Which antihistamine should be avoided by a patient who is patch test positive to ethylenediamine:
A. Terfenadine
B. Hydroxyzine
C. Cyproheptadine
D. Diphenhydramine
E. Chlorpheniramine

Topical steroids

- **Class A**: Hydrocortisone & triamcinolone acetonide (test antigen) type
  - Oral steroids
- **Class B**: Triamcinolone acetonide & budesonide (test antigen) type
  - Flucinonide, desonide
- **Class D**: Hydrocortisone-17-Butyrate (Locoid) & budesonide (test antigen)
  - May be less allergenic: Mometasone furoate and fluticasone propionate

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Topical steroids
- Class A: Hydrocortisone & tixocortol pivalate (test antigen) type
  - Orals:
    - Hydrocortisone
    - Tixocortol pivalate

- Class B: Triamcinolone acetonide & budesonide (test antigen) type
  - Fluocinonide, desonide

- Class C: Hydrocortisone-17-Butyrate (Loid) & budesonide (test antigen)
  - Hydrocortisone valerate, betamethasone valerate, clobetasol propionate
  - May be less allergenic: Mometasone furoate and fluocortisol propionate

- Class D: Hydrocortisone-17-Butyrate (Loid) & budesonide (test antigen)
  - Budesonide cross-reacts with Hc-17-B and seems to be a better marker for Hc-17-B allergy than is Hc-17-B itself

Topical steroids (continued)
- Class A: Hydrocortisone & tixocortol pivalate (test antigen) type
  - Oral steroids

- Class B: Triamcinolone acetonide & budesonide (test antigen) type
  - Fluocinonide, desonide

- Class D: Hydrocortisone-17-Butyrate (Loid) & budesonide (test antigen)
  - Hydrocortisone valerate, betamethasone valerate, clobetasol propionate
  - May be less allergenic: Mometasone furoate and fluocortisol propionate

Class C: Betamethasone phosphate (not valerate) type
  - Does not cross-react with A, B, & D, likely to cause allergy
  - Desoximethasone (Topicort)

A word on photopatch...
- The 2014 contact allergen of the year: OXYBENZONE (BENZPHENONE-3)
  - Low prevalence of reactivity (.9% of those patch tested) but nominated because of increasing use in sunscreen-containing personal health products
  - But is the most relevant photocontact allergy
  - Remember that most common sunscreen allergy is actually to fragrances, vitamin E, and preservatives

Plant dermatoses
- Phototoxic (phytophotodermatitis)
- Allergic contact dermatitis
- Contact urticaria
  - Toxic-mediated/Immunologic
- Irritant contact
  - Chemical/Physical

Phototoxic (phytophotodermatitis)
- A phototoxic reaction (increased sunburn response)
- Direct tissue and cellular injury after UVA-induced activation of a phototoxic agent
- No prior allergic sensitization
- Erythema/edema after 24 hours → delayed hyperpigmentation
- Plants containing furocoumarins
Phototoxic (phytophotodermatitis)

- **Apiaceae family (Umbilliferae)** - #1 cause
  - Sources: Dill, wild carrot, celery, rhubarb, hogweed, fennel, parsley, parsnip, angelica, wild chervil
  - Sensitizer: Furocoumarins
  - “Strimmer” dermatitis – from lawn mower
  
- **Rutaceae family** - #2 cause
  - Sources: Lemon, lime, grapefruit, orange, blister plant, gas plant, rue, burning bush, bergamot orange, Hawaiian lei flowers (mokihana), sandalwood
  - Sensitizer: Furocoumarins
  - Berloque dermatitis – Perfume with oil of bergamot (S-MOP)

- **Hypericaceae**
  - St John’s wort

- **Moraceae family**
  - Sources: Figs, mulberries

- **Fabaceae (Leguminose) family**
  - Sources: Scurf-pea

A grocery worker has phytophotodermatitis to celery.

