Metal Hypersensitivity Dermatitis

Peter C. Schalock, MD

Disclosures

- I have no relevant commercial interests or relationships to disclose

- Common reactions to metals
- Metal Hypersensitivity Reactions (MHR) to implanted devices
- Evaluation of MHR
- Distant reactions to systemic metal exposures


Metal
Mania

Epidemiology

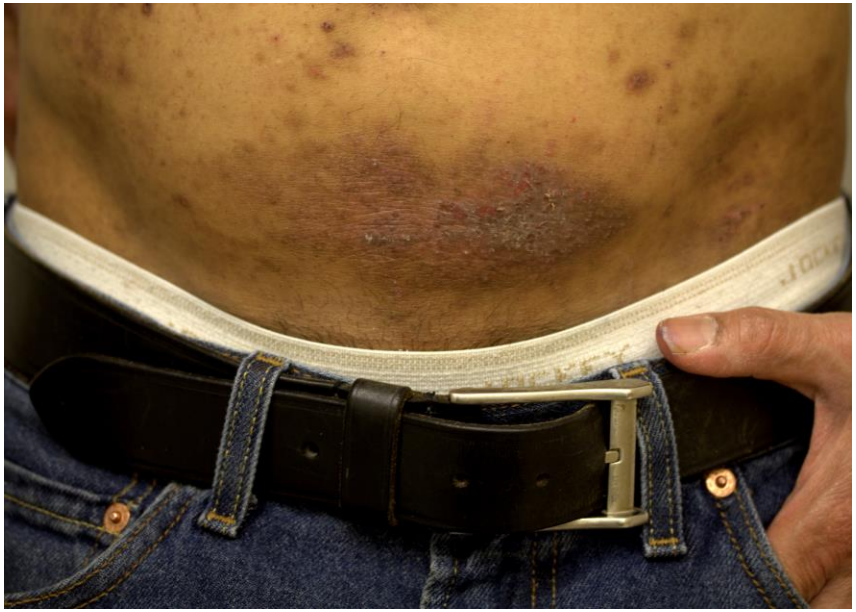
- Metal allergy is common
  - NACDG 2017-18: 16.2% Ni, Co 6.7%, Cr 1.6% (Dekoven 2021)
    - Ni: ~ 19% of adult women; 3% of adult men (Thyssen et al. 2007)(Warshaw 2015)
    - Au: ~23% of both genders (Tam, 2020 in press)
  - Prevalence of other metals, e.g. titanium, platinum, molybdenum, manganese, vanadium
    - Generally infrequent in dermatitis patients
    - Few large studies examining patch test results for less common metals

TABLE 4. Comparison of Metal Sensitivity Prevalence by Sex and Age

Allergen*	Overall		Female		Male		
	PPT, %	RPPT, %	PPT, %	RPPT, %	PPT, %	RPPT, %	P†
Nickel sulfate hexahydrate 2.5 pet	26.2	23.4	33.7	29.8	5.4	5.4	0.001
Gold sodium thiosulfate 0.5 pet	23.0	12.2	26.4	13.2	14.3	9.5	0.11
Gold sodium thiosulfate 2.0 pet	20.7	10.0	25.9	13.9	7.1	0.0	0.01
Palladium chloride 2.0 pet	19.6	14.2	25.5	18.5	4.8	2.5	0.004
Cobalt (II) chloride hexahydrate 1.0 pet	12.0	9.8	14.3	12.2	5.7	2.9	0.24
Manganese (II) chloride 2.0 pet	10.1	4.1	10.4	1.9	9.5	9.5	>0.99
Vanadium 5.0 pet	7.5	4.1	7.6	4.8	7.1	2.4	>0.99
Potassium dicyanoaurate 0.1 aq	6.8	3.4	8.6	3.8	2.4	2.4	0.28
Potassium dichromate 0.25 pet	6.5	5.8	7.8	6.9	2.8	2.8	0.45
Copper sulfate 2.0 pet	6.0	2.7	6.5	1.9	4.8	4.8	>0.99
Stannous chloride 1.0 pet	5.4	0.0	6.6	0.0	2.4	0.0	0.44
Mercury 0.5 pet	3.4	2.0	4.7	2.8	0.0	0.0	0.32
Mercury ammonium chloride 1.0 pet	2.7	2.0	3.8	2.9	0.0	0.0	>0.99
Vanadium (III) chloride 1.0 pet	2.7	1.4	3.8	1.9	0.0	0.0	0.58
Mercuric chloride 0.1 pet	2.7	0.7	2.9	1.0	2.4	0.0	0.32
Iridium (III) chloride trihydrate 10.0 aq	2.7	2.0	1.9	0.0	4.8	4.8	0.58
Iron (III) chloride 2.0 pet	2.7	2.0	2.8	1.9	2.4	2.4	>0.99
Zirconium chloride 1.0 pet	2.0	2.0	2.8	0.9	0.0	0.0	0.19
Zinc chloride 2.0 pet	2.0	2.0	0.9	0.9	4.8	4.8	0.56
Iridium 1.0 pet	1.4	0.7	1.9	1.0	0.0	0.0	>0.99
Indium 1.0 pet	1.4	0.0	0.9	0.0	2.4	0.0	0.49
Calcium titanate 10.0 pet	0.7	0.7	1.0	1.0	0.0	0.0	0.29
Copper (I) oxide 5.0 pet	0.7	0.0	0.0	0.0	2.4	0.0	>0.99
Zinc 2.5 pet	0.7	0.0	0.9	0.0	0.0	0.0	0.29
Lead acetate trihydrate 0.5 aq	0.7	0.0	0.9	0.0	0.0	0.0	>0.99
Molybdenum 5.0 pet	0.7	0.0	0.9	0.0	0.0	0.0	>0.99
Stannous oxalate 1.0 pet	0.7	0.0	0.9	0.0	0.0	0.0	>0.99
Cadmium chloride 1.0 aq	0.7	0.0	0.0	0.0	2.4	0.0	>0.99
Titanium oxalate 5.0 pet	0.7	0.7	0.0	0.0	2.4	2.4	0.28
Titanium oxide 10.0 pet	0.7	0.7	0.0	0.0	2.4	2.4	0.28

Tam et al, Dermatitis. 2020;31(6):359-66

Cutaneous ACD to metals



- Stainless Steel
  - Ni, Co, Cr, V, Mb
- Gold
  - Skin
  - Mucosal
- Ni, Co, Cr, Au on many standard series

Nickel sulfate

- One of the most common allergens (all ages)
  - Adults 16-18%
  - Children 13 – 28% (Bruckner)(Zug)

