INTRODUCTION
Cutaneous and excessive local reactions to metals utilized in orthopaedic implants have been documented for decades. In the last couple of decades there has been a rise in the incidence of cutaneous reactions to certain metals and materials in the general population. The association between cutaneous reactions and reaction to an implanted orthopaedic device has been less understood. There have been reports that have shown poor correlation to those who react to a skin test and those that react to an implanted material within a Total Joint Arthroplasty (TJA), while some reports have shown a subset of patients may convert their patch test after surgery is performed. This exhibit will review the available literature on this topic and the possible approaches orthopaedic surgeons may consider when a hypersensitivity comes into question.

METHODS
A literature search on PubMed was conducted to review the literature pertaining to skin patch testing, LTT and outcomes in Total Joint Arthroplasty. The past few reports of the North American Skin Patch Testing Group were reviewed to show the general population trends in the past decade. Several reports have demonstrated a correlation between skin patch testing and painful, swollen, stiff TKA. There have also been several reports concerning negative pre-operative patch tests and subsequent positive post-operative patch tests to metal contained in a TJA.

RESULTS
The North American Skin Patch testing group in 2009 reported the results of testing almost 5000 patients to represent a cross section of the population to a wide variety of materials. They found that nickel (Ni) was the most common reactant (21%) with other substances found in orthopaedic implants (cobalt 8% and chrome 8%) were on the rise. Symptoms that were associated with metal hypersensitivity included: pain, swelling, epicutaneous rash, patient dissatisfaction, and loss of function. Patch testing, however, involves the incorporation of a metallic material into an aqueous solution and then into petroleum jelly and applied by an adhesive tape to the skin for 24-96 hours, at which point it is removed and the reaction can be recorded from mild to severe (1-4). There is a significant subjectivity to the intermediate reaction grades in patch test reporting. Skin testing also involves a different exposure mechanism with Langerhans cells being the primary cell initiating hypersensitivity reaction compared to the periprosthetic environment where corrosion products and local macrophages and lymphocytes are involved in the reaction process. All of these differences will be compared and contrasted in the exhibit.

DISCUSSION
When extensive patient workup reveals aseptic inflammation, along with negative radiological findings in a patient with a painful TJA, the surgeon often times thinks about hypersensitivity to an implant material as the cause for concern. Patch testing can be performed and/or an in-vitro lymphocyte transformation test can be performed to aid in possibly diagnosing an allergy as a cause for the pain. Currently, this diagnosis is mainly one of exclusion and all other possible causes of pain after TJA need to be ruled out as well. This report will aid in serving as a source for all surgeons concerning the possible diagnosis of a hypersensitivity reaction for some TJA patients with poor outcomes.
INTRODUCTION

All patients react to the presence of metal and debris, which is produced by mechanical wear and by corrosion. Typically wear is responsible for the most debris about a THA/TKA and the debris can be particulate or ionic (soluble). There are two types of responses to debris from a TJA:

1. Innate (non-specific immunity)
   - Immediate maximal response, not antigen specific
   - No immunologic memory developed from exposure
   - Controlled by macrophage (osteolysis)

2. Adaptive (specific immunity)
   - Antigen dependent with a time line from exposure to maximum response
   - Results in immunologic memory controlled by lymphocytes (acute local tissue response)

---

**Table depicts the concentration of particles that are toxic to different types of cells about a TJA**

<table>
<thead>
<tr>
<th>Less Toxic</th>
<th>More Toxic</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph</td>
<td>Co, Ni, V, (Nb)</td>
<td>1 mM</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>V, Co, (Fe)</td>
<td>5 mM</td>
</tr>
<tr>
<td>Osteoblasts</td>
<td>Co, Ni, V, (Fe), (Nb)</td>
<td>1 mM</td>
</tr>
</tbody>
</table>

Hallab, et. Al, *JBMR*, 2005
Symptoms ascribed to metal hypersensitivity include: pain, swelling, cutaneous rash, patient dissatisfaction, loss of function.