- **Name the plant family:** Apiaceae/Umbilliferae
- **Name the sensitizer:** Furocoumarins

Allergic contact dermatitis

- **Anacardiaceae (Toxicodendron genus)**
  - Sources: Poison oak/ivy/sumac
    - Also in the family: Brazilian pepper, cashew, Japanese lacquer tree, mango peel, Indian nut tree, black varnish tree, ginkgo
    - Sensitizer: Catechols, oleoresin (urushiol) – “rhus dermatitis”
    - “Black dot dermatitis” (urushiol self-melanizes on O2 exposure)
    - Vinyl gloves protective (not nitrile)

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    - Vinyl gloves protective (not nitrile)
Allergic contact dermatitis

• **Compositae family (Asteraceae)**
  - Sources: Chrysanthemum, daisy, sunflower, dandelion, marigold, ragweed, pyrethrum, feverfew, chamomile, liverwort, sagebrush, chicory, endive, tarragon, marigold, artichoke
  - Sensitizer: Sesquiterpene lactone
  - Those with tea tree oil allergy can cross-react to d-limonene fragrance allergen, compositae mix, and colophony
  - Permethrin is made from chrysanthemums

  ![Images of flowers](Image)

Allergic contact dermatitis

• **Alstroemeriaeae**
  - Source: Peruvian lily / Alstroemeria
  - Sensitizer: glycoside Tuliposidase A

• **Liliaceae**
  - Source: Tulip, asparagus, hyacinth
  - Sensitizer: Tulipalin A

  ![Image of a flower](Image)

Allergic contact dermatitis

• **Primulaceae**
  - Sources: Primula (primrose)
  - Sensitizer: Primin
  - Cross-react: Other naturally occurring quinones, e.g. orchids or tropical woods (teak, rosewood)

• **Alliaceae family**
  - Onions, garlic, chive
  - Sensitizer: Diallyl disulfide (allylpropyl disulfide, allicin)

Which of the following is likely to cause an allergic contact dermatitis in a person sensitized to toxicodendron?

A) Banana
B) Almond
C) Lime peel
D) Mango peel
E) Avocado peel
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E) Avocado peel

If an allergy to chrysanthemums or ragweed is suspected, the most appropriate allergen to test with is:

A. pantadecacatechol  
B. tuliposide A  
C. dialyldisulfide  
D. dipentene  
E. sesquiterpene lactones

Contact urticaria

- Non-immunologic urticaria – toxin-mediated (no sensitization)
  - *Urtica dioica* (stinging nettle; trichome hairs → histamine, serotonin, Ach)

- Immunologic - Prior sensitization required
  - A long list of plants – celery most common
  - *Latex (Hevea brasiliensis)* rubber tree plant
    - Cross reactivity: Avocado, banana, chestnut, kiwi
  - Atopics are more likely to have this type of contact urticaria

Chemical irritant contact

- Family amaryllidaceae
  - *Daffodil* (*narcissus*) – #1 cause of irritant dermatitis in florists
    - Irritant: Calcium oxalate

- Family araceae family - *Dumb cane* (*dielephalia picta*)
  - House plant; Ca oxalate released after contact w/ moist surface → edema, blisters, hoarseness (“dumb cane”)
    - Irritant: Calcium oxalate

- Pineapple
  - Irritant: Calcium oxalate, bromelin

Match the plant with its associated chemical component:

1) Daffodil  
2) Onion  
3) Parsnip  

A) Diallyl disulfide  
B) Calcium oxalate  
C) Furocoumarin
<table>
<thead>
<tr>
<th>Daffodil</th>
<th>Onion</th>
<th>Parsnip</th>
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<tbody>
<tr>
<td>A) Diallyl disulfide</td>
<td>B) Calcium oxalate (irritant)</td>
<td>C) Furocoumarin</td>
</tr>
</tbody>
</table>

Onion can also cause chemical irritant dermatitis via thiocyanates.

Thank you!

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