  - Jewelry/Everyday products
  - Orthopedic implants & Endovascular devices
  - Oral Ingestion
  - Medical devices

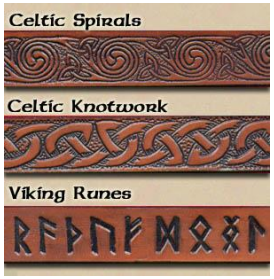
Cobalt II chloride hexahydrate

- Co-reacts with Nickel (Brandão, 2012)
- Many orthopedic devices are cobalt-chromium-molybdenum (Ni ~1%)

Potassium Dichromate

- **Leather**
- **Cement industry**
- **Tattoos**

- **Orthopedic joint systems**
  - especially cobalt-chrome alloys



Nitinol

- Nickel-Titanium systems = Nitinol
  - 55% Nickel / 45% Titanium
  - Superelastic/Temp dependent
  - Stents, Gynecological Devices

https://en.wikipedia.org/wiki/Nickel_titanium

Biomedical Devices

- Primarily composed of metal alloys, plastic components, Silicone
  - Stainless Steel
    - 316L (~16% Ni)
    - CoCrMo (~1% Ni)
  - Nitinol (55% nickel/45% titanium)
  - Oxidized Zirconium
  - Titanium
    - Ti6Al4V/TiNbN
    - Trace Ni

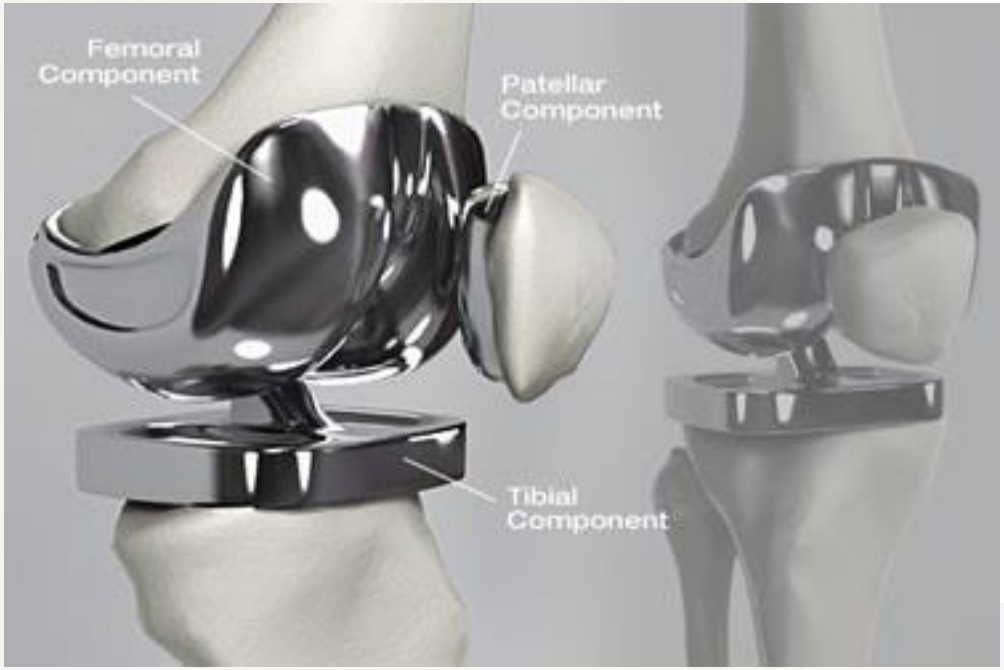
Review Article

Biomaterial Hypersensitivity: Is It Real?

- Does it make a difference for our patients?
- Do we care about potential MHR?

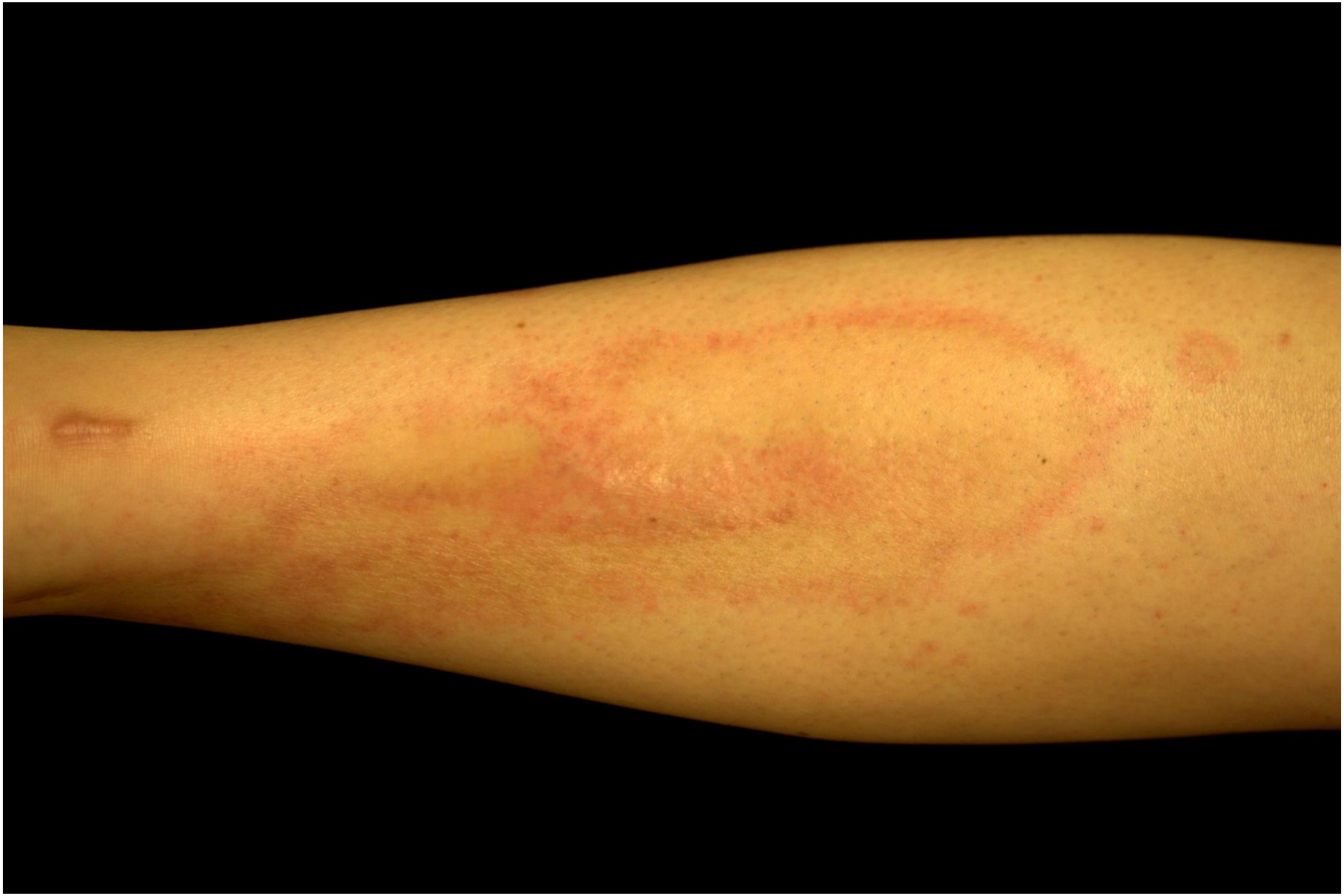
BioMed Research International
Volume 2015, Article ID 137287, 10 pages

