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

N. American Contact Dermatitis Group Patch Test Results ‘13-14 (13 centers, 70 allergens) - Dermatitis Jan/Feb, 2017

1. Nickel (18.5%)
2. Fragrance Mix I
3. Methylisothiazolinone (newly added)
4. Neomycin
5. Cobalt chloride
6. Benzocaine
7. Balsam of Peru/myroxylon pereirae
8. Formaldehyde 2% eq
9. Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI, Kathon CG) ↑
10. Fragrance Mix II
11. Formaldehyde 1% eq
12. Lecithin (soy alchohol)
13. Quaternium-15 (Dowcic 200)
14. Carba mix
15. Iodopropnyl butylcarbamate
16. Diethylene glycol
17. Diazolidinyl urea
18. Imidazolidinyl urea
19. Propylene glycol
20. Methylisothiazolinone
21. Thiomersal mix
22. Oxirane glycol (vehicle)
23. Hydroxyethyl methacrylate (HEMA) ↑ - nail acrylate

**Formaldehyde Releasers**

- Quaternium-15 (Dowcic 200)
- Imidazolidinyl urea
- Diazolidinyl urea (Germall)
- DMDM hydantoin
- 2-bromo-2-nitropropane-1,3-diol (Bronopol)
- Tris(hydroxymethyl)aminomethane

**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 #3
  - 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"
• Take-home points:
  – 21% of patients had a relevant allergen outside of the 70-allergen NACDG panel; 14% of these were occupationally related
  – ¼ to 1/3 of allergens detected by NACDG panel would have been missed by T.R.U.E. test

How about in pediatrics?

Most common allergens in children in North America:
• Nickel
• Neomycin
• Cobalt
• Fragrance
• Balsam of Peru
• Gold
• Formaldehyde
• Lanolin/wool alcohols
• Thimerosal
• Potassium dichromate

Textiles

• 3 main categories:
  1. Textile finishes
  2. Dyes
  3. Rubber additives
• Clinical: Often diffuse; worse in areas of friction/sweating; axillary folds involved, vault spared

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)
  • Paraphenylenediamine – 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 (Docosyl 200)
    • Imidazolidinyl urea, diazolidinyl urea (Germain)
    • DDMH hydantoin
    • 2-bromo-2-nitropropane-1,3-diol (Bronopol)
    • Tris(hydroxymethyl)nitromethane
  – There don’t necessarily x-react; imidazolidinyl urea may x-react the least

p-tert-butyphenol (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
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
   - Filler
   - 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
  2. Mercaptobenzothiazole (MBT) derivatives – vulcanization accelerators
     - N-cyclohexyl-2-benzothiazyl-sulfenamide (CBS), 2-mercaptobenzothiazyl disulfide (MBTS)
  3. Thiuram mix – 4 vulcanization accelerators (all with methylthiuram in name)
     - Tetramethylthiuram disulfide (TMTD)
     - Tetramethylthiuram monosulfide (TMTM)
     - Tetramethylthiuram disulfide (TETD)
  4. Carbam mix – 3 stabilizers/vulcanization accelerators
     - Diphenylguanidine (DPG)
     - Zincdibutyldithiocarbamate & zincdiethyldithiocarbamate
  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:

 Mercaptobenzothiazole  
 Thiuram
Rubber Dermatitis

- Monobenzyl ether of hydroquinone
  - Preservative (rubber antioxidant, among many other uses)
- Mixed dialkyl thioureas – 2009 Allergen of the Year
  - Vulcanization of rubber, especially neoprene
  - If all other patch testing to rubber is negative, consider this
  - Mouse pads, Spanx, 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: Mercaptos and paraphenylenediamines
- 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), monobenzyl ether of hydroquinone, mixed dialkyl thioureas, dithiodimorpholine (DTDM)
- Leather tanning
  - Potassium dichromate - #1 shoe ACD, some newer series
  - Formaldehyde (white leather)
- Adhesives
  - p-tert-butylphenol (BTBP) formaldehyde resin - #1 shoe ACD, some newer series
  - Colophony resins
- Foam padding (polyurethane): Diisocyanates
- Metals: Cobalt - #3 shoe ACD in newer series; 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, cosmetics
  - Foods high in chromium may exacerbate chromate dermatitis
- Allergy to shiny material? Think nickel/cobalt, not chrome.

Colophony rosin

- Mixture of >100 compounds from trees
- Multiple different forms of colophony, with different allergens
  - In its unmodified form, specific allergen is abetic acid
- Used for “stickiness” in cosmetics (colophonium), adhesives, creams, grip aids, gum, paper products
- Allergies: Neoprene glues, insoles
- Can also cause allergic contact photodermatitis

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

Chemo Cobalt Test™ contains Nitroso R salt solution. Used on cobalt-containing objects, the solution will turn bright, reddish-pink.