Examination and Testing
As with any painful TKA, the clinician should perform a careful history and physical examination, including blood tests (ESR, CRP, CBC and differentials) along with the possibility of an arthrocentesis to rule out the presence of an infection.

Explore other causes of chronic pain after TKA including mid-flexion instability, complex regional pain syndrome, or somatization disorder.

Consider metal hypersensitivity only after these laboratory tests along with negative radiological findings indicate no loosening, infection or other tissue abnormalities.

Patch testing or an in vitro lymphocyte transformation test (LTT) can be performed.

Cons of LTT and patch testing:
- Clinical cause for pain and the results of the patch testing or lymphocyte transformation test cannot be easily correlated
- Lack of large scale prospective evidence implicating pre-existing metal allergy as a cause of implant failure in people knowingly implanted with components containing metal(s) they are reactive to. Conducting these studies are problematic given the number of retrospective studies showing elevated levels of metal sensitivity in cohorts of failing or failed implants. (7-11)

Patch Testing
- Is not a test of reactivity of deep tissue
- Mechanism is mediated by Langerhans Cell
- Involves the soluble forms of metallic ions and not debris
- Testing is performed in a grid pattern with known locations of suspected allergens

It is important to note that there are problems associated with skin patch testing that are considerations for the patient undergoing implantation of a metal device. 1) **SUBJECTIVITY:** There is often a subjective nature to interpretation of the +1 to +3 dermal reaction results which are far from optimal given the number of different observer biases. 2) **CHALLENGE LOCATION:** Another concern is that antigen presenting cells (Langerhans cells) within the skin layers do not react in the same way as macrophages and dendritic cells located in the deep tissues around the implant. (This calls into question the results and correlations to orthopaedic implant performance.) 3) **SENSITIZATION:** Perhaps of most concern for orthopedic surgeons is that the method of patch testing involves mixing metal chlorides in petroleum jelly and applying them to the patient’s skin for at least 48 hours. This same phenomenon (T-cell response) that provokes a response can theoretically induce sensitivity in people (as it has been shown to do in animal models) and while considered minimal, this risk has been consistently mentioned in the literature on the topic. Currently, the interpretation of the results of skin patch testing should be considered only in the context of the history and physical examination as well as the results of other diagnostic testing modalities.
Soluble metals (Al, Co, Cr, Mo, V, Ni, Zr) quantified by a stimulation index

**Metal treated lymphocyte proliferation / Non-treated (control)**

lymphocyte proliferation = Relative Amount of Proliferation

The average for each treatment is normalized to that of the negative control (no treatment) producing a ratio, generally termed a proliferation factor, proliferation index, proliferation ratio or stimulation index, SI. The SI is used to compare lymphocyte reactivity to the different metals.

**Mild, Moderate, and High reactivity scores based on quartile squares and not clinical outcome**

**REVIEW OF THE LITERATURE**

- An analysis of the literature concerning patch testing in TJA was performed.
- The PubMed database was searched using combinations of the terms Arthroplasty, Hyper sensitivity, Patch Testing, and Allergy.
- Studies published in a foreign language, reviews and case reports were excluded.
- Prospective and retrospective studies were tabulated and summarized into each category.
- Ten retrospective reports were included in the summary (Table 1).
- Results revealed 33/138 patients revised for any reason had a positive skin patch test to an implant material (23.9% of revisions pre-op patch test positive).
- In 44/303 TJA surviving at the end of these studies had a positive skin patch test (14.5% of stable TJAs had a positive patch test).

**TABLE 1: REVIEW OF RETROSPECTIVE STUDIES**

<table>
<thead>
<tr>
<th>MANUSCRIPT TITLE</th>
<th>JOURNAL</th>
<th>FIRST AUTHOR</th>
<th>SUMMARY OF RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact allergy to metals and bone cement components in patients with intolerance of arthroplasty</td>
<td>Dtsch Med Wochenschr</td>
<td>Eben R</td>
<td>In cemented TJA: 22/66 Symptomatic pts patch+, asymptomatic patch 3/26</td>
</tr>
<tr>
<td>Allergy to metals as a cause of orthopaedic implant failure</td>
<td>Int J Occup Med Environ Health</td>
<td>Krecisz B</td>
<td>14 poor implants, 8 patch+ (7 Ni, 6 Cr), 3 underwent revision and improved</td>
</tr>
<tr>
<td>Early osteolysis following second-generation metal-on-metal hip replacement</td>
<td>J Bone Joint Surg Am</td>
<td>ParkYS</td>
<td>8/9 MoM w/ osteolysis patch+ to Co, 2/9 w/o osteolysis patch+; retrospective</td>
</tr>
<tr>
<td>Metal sensitivity as a cause of bone necrosis and loosening of the hip prosthesis in total joint replacement</td>
<td>J Bone Joint Surg Br</td>
<td>Evans EM</td>
<td>9/14 w/ loose joints patch+, 0/24 w/ stable joints</td>
</tr>
<tr>
<td>Incidence of metal sensitivity in patients with total joint replacements</td>
<td>Br Med J</td>
<td>Elves MW</td>
<td>15/23 failed TJA patch+, 4/27 stable patch+, 8/13 w/ derm rxn were patch+</td>
</tr>
<tr>
<td>Dermatitis on the knee following knee replacement: a minority of cases contact allergy to chromate, cobalt, or nickel but a causal association is unproven</td>
<td>Contact Dermatitis</td>
<td>Verma SB</td>
<td>7 of 15 patients w/ cutaneous symptoms patch+</td>
</tr>
<tr>
<td>Metal sensitivity in patients with metal-to-plastic total hip arthroplasties</td>
<td>Acta Orthop Scand</td>
<td>Carlsson AS</td>
<td>13/134 MOP patch+ post-op; unsure if hypersensitivity caused by THA, but in pts w/ hx of allergy, proceed w/ caution</td>
</tr>
<tr>
<td>Retrospective evaluation of patch testing before or after metal device implantation</td>
<td>Arch Dermatol</td>
<td>Reed KB</td>
<td>5/22 with history of hypersensitivity pre-op patch+, 0/22 referred for patch test post-op were patch+</td>
</tr>
<tr>
<td>Lymphocyte responses in patients with total hip arthroplasty</td>
<td>J Orthop Res</td>
<td>Hallah NJ</td>
<td>More + LTT and cytokine release in THA, and esp in loose THA</td>
</tr>
</tbody>
</table>

**RETROSPECTIVE STUDY SUMMARY**

Revised: 33/138 (23.9%) patch+, 44/303 (14.5%) patch+ stable in TJA
Failed/loose: 113/261 (43.3%) patch+, 32/146 (21.9%) patch+ in TJA
Total: 146/399 (36.6%) patch+, 76/449 (16.9%) patch-10/16 (62.5%) revised TJAs LTT+
**TABLE 2: REVIEW OF PROSPECTIVE STUDIES**

<table>
<thead>
<tr>
<th>Manuscript Title</th>
<th>Journal</th>
<th>First Author</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity to implant materials in patients undergoing total hip replacement</td>
<td>J Biomed Mater Res</td>
<td>Granchi D</td>
<td>Patch test unable to differentiate stable vs stable implants, equivalent lifespan in metal patch +; 10 yr survival for metal patch + 44% vs patch - 47%; POOR survival for cement patch +</td>
</tr>
<tr>
<td>Allergy to components of total hip arthroplasty before and after surgery</td>
<td>Ital J Orthop Traumatol</td>
<td>Cancilleri F</td>
<td>10/66 THA patch + (1/12 w/ aseptic loosening patch +), 2/41 pre-op patch +; hypersensitivity may play role in loosening, but likely small</td>
</tr>
<tr>
<td>Metal sensitivity in patients with metal-to-plastic total hip arthroplasties</td>
<td>Acta Orthop Scand</td>
<td>Carlsson AS</td>
<td>9/112 patch + pre-, 12/112 patch + post-; All complications except 1/246 explained by reasons other than hypersensitivity</td>
</tr>
<tr>
<td>Allergy in hip arthroplasty</td>
<td>Contact Dermatitis</td>
<td>Waterman AH</td>
<td>13/85 patch + pre-op (13 metal), 25/85 patch + post-op (23 metal, 2 cement), 0/10 loose THA patch +; no evidence to suggest loosening because of hypersensitivity</td>
</tr>
<tr>
<td>The development of metal hypersensitivity in patients with metal-to-plastic hip arthroplasties</td>
<td>Contact Dermatitis</td>
<td>Nater JP</td>
<td>0/66 patch + pre-op, 4/66 patch + MOP conversion post op; no clinical sequelae, no emphasized the need to test patients</td>
</tr>
<tr>
<td>Metal sensitivity in patients w/ orthopedic implants: a prospective study</td>
<td>Contact Dermatitis</td>
<td>Frigerio E</td>
<td>16/72 (22%) pre-op + patch or LTT, 19/72 (29%) post-op (5 conversions of 72 total); if pre-op history insufficient, rec for screening tests</td>
</tr>
<tr>
<td>Metal sensitivity before and after total hip arthroplasty</td>
<td>J Bone Joint Surg Am</td>
<td>Deutman R</td>
<td>10/173 patch + pre-op, 4/66 converted patch + post op MOP; no conclusion</td>
</tr>
<tr>
<td>Metal sensitivity in patients undergoing hip replacement</td>
<td>J Bone Joint Surg Br</td>
<td>Rooker GD</td>
<td>6/69 patch + pre-op MOP; only 1/54 patch + post-op; patch + may be effect not cause, no need to screen in MOP</td>
</tr>
<tr>
<td>The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants</td>
<td>Arch Dermatol</td>
<td>Atanaskova Mesinkovska N</td>
<td>31 with history of hypersensitivity pre-op, 21 patch +, all did well with “allergen-free” implants; 41 suspected of hypersensitivity w/ TJA, 10 patch +, 6/10 had resolution of symptoms with allergen free implant; recommend patch testing in those with history</td>
</tr>
<tr>
<td>Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty</td>
<td>Biomaterials</td>
<td>Niki Y</td>
<td>24/92 TKA were mLST+ pre-op, 5/24 developed eczema, Cr + in eczema patients but not others; screening indicated</td>
</tr>
</tbody>
</table>

**PROSPECTIVE STUDY SUMMARY**

Pre-op patch/LTT+: 9.1%, Post-op: 14.0%
Some studies included LTT and patch testing
MOP = metal on polyethylene implant bearing
The resulting question is - What to do with a patient prior to a primary TKA when they come into the office stating they are sensitive to a specific metal and want to know their options?

If the reactivity is high as determined by patch testing or LTT testing, then options for avoidance of the reaction-producing metal(s) in question, if possible, should be discussed with the patient. For example, if results of patch testing or LTT indicate high reactivity to a prominent implant metal such as Co or Cr, then using an implant comprised of a Cobalt alloy articulating surface may not be the optimal choice.

**Alternative bearing surfaces** that are comprised of metal(s) less environmentally prevalent, have the advantage of less pre-operative patient exposure. Some alternative bearing surfaces may also release less reactive metals and less metal in general, such as oxidized zirconium.

Other options include **titanium or zirconium nitride coatings**, and alumina (currently in PMA trials in the USA). Oxidized zirconium is a metal in which the surface is transformed into a ceramic layer. The element is in the same family as titanium in the periodic table but harder and forms a thick enough ceramic layer to be a more wear resistant surface compared to typical cobalt-chrome-molybdenum (Co-Cr-Mo) alloy TKA femoral components. Titanium nitride is coated onto the surface of a titanium-alloy femoral component facilitating improved wear performance while eliminating exposure to cobalt and chromium metals while zirconium nitride is a ceramic surface coating applied to a cobalt chrome alloy but encases the implant and significantly reduces the metal ion exposure. Therefore, if oxidized zirconium or a nitrided femoral component is used and an all polyethylene or titanium alloy/zirconium nitride coated tibial component is used, the risk of Co, Cr and/or Ni reaction in this patient is minimized. This does not preclude the risks associated with nickel and other metallic byproducts that could be emanating from the stainless steel instrumentation during implantation or issues with uncoated implants and titanium alloys.
REFERENCES

The lymphocyte response to nickel salt in patients with orthopedic implants.
Bjurholm A, al-Tawil NA, Marcusson JA, Netz P.

Metal determination in organic fluids of patients with stainless steel hip arthroplasty.
Pazzaglia UE, Minoia C, Ceciliani L, Riccardi C.

Cutaneous complications of orthopedic implants. A two-year prospective study.
Kubba R, Taylor JS, Marks KE.

Resurfacing knee arthroplasty in patients with allergic sensitivity to metals.

Study rationale and protocol: prospective randomized comparison of metal ion concentrations in the patient's plasma after implantation of coated and uncoated total knee prostheses.
Lützner J, Dinnebier G, Hartmann A, Günther KP, Kirschner S.

Metal sensitivity in patients with joint replacement arthroplasties.
Benson MK, Goodwin PG, Brostoff J.

Considerations of allergy and mechanics in the selection of orthopaedic implant materials [proceedings].
Brown SA, Merritt K, Mayor MB.
Metal sensitivity reactions to orthopedic implants.
Merritt K, Brown SA.

Etiology of osteolysis around porous-coated cementless total hip arthroplasties.
Jasty M, Bragdon C, Jiranek W, Chandler H, Maloney W, Harris WH.

Failed metal-on-metal hip arthroplasties: a spectrum of clinical presentations and operative findings.
Browne JA, Bechtold CD, Berry DJ, Hanssen AD, Lewallen DG.

Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni.
Summer B, Paul C, Mazoochian F, Rau C, Thomsen M, Banke I, Gollwitzer H, Dietrich KA, Mayer-Wagner S, Ruzicka T, Thomas P.

The effect of patch testing on surgical practices and outcomes in orthopedic patients with metal implants.

Cutaneous and systemic hypersensitivity reactions to metallic implants.
Basko-Plluska JL, Thyssen JP, Schalock PC.

Benzoyl peroxide: is it a relevant bone cement allergen in patients with orthopaedic implants?
Treudler R, Simon JC.
Contact Dermatitis. 2007 Sep;57(3):177-80.
Metal sensitivity in patients with orthopaedic implants.
Hallab N, Merritt K, Jacobs JJ.

Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty.
Hallab NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ.

A painful metal-on-metal total hip arthroplasty: a diagnostic dilemma.
Blumenfeld TJ, Bargar WL, Campbell PA.

Sensitivity to titanium. A cause of implant failure?
Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA.

Comparative Study of Clinical and Radiological Outcomes of Unconstrained Bicondylar Total Knee Endoprostheses with Anti-allergic Coating.
Open Orthop J. 2011;5:354-60.

Failure modes of 433 metal-on-metal hip implants: how, why, and wear.
Ebramzadeh E, Campbell PA, Takamura KM, Lu Z, Sangiorgio SN, Kalma JJ, De Smet KA, Amstutz HC.

Metal hypersensitivity in total knee arthroplasty: revision surgery using a ceramic femoral component - a case report.
Bergschmidt P, Bader R, Mittelmeier W.

Metal sensitivity causing loosened joint prostheses.
Christiansen K, Holmes K, Zilko PJ.
**Metal allergy and the surgical patient.**
Mayor MB, Merritt K, Brown SA.

**Metal sensitivity in patients with joint replacement arthroplasties.**
Benson MK, Goodwin PG, Brostoff J.

**An interesting case of joint prosthesis allergy.**
Beecker J, Gordon J, Pratt M.

**Metal sensitivity in a patient with a total knee replacement.**
Handa S, Dogra S, Prasad R.
Contact Dermatitis. 2003 Nov;49(5):259-60.

**Metal allergy and second-generation metal-on-metal arthroplasties.**
Cousen PJ, Gawkrodger DJ.

**Allergy to endoprostheses.**
Milavec-Puretić V.