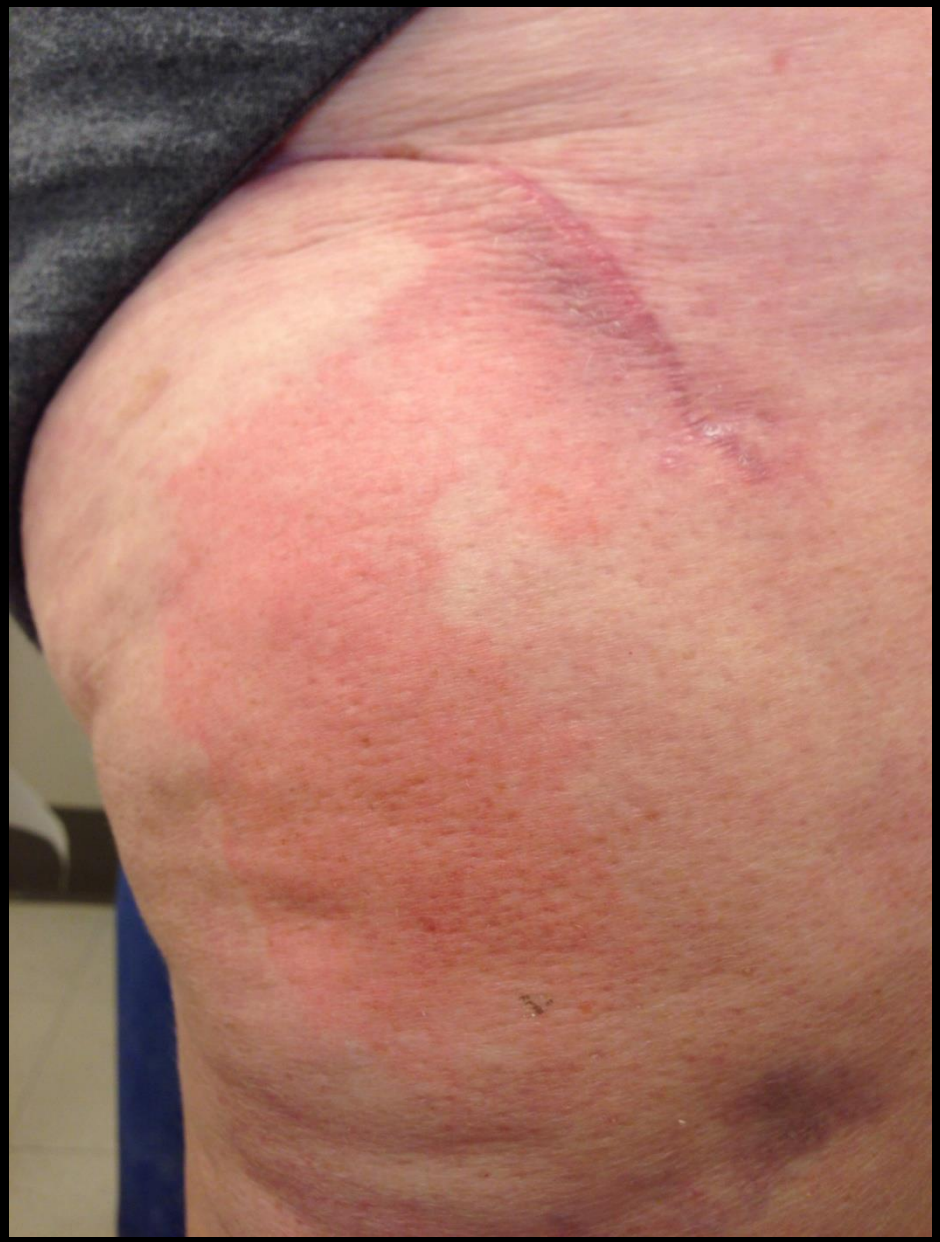

YD 32
YD 32

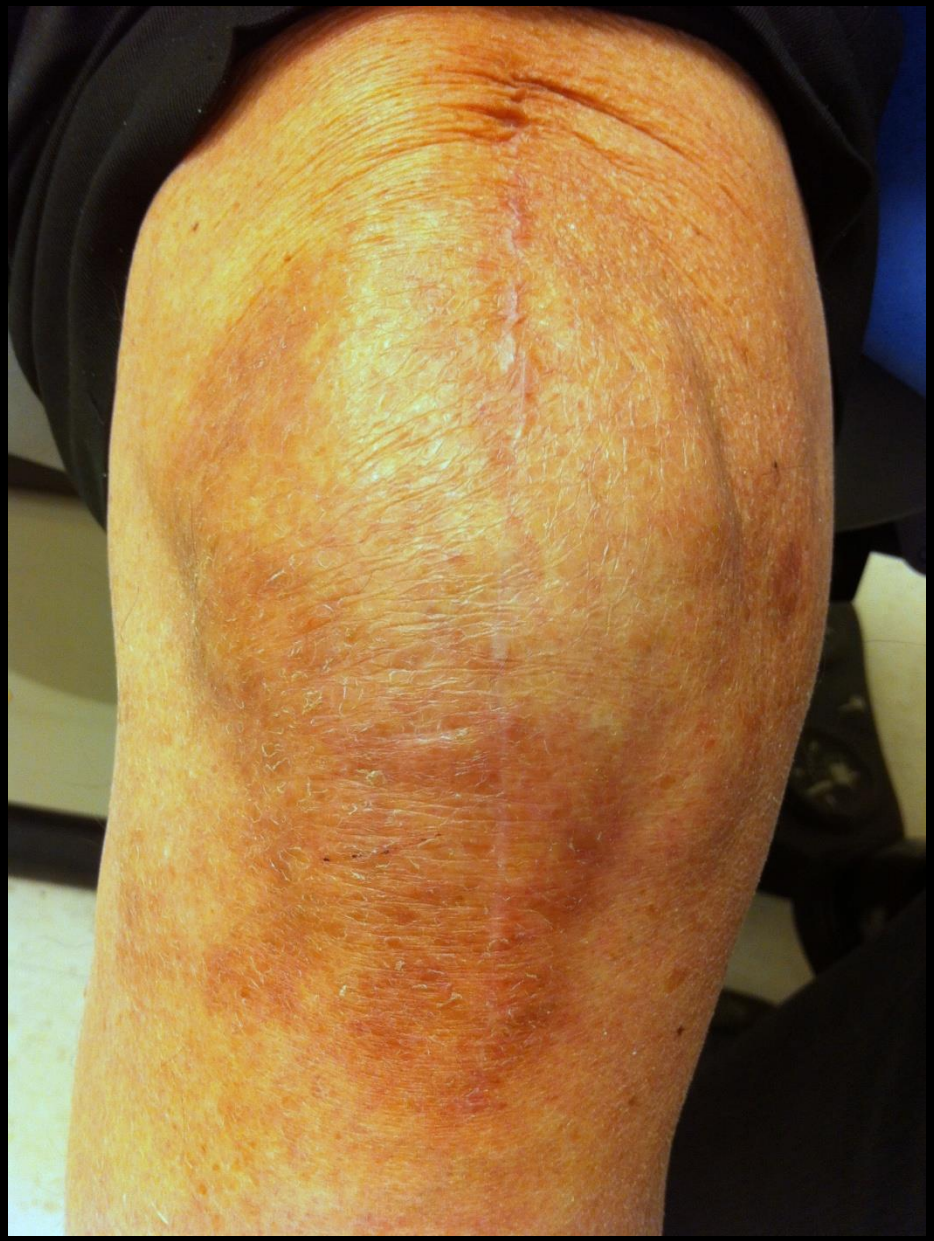


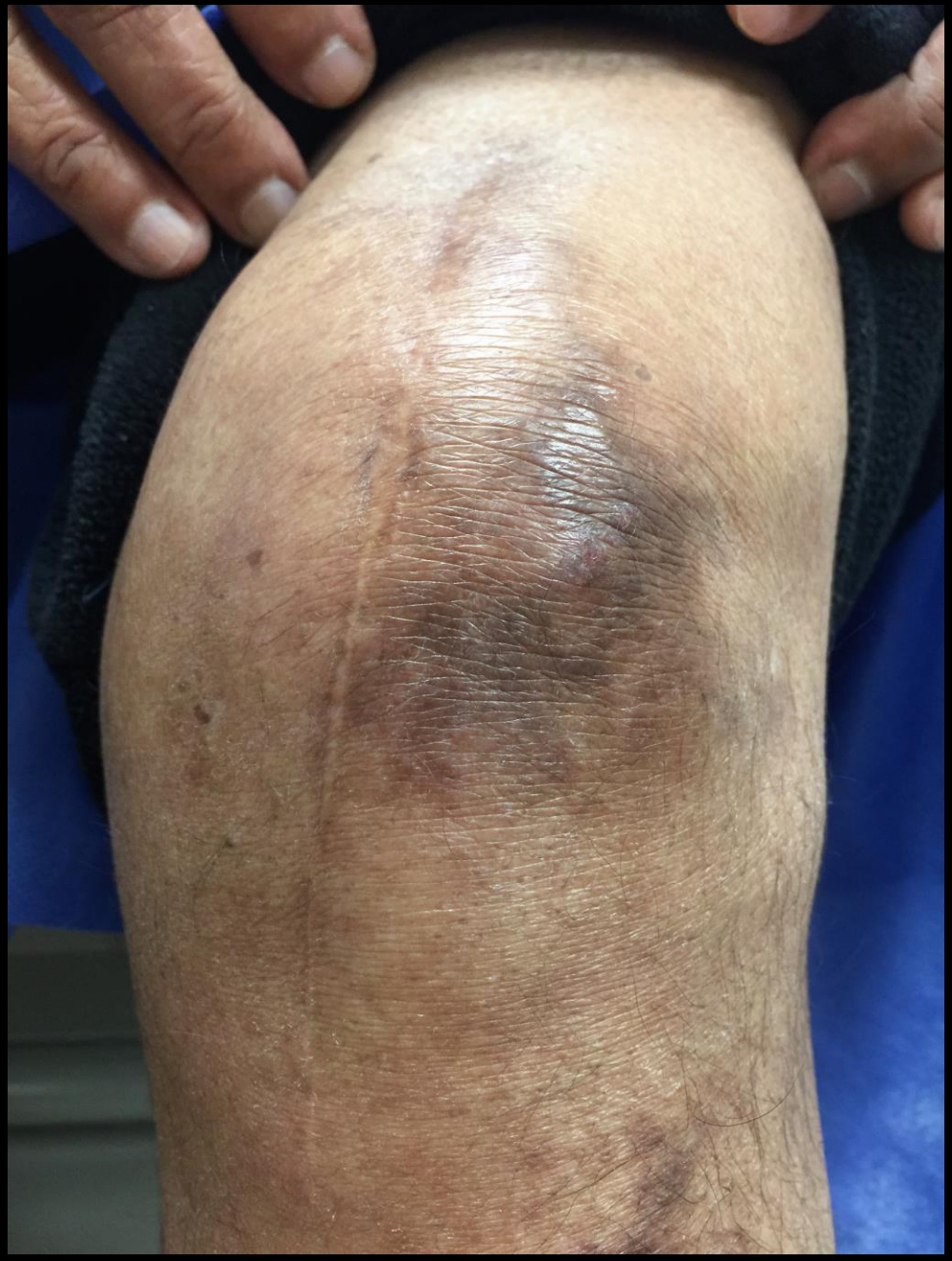
CASES

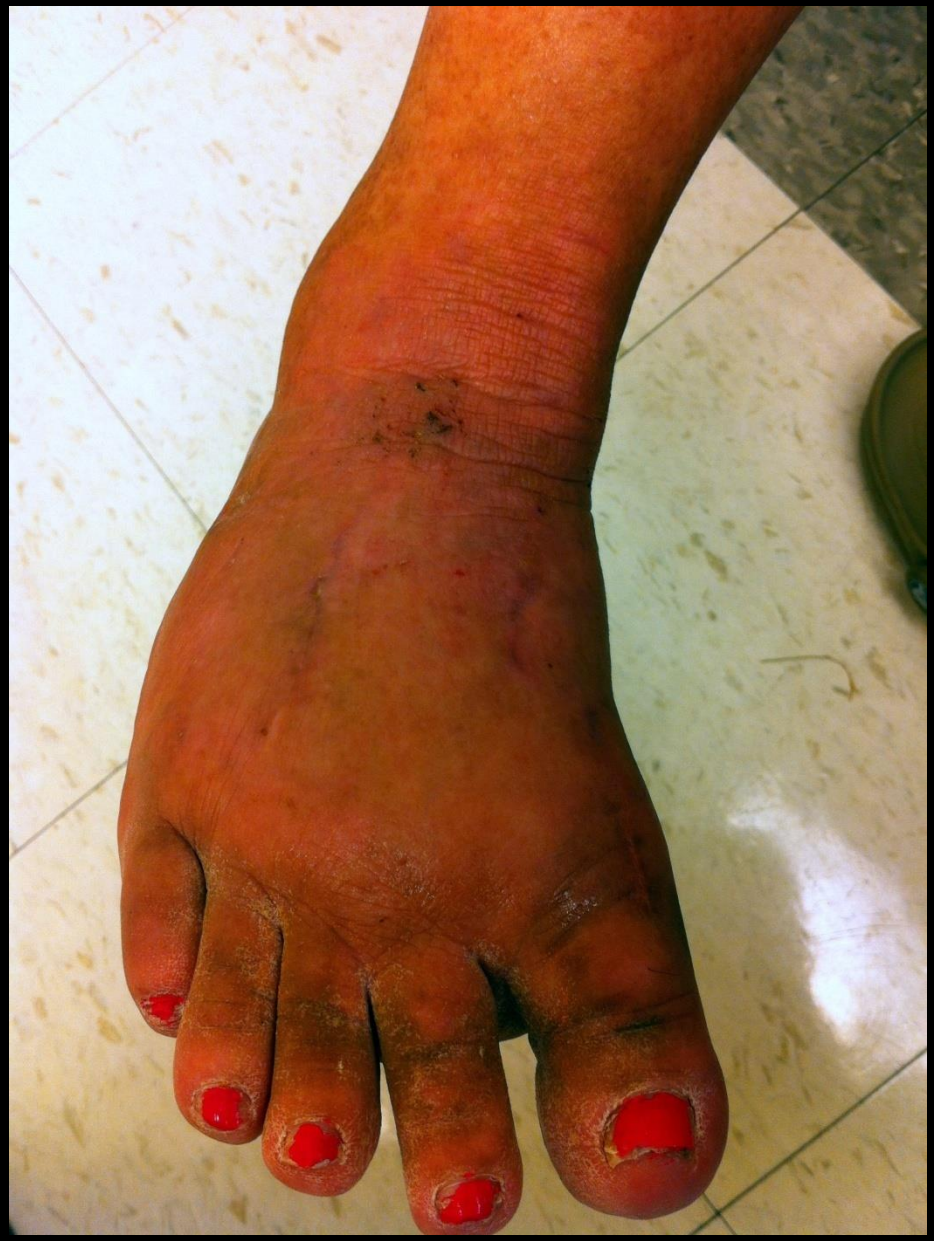
Is MHR to implanted devices real?











52 y/o woman

- Metal reactions “since childhood”
- Causes itchy, blisters and redness with “any metal exposure” on the skin snaps/ear rings and really anything metal bothers
- TMT joint fusion for hallux valgus and arthritis on right foot March 5, 2012
  - Within 24 hours with itching/redness and blistering started on dorsal foot around the incision site
- Surgical wounds – 6 months to close
- Fatigue and "tin can" taste in mouth since the surgery
- Patch test +: Nickel, Chromium, Bacitracin

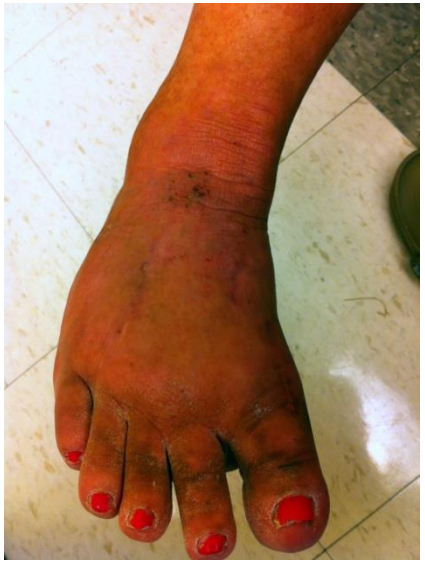
Past skin history:
No personal or family history of psoriasis.

Atopic history:

Asthma -

Seasonal Allergies -

Atopic Dermatitis -



MOST FREQUENT COMPLICATIONS OF METAL IMPLANT HYPERSENSITIVITY

MHR is uncommon

- Orthopedic devices
  - Old MoM -> definitely happened
  - Newer MoP -> much rarer reactions

Cutaneous allergic complications orthopaedic implants

- Reports starting in the 1960's
  - localized allergic dermatitis