Stringed instrument bow and rosin
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, methylchloroisothiazolinone/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
      - Biocide in cosmetic products
      - Goes thru rubber gloves

• Thimerosal

Thimerosal

- Preservative in solutions, containing ethylmercury and thiosalicylate
- Sensitivity to molecule’s mercury portion > thiosalicylic acid portion
  - But patients with ACD to thiosalicylic acid may show photosensitivity to NSAID piroxicam (thimerosal cross-reacts with a photoproduct of piroxicam and L-cysteine)
- Eye and nose drops can cause conjunctivitis & eyelid dermatitis
- Vaccines → substitute phenol
  - Since 2001, with the exception of some inactivated influenza vaccines, thimerosal is not used in vaccines for < 6 years old
  - Single dose flu vaccines do not contain 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:
  - Benzocaine/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 (clove)
  - Isoeugenol
  - Cinnamal
  - Cinnamic alcohol (very common, also in Balsam of Peru)
  - Hydroxyctronnellal
  - Geraniol
  - Amyl cinnamal

- **New in 2005:** Fragrance Mix II (2005)
  - Citronnellol
  - Hexyl cinnamal
  - Citral
  - Coumarin
  - Farnesol
  - Hydroxycitronelal 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
Hair

• Hair Dyes
  • Para-phenylenediamine (also in black henna tattoos)
  • Printer inks, black rubber, photodevelopers
  • Purpuric contact dermatitis
  • Penetrates latex gloves (but nitrile is protective)
  • Metallic hair dyes that contain metals

• Hair bleaches: Ammonium persulfate
  • Boosts peroxide bleaches, causes contact urticaria & anaphylaxis

• Perms:
  • Salon - Glyceryl monothioglycolate – acid permanent
    • Penetrates latex gloves; stylists; stays in shaft for months → chronic ACD
  • Home – Ammonium thioglycolate – alkali permanent
    • Causes ICD not ACD
  • Home - Sulfite

NB: Scalp is particularly resistant to contact dermatitis; allergens applied to the scalp often show dermatitis of the eyelids, ears, neck, hands, while scalp remains uninvolved

Your patient has ACD to glyceryl monothioglycolate. Help her safely perm her hair by telling her to use:

1. Methyl methacrylate
2. PTBP formaldehyde resin
3. Ammonium thioglycolate
4. Cyanoacrylate
5. Potassium dichromate

Black henna allergic contact dermatitis is due to sensitivity to:
A. sesquiterpene lactones
B. paraphenylenediamine
C. carbon
D. cadmium sulfide
E. colophony

Nails

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

• Artificial (acrylic) nails: Cyanoacrylate, 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

A few other misc. contact allergens

• Lanolin - Emollient. Test with wool alcohols

• Vehicles
  • Propylene glycol
  • Polyethylene glycol (PEGs)
  • Propyl gallate (antioxidant, cosmetics, medicaments, foods)
  • Cocamidopropyl betaine (thickening/foaming agent; cosmetics, shampoos; head and neck dermatitis)
Neomycin

- Dermatitis often develops > 7 days after exposure
- Aminoglycoside; cross-reacts with gentamycin and tobramycin
- Frequent simultaneous allergy to bacitracin (likely due to similar exposure patterns)
- 2010 contact allergen of the year

Systemic cross-reactivity

Para-phenylenediamine (PPDA)
- HCTZ
- Procaainamide
- Para-aminobenzoic acid (PABA)
  - PABA-esters (anesthetics, ie benzocaine)
  - PPDA is derived from PABA
  - Amyl dimethyl PABA (padimate A)
  - Glycyl dimethyl PABA (padimate O)
- Parabens (ester of para-hydroxybenzoic acid)
- Para-aminalsalicylic acid
- Sulfonamides (bactrim)
- Sulfonylureas (glyburide)
- Azo and aniline dyes

Ethylenediamene
- Hydroxyzine
- Theophylline
- Aminophylline (Theophylline/ethylenediamine)
- EDTA – controversial
- Mycolog - historical
- Antazoline
- Promethazine
- Piperazines
- Preservatives in medicated creams, esp. antifungals, among other uses

Topical steroids

- Class A: Hydrocortisone & triamcinalone pivalate (test antigen) type
  - Oral steroids
- Class B: Triamcinolone acetonide & budesonide (test antigen) type
  - Flucinonide, desonide
- Class D: Hydrocortisone-17-Butyrate (Lecithin) & budesonide (test antigen)
  - Hydrosolubilizer valerate, betamethasone valerate, clopeterol propionate
  - May be less allergenic: Mometasone fluorate and fluticasone 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, preservatives

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

Dimethyl fumarate

- “Sofa dermatitis”
- Preservative
- Chinese furniture, clothes
- 2011 contact allergen of the year

Coulson et al, BJD 2008
Plant dermatoses

- Phototoxic (phytophotodermatitis)
- Allergic contact dermatitis
- Contact urticaria
  - Toxin-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

Phototoxic (phytophotodermatitis)

- 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 (5-MOP)

Phototoxic (phytophotodermatitis)

- 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:
- 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)

- Sensitizer:
  - Oak - heptadecylcatechols
  - Ivy - pentadecylcatechols

Allergic contact dermatitis

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

- The most frequent contact allergens in florists are
  - Tuliposidase A (Peruvian lily/Alstroemeria species)
  - Sesquiterpene lactones (chrysanthemum/Asteraceae species)
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, allision)

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

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

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* (*dieffenbachia picta*)
  - House plant; Ca oxalate released after contact w/ moist surface → edema, blisters, hoarseness ("dumb cane")
  - Irritant: Calcium oxalate

- **Pineapple**
  - Irritant: Calcium oxalate, bromelin

Chemical irritant contact

- **Family euphobiaceae** - *Poinsettia*
  - Irritant: Phorbol ester

- **Family alliaceae** – Garlic, onions, chive
- **Family brassicaceae** - Mustard, radish
  - Irritant: Thiocyanates
Physical irritant contact

- **Prickly pear** (*Opuntia spp.*) – spines or glochids (barbed hairs which imbed in the skin)
  - "Sabra dermatitis"
  - Colonized by the cochineal insects (carmine)

Match the plant with its associated chemical component:

1) Daffodil
2) Onion
3) Parsnip

- A) Diallyl disulfide
- B) Calcium oxalate
- C) Furocoumarin

Thank you!