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A review of the biologic effects of spine implant debris: Fact from fiction

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Abstract

Background: Biologic-reactivity to implant-debris is the primary determinant of long-term clinical performance. The following reviews: 1) the physical aspects of spinal-implant debris and 2) the local and systemic biologic responses to implant debris.

Methods: Methods included are: 1) gravimetric wear analysis; 2) SEM and LALLS; 3) metal-ion analysis; 4) ELISA, toxicity testing, patch testing; and 5) metal-lymphocyte transformation testing (metal-LTT).

Results: Wear and corrosion of spine-implants produce particles and ions. Particles (0.01–1000 μm) are generally submicron (<1 μm). Wear rates of metal-on-polymer and metal-on-metal disc arthroplasties are approximately 2–20 and 1 mm³/yr, respectively. Metal-on-metal total disc replacement components have significant increases in circulating metal (less than 10-fold that of controls at 4 ppb-Co and 3 ppb-Cr or ng/mL). Debris reactivity is local and systemic. Local inflammation is caused primarily by ingestion of debris by local macrophages, which produce pro-inflammatory cytokines TNFα, IL-1β, IL-6, and PGE2. Systemic responses associated with implant-debris have been limited to hypersensitivity reactions. Elevated amounts of in the liver, spleen, etc of patients with failed TJA have not been associated with remote toxicological or carcinogenic pathology to date. Implant debris are differentially bioreactive. Greater numbers are pro-inflammatory; the smaller-sized debris are more bioreactive by virtue of their greater numbers (dose) for a given amount of implant mass loss (one 100-μm-diameter particle is equivalent in mass to 1 million 1-μm-diameter particles). Elongated particles are pro-inflammatory (ie, aspect ratio of greater than 3). Metal particles are more proinflammatory than polymers, *ceteris paribus*.

Conclusion: Spinal arthroplasty designs have been in use for more than 20 years internationally; therefore, concerns about neuropathology, toxicity, and carcinogenicity are mitigated. Debris-induced inflammation still depends on the individual and the type of debris. The consequence of debris-induced inflammation is continued; vigilance by physicians is recommended monitoring of spinal implants using physical exams and testing of metal content and bioreactivity, as is planning for the likelihood of revision in younger individuals.

Bioreactivity (pro-inflammatory reactivity) to orthopedic implants debris is generally the main determinant of clinical performance of established total joint arthroplasties (TJA).[1] Aseptic osteolysis has been reported as high as more than 75% of TJA of all implant failures and is the central factor limiting the longevity of current total joint arthroplasties; other reasons for failure include infection (7% of failures), recurrent dislocation (6% of failures), periprosthetic fracture (5% of failures), and surgical error (3% of failures).[2] Debris-induced aseptic failure has been reported to be as high as 5% at 7 years postop in current generation metal-on-metal total hip arthroplasties.[3–5] Wear and corrosion products that are attributed with these local inflammatory responses leading to aseptic failure.[6–10] In fact, a 15% revision rate at 20 years has been singularly correlated/predicted by a wear rate of greater than 0.1 mm per year of older model UHMWPE acetabular liners (nonhighly cross-linked).[11] To date, wear remains the strongest correlate of aseptic osteolysis and implant loosening. Understanding what the difference is between popular misconceptions and what is known of spinal implant debris is key for physicians to understand the risks associated with modern spine arthroplasty implants. The following review addresses 2 questions: 1) What kinds of spinal implant debris are produced and 2), clinically, what exactly is implant debris reactivity

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locally and systemically? Unfortunately, the amount of data from total disc arthroplasty studies is limited. Thus extrapolation from hip and knee arthroplasty experience to the spine is still necessary.

Methods

Methods included in this review are those associated with physical characterization of implant debris and those associated with measuring the biologic responses to implant debris: 1) gravimetric wear analysis; 2) particle characterization by scanning electron microscopy (SEM) and low-angle laser light scattering (LALLS); 3) metal ion analysis; 4) enzyme linked immunoassay (ELISA); and 5) lymphocyte transformation testing (LTT).