  - urticaria
  - impaired wound healing overlying the metallic implant
  - systemic allergic dermatitis reactions distant anatomical sites
  - cutaneous vasculitis

Extra-cutaneous allergic complications orthopaedic implants

- Pseudotumor/Metallosis
  - Delayed type hypersensitivity reactions (Hallab & Jacobs 2009)
    - Solid or cystic masses communicate with the prosthesis
    - Cell and tissue necrosis/heavy macrophage response to wear particles and are often accompanied by an ALVAL infiltrate
  - Metal ions activate, **adaptive type IV response** (Hallab 2008)
  - Large particulate wear debris phagocytosed by macrophages
- ALVAL (aseptic lymphocyte-dominated vasculitis-associated lesion)
  - Perivascular lymphocytic/plasma cell infiltrate
    - Found in peri-prosthetic tissues in response to the deposition of cobalt-chromium wear particles
  - Immune reactions INCLUDE Type IV reactions (multifactorial)

- Aseptic Loosening
  - implant debris recruits macrophages/osteoclasts to peri-prosthetic regions = **bone resorption**

- Cutaneous Reactions
  - Bx often c/w type IV hypersensitivity

ACD from Bone Cement Components

Allergen	Use	~% Positive
N,N,-dimethyl-p-toluidine	Reaction initiator	10
Polymethyl methacrylate (MMA)	Cement base	25
Benzoyl Peroxide	Activator	8-10
Hydroquinone	MMA stabilization	5
Gentamicin	Antibiotic	17-24

Dermatitis, Vol 22, No 2 (March/April), 2011: pp 65–79

MHR to Vascular/Cardiac Implants

Cardiac Stents

- Materials used in US:
  - 316L stainless steel (Ni 12%, Cr17%, Mb2%)
    - Gold plated stents – use discontinued due to clear ISR risk (Svedman, 2009)
  - Cobalt-chromium alloys (Ni 9-35%)
  - Platinum-cobalt alloys (Ni 9%)
  - Nitinol (55% nickel, 45% Titanium)
- Drug Eluting stents
  - ISR rates decreased initially, ISR increases again after the immunosuppressive coating diminishes

MHR to Vascular/Cardiac Implants

- Gong, 2013
  - Increased risk of ISR with metal allergy
  - Meta-analysis 2013: 9 studies, 1,223 patients
    - Pre-existing metal allergy pose an increased risk of ISR, with an odds ratio of 2.65
  - OR for Asian patients were higher than European patients (3.71 vs 2.25)
    - Former group may be more susceptible to ISR

Gong Z, Li M, Guo X, Ma Z, Shi J.Stent implantation in patients with metal allergy: a systemic review and meta-analysis. Coron Artery Dis. 2013 Dec;24(8):684-9.

In-stent Restenosis

- Retrospective studies – nickel implicated in ISR of bare metal stents
- Prospective studies – No confirmed association
- Drug eluting stents
  - Case series – late ISR in metal allergic patients
- Recurrent restenosis patients
  - 2 studies: higher rates of ISR in Ni allergic patients

Kounis syndrome

- Acute ISR secondary to hypersensitivity to stent components (Nickel)
  - Involves release of inflammatory cytokines through mast cell activation, which leads to coronary artery vasospasm and/or atheromatous plaque erosion or rupture
- Tangent –> Nickel exposure elicits type I reactions (acute and chronic urticaria)

Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? Int J Cardiol. 2006;110(1):7–14.

Role of contact sensitization in chronic urticaria

Laura Guerra, MD, Anthi Rogkakou, MD, Piera Massacane, MD, Cinzia Gamalero, BS,
Enrico Compalati, MD, Cristian Zanella, MD, Antonio Scordamaglia, MD,
Walter G. Canonica, MD, and Giovanni Passalacqua, MD
Genoa, Italy

Table II. Patch test results

Compound	No. of patients testing positive	M/F (No.)	Details
Metals	20	5/15	13 nickel, 6 cobalt + nickel 1 cobalt
Chemical	16	7/9	6 parabens, 3 colophony, 2 benzocaine, 1 thiuram mix, 1 bisulfites, 1 potassium dichromate
Cleaning agents/cosmetics	9	3/6	6 balsam of Peru, 1 fragrances mix 1 Kathon, 1 thimerosal
Stabilizers/accelerators	5	1/4	3 ethylenediamine 2 mercaptobenzothiazole

(J Am Acad Dermatol 2007;56:88-90.)

Other intravascular devices

- Amplatzer Devices (NiTi) for VSD closure
  - Arrythmias
  - Systemic Dermatitis
  - Chronic Migraine headaches

- Other stent devices

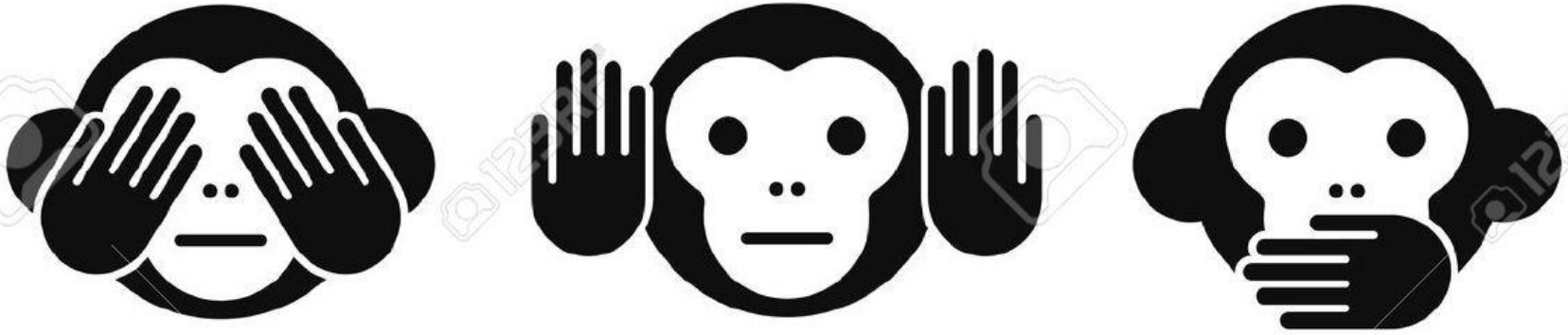
MHR to other implants

- Pacemakers & Spinal cord stimulators
  - Titanium, polyurethanes, silicone rubber, silicone adhesive -> External exposures
  - Alternative coatings
    - Parylene
    - Gold
- Stainless steel sternal wires
- Nuss Procedure
  - Patch testing prior recommended for all patients
    - Selvick A, Lloyd R.Dermatitis. 2018 Mar/Apr;29(2):63-65.

Approaches to MHR

Who should get tested?

- Two common scenarios
  - ***Pre-implantation***
  - *Post-implantation*



Metal Allergy Screening Prior to Joint Arthroplasty and Its Influence on Implant Choice: A Delphi Consensus Study Amongst Orthopaedic Arthroplasty Surgeons

Arif Razak, MRCS, Ananthan Dave Ebinesan, MRCS, and Charalambos Panayiotou Charalambous, MD, FRCS
Department of Orthopaedic Surgery, Blackpool Victoria Hospital, Lancashire, UK

Delphi analysis (N=18)

- See no evil (Ignore the data)
  - "Most respondents agreed in proceeding with cobalt chromium or stainless steel implant in patients suspected of metal allergy regardless of the results of cutaneous patch testing"
- Hear no evil (Don't ask)
  - "Patients having metal arthroplasty surgery should not be routinely questioned about metal allergy prior to surgery"
- Speak no evil (Don't tell)
  - "Patch testing is not necessary even if metal allergy is suspected"

Knee Surg Relat Res, Vol. 25, No. 4, Dec. 2013

Who should be tested prior to implant?

- European Perspective: Nobody needs testing:
  - UK: "standard cobalt chromium/stainless steel implants should be used regardless of the patient's metal allergy status"
  - Sweden: "virtually no such patients are evaluated" **Bruze, 2008**
  - Germany: if metal allergy suspected, use titanium alloys **Thomas, 2008**
  - Denmark: h/o "clinical metal intolerance of a magnitude sufficient to cause concern to the patient or the doctor" **Thyssen, 2011**
- United States
  - ACDS: **Schalock, 2016**
    - Pre-implantation:
      - "Routine preoperative evaluation in individuals with no history of metals reaction or history of previous implant-related adverse events is not necessary."
      - "Patients with a clear self-reported history of metal reactions should be evaluated by patch testing before device implant"
    - Post-implantation testing:
      - Patients with chronic unexplained issues such as implant loosening or failure.

Assessing the validity of self-reported history of rash caused by metal or jewellery

- 10 years, MGH Contact Clinic; N=2,132
- "Do you get rashes when your skin is exposed to jewelry?"
  - 40% sensitive
  - PPV 51%, NPV 82%
- **"Do you have rashes when your skin is exposed to metal?"**
  - 77% sensitive
  - PPV 71%, NPV 84%
  - Q2 was both 37% more sensitive than Q1 ($p<0.0001$), with a higher relative risk (4.75, $p<0.001$) compared to Q1 (RR=3.01, $p<0.001$)

Ko, 2018

Patient is referred prior to surgery for evaluation

- No routine screening is indicated unless significant concern exists (surgeon or patient)
- Do they have a history of cutaneous metal reactions?
  - Yes? Yes.
  - No? No testing is indicated unless significant concern exists (surgeon or patient)
- Prior to implantation of Nuss bar placement
  - Test everyone

Who should get tested?

- Two common scenarios
  - *Pre-implantation*
  - ***Post-implantation***

Patient is referred after surgery with symptoms

- History of metal reaction?
- Dermatitis above or adjacent to the implant?
- Widespread/generalized dermatitis following implant placement?
- Histopathology c/w hypersensitivity reaction?

- Consider patch testing for these individuals
- Post-implant MHR -> Diagnosis of exclusion

What test is best?

- Patch test vs. Lymphocyte transformation test
  - Or both (?)
- What do you test for?
  - Let the testing fit the question

- NO test is clearly predictive of implant reactions

SYSTEMIC HYPERSENSITIVITY TO CHRONIC METAL EXPOSURE

Other Medical Devices

- Orthodontic devices
  - Usually local reactions, but regional/systemic ACD possible

- Gynecological device - Essure

Facial eczema because of orthodontic fixed retainer wires

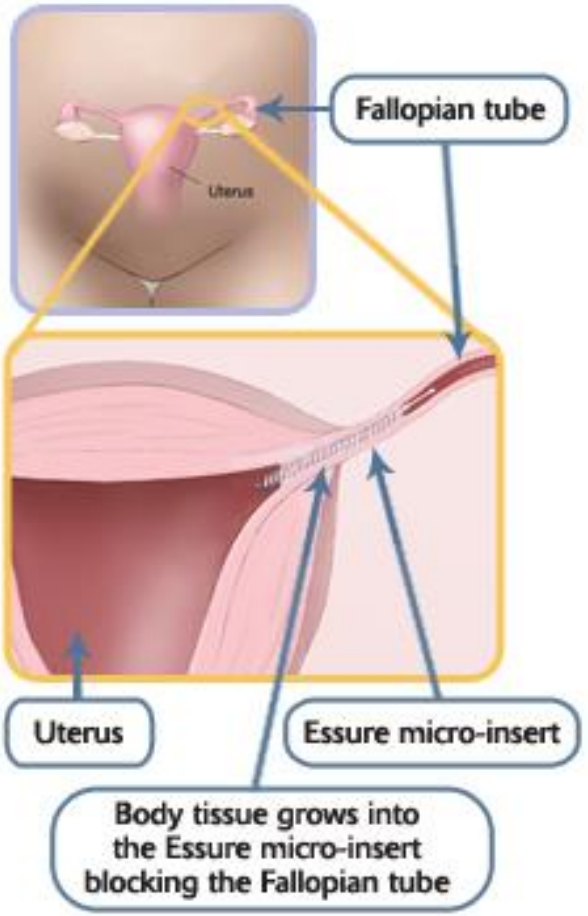
Contact Dermatitis 2008: 59: 118–120

A. J. Feilzer[1], R. Laeijendecker[2], C. J. Kleverlaan[1], P. van Schendel[1] and J. Muris[1]

Fig. 1. (a) Before removal of orthodontic retainer wire and (b–d) 2 weeks, 3 months and 6 months, respectively, after removal of orthodontic retainer wire.

Essure

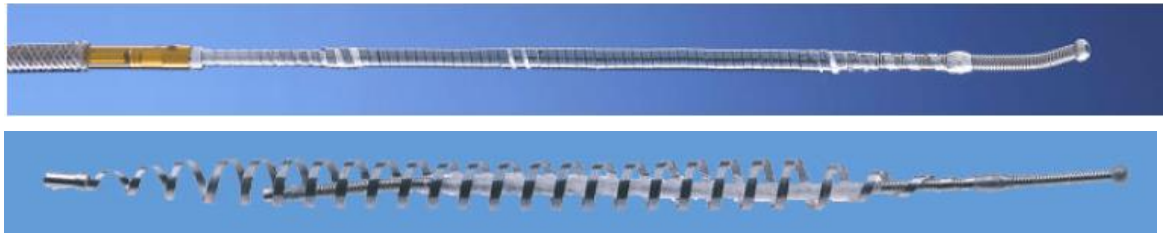
- Permanent contraceptive implants
- Outpatient placement



http://www.essure.com/Home/Understanding/WhatisEssure/tabid/55/Default.aspx

Essure Contraceptive

- Components
  - Inner coil: Stainless steel
  - Outer coil: Nitinol
  - Central core: polyethylene (PET) fibers (Dacron)
  - Expands in the Fallopian Tubes
- Taken off the market by Bayer in 2018



http://www.essuremd.com/LinkClick.aspx?link=Skins%2fConceptus_Skin%2fPDFs%2fCC-0533-safety-effectiveness.pdf&tabid=66

Systemic Nickel Allergy Syndrome (SNAS)

- Systemic nickel exposure causes **systemic** issues, not just a cutaneous contact dermatitis
- Currently, SNAS includes those with:
  - positive nickel skin test that have symptoms flare with *gastrointestinal* nickel exposure
  - ~1-5% of all individuals who are nickel hypersensitive have a SNAS-like reaction

Systemic Hypersensitivity to Chronic Metal Exposure

- Systemic Nickel Allergy Syndrome (SNAS)
  - *Skin*: Urticaria, “rashes”, AD flares, pompholyx or “hand dermatitis”, alopecia
  - *Respiratory*: Asthma flares, rhinitis
  - *Gastrointestinal*: Intestinal inflammation leading to abdominal bloating and gastric pain, diarrhea or constipation, vomiting and nausea
  - *Systemic*: Headaches, chronic fatigue, fever, arthralgias.