Wear

Gravimetric wear is measured by the weight loss of the individual component after simulator or in vivo use. The accuracy of this testing is typically on the order of 0.02 mg. Wear involves the loss of material (weight or mass) as a consequence of relative motion between 2 surfaces. The amount of wear depends on predictable factors: the amount of force pressing the 2 materials together; ie, the contact force, amount of relative sliding distance, type of bearing materials, and the type and amount of lubrication.

Particle characterization

Traditional particle sizing techniques, such as SEM or transmission electron microscopy (TEM) (number-based counting methods), indicated that the majority of the wear (mass loss) from an implant is comprised of particles in the nanometer to submicron range. This understanding stems largely from the relatively low numbers of particles (hundreds to thousands) used in traditional number-based analysis techniques such as SEM. Newer analytical techniques, such as LALLS which samples millions to billions of particles, catch the one-in-a-million large particle that comprises a significant portion of the total mass loss (total debris). This contribution of large particles to the total debris mass, but insignificant contribution to the total number of particles, is made apparent in graphical representation of number and volume particle size distributions (Figure 1). The counting of millions to billions of particles facilitates not only a number-based analysis, but because the one-in-a-million larger particle is also counted a volume-based analysis is also facilitated.

The ability to accurately, and as comprehensively as possible, characterize implant debris is critically important to the new generation of bearing surfaces used in novel spinal implants where weight loss from the implant after a year of use (eg, less than 0.2-mm^3 volume loss after a million cycles of use) could be attributed to the loss of a relatively few large particles or hundreds of millions of small particles (200 particles of 100-μm diameter are equivalent in mass to 200 million particles only 1 μm in diame-

ter). This phenomenon is illustrated in Fig. 1, where different samples of particles look demonstrably very different when viewed as a volume-based distribution, though they look very similar when analyzed using a number-based distribution. This shows how important it can be to have number- and volume-based distributions of the same particles to characterize fully the types of particles in the mix.

Biologic assays

Cell culture. Growth medium for the human cell lines such as macrophage THP-1 (ATCC) is typically RPMI 1640 supplemented with L-Glutamine, Penicillin, Streptomycin, 25 mM Hepes (Lonza, Walkersville, MD) and 10% heat inactivated fetal bovine serum (FBS; Hyclone Laboratories, Logan, UT). Implant debris that are usually produced using implant components in a cryo-milling or cryo-pulverization techniques (Bioengineering Solutions Inc, Chicago, IL) were generated from metal orthopedic implant components (Cobalt alloy, ASTM F-75). Collected metal particles are characterized for size and number by laser diffraction technology and have a mean diameter of less than 10 μm, usually approximately 1–2 μm (number-based analysis) with a size range of 1–10 μm.

Isolation of different cell types for study of human peripheral blood monocytes and CD4+ T cells. Peripheral blood mononuclear cells (PBMCs) are typically isolated from heparanized whole blood from healthy donors by Ficol-Hypaque density gradient separation and collected for further cell isolation. Peripheral blood CD14+ monocytes are isolated from collected PBMCs by negative selection with a magnetic bead antibody cocktail specific for CD3, CD7, CD16, CD19, CD56, CD123, and Glycophorin A (Miltenyi Biotec). All isolated cell populations are typically assessed for purity by flow cytometry analysis.

ELISA/Luminex assays. Cytokines and chemokines secretion by cells, such as THP-1 monocytes, human primary macrophages, and CD4+ T cells, are analyzed with ELISA or Luminex suspension multiplex array technology. Supernatants from both metal-challenged monocytes and co-culture experiments are collected after 30 minutes to 5 days and stored at $-80°$C. Monocyte-macrophage supernatants are typically analyzed for IL-6, IL-1β, TNFα, GMCSF, PGE2, and IL-8 with pro-inflammatory multi-plex cytokine array kits (millipore).