- Ricciardi et al. Systemic nickel allergy syndrome: epidemiological data from four Italian allergy units. Int J Immunopathol Pharmacol. 2014 Jan-Mar;27(1):131-6.
- Calogiuri GF et al. Nickel Hypersensitivity: A General Review on Clinical Aspects and Potential Co-Morbidities. J Allergy Ther 2016, 7:5; DOI: 10.4172/2155-6121.1000243.

Should the concept of SNAS be expanded?

Hypothesis only…

- Does systemic nickel/metal exposure (Non-GI) cause a SNAS-like reaction in a minority of patients?

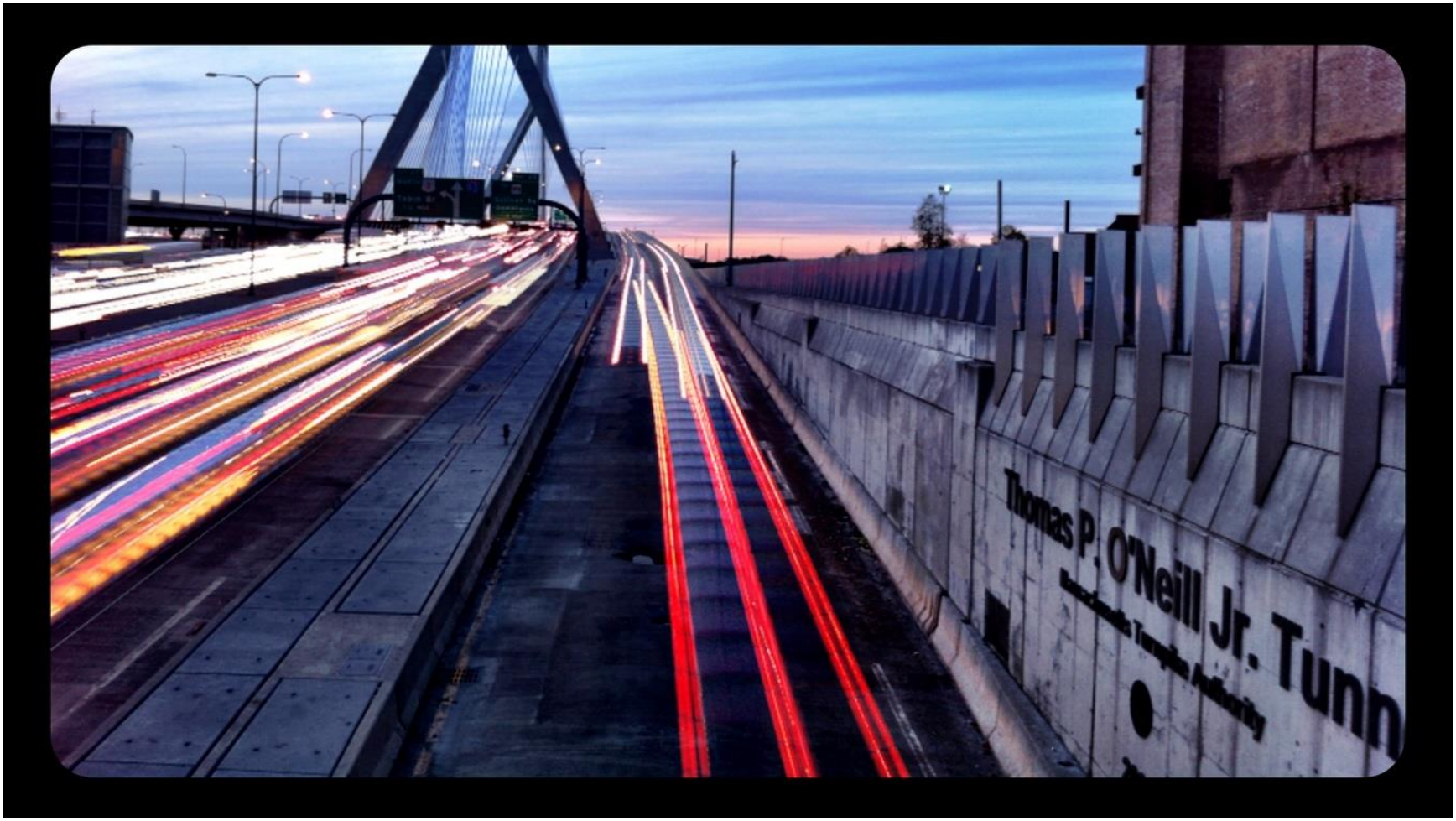
Metal hypersensitivity may contribute to autoimmunity?

- Metal-specific T cell reactivity may cause the development and chronification of rheumatic disease (SLE/RA/SS) [Bjørklund]
  - increased frequency of metal delayed-type hypersensitivity, to nickel, titanium as well as other metals
- Reported autoimmunity (ASIA) from a nitinol device [Loyo]
- Nickel chloride exposure by an oral or subcutaneous route inducted autoimmunity and systemic sclerosis in rats. [Al-Mogairen]
  - Prolonged exposures increased the risk of developing autoimmunity

- Bjørklund G et al. Delayed-type hypersensitivity to metals in connective tissue diseases and fibromyalgia. Environ Res. 2018 Feb;161:573-579.
- Loyo E et al. Autoimmunity in connection with a metal implant: a case of autoimmune/autoinflammatory syndrome induced by adjuvants. Auto Immun Highlights. 2013 Apr; 4(1): 33–38.
- Al-Mogairen SM et al. Nickel-induced allergy and contact dermatitis: does it induce autoimmunity and cutaneous sclerosis? An experimental study in Brown Norway rats. Rheumatol Int. 2010 Jul;30(9):1159-64.

Nickel allergy and other autoimmunity

- **Autoimmune thyroiditis** may develop at a significantly higher rate in individuals with nickel allergy and especially a history of systemic nickel allergy syndrome (SNAS) [Andrioli, 2015] [Wesner, 2019]
- **Fibromyalgia** and **Chronic Fatigue Syndrome** are associated with delayed-type hypersensitivity to metals, especially nickel [Stejskal, 1999][Stejskal, 2014] [Bjørklund, 2018]
- **Systemic Lupus Erythematosus, Rheumatoid Arthritis** and **Systemic Sclerosis** patients have increased frequency of metal delayed-type hypersensitivity compared to control populations.
  - Metal-specific T cell reactivity may be the cause of development and chronification of rheumatologic disease [Bjørklund, 2018]


Thomas P. O'Neill Jr. Tunn

My Conclusions

- Type IV reaction to implanted devices is a real, but rare problem
- Ignoring a patient's concern about allergy isn't a good choice
- If possible, the most functional device with lowest allergen % should be chosen
- In some cases, systemic type IV reactions may drive systemic symptoms (i.e. non-dermatologic)

Bored yet?

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