Testing for metal sensitivity. Testing for metal sensitivity has historically been conducted in vivo by skin testing (ie, so-called patch testing or intradermal testing) and in vitro by lymphocyte transformation testing (LTT). While general patch testing protocols and commercial kits do exist for a variety of commonly antigenic substances[12,13] (eg, TrueTest, Glaxo Dermatology, Research Triangle Park, NC), there is continuing concern about the applicability of skin testing to the study of immune responses

Number Distributions
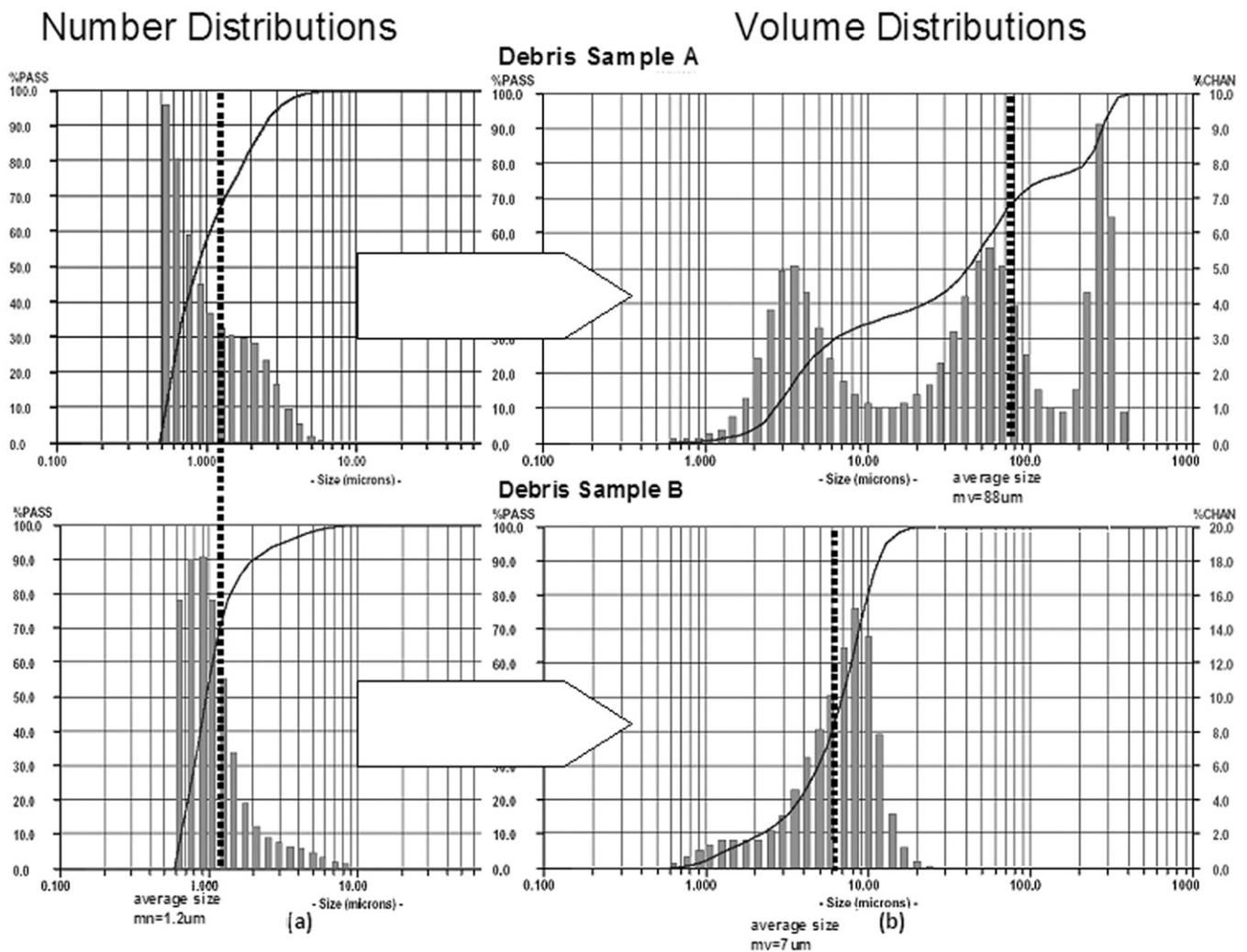
Debris Sample A

Volume Distributions

Fig. 1. These analyses of (a) volume and (b) number distributions of two debris samples demonstrate how similar number distributions can result from very different actual size distributions as evident in (a) the volume distributions. Note: The x-axis represents increasing particle diameter and the y-axis is (a) percentage of total number of particles in each size range and (b) the percentage of total mass of each sample that is of that size range. (Courtesy of BioEngineering Solutions Inc.)

to implants regarding the questionable equivalence of dermal Langerhans cells to peri-implant antigen presenting cells[14,15] and/or the possible induction of hypersensitivity in a previously nonsensitive patient.[16]

Metal-LTT testing is lymphocyte proliferation testing (also known as lymphocyte transformation testing, hence LTT), and involves measuring the proliferative response of lymphocytes obtained from peripheral blood by routine blood draw (eg, Orthopedic Analysis Inc, Chicago, IL). Metal-LTT assays are typically performed using 96-well cell-culture plates (Sigma) at a density of approximately 0.2×10^6 cells/well for 6 days in 150 μl/well of complete media (DMEM 10% FBS) at 37°C and 0.5% CO_2, with or without metal treatments. Radio-labeled thymidine (1 mCi/well) is added during the last 12 hours of the 6-day culture period, where it is incorporated into dividing cells. Cell proliferation is normalized to that of cells treated with media alone (controls)

producing a ratio, referred to as the proliferation index or stimulation index (SI). The formula is SI = (mean cpm cells + treatment) / (mean cpm cells + medium alone). All tests should be conducted in triplicate to facilitate an average and standard deviation.

Results

The following results are broken into 2 main sections: a review of the physical aspects of spinal implant debris production and local and systemic biologic responses to implant debris.

Physical aspects of spinal implant debris production

The fiction is that there are many different kinds of implant degradation processes. The fact is that there are only 2. Immediately upon implantation all implants begin to
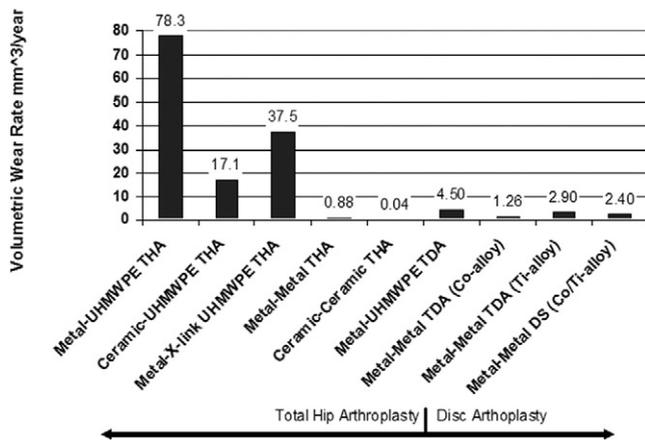
Fig. 2. A graphical comparison of data showing the amount of wear debris generated from different types of total joint arthplasties demonstrating that there is relatively less (10×) polymeric debris generated by a total disc arthroplasty with a metal-on-polymer articulation. However, this difference is not apparent with metal-on-metal articulating implants. Note: Figure References: Metal-Poly:24Ceramic-Poly:25, Metal-X-linked Poly: 22 Metal-X-linked Poly: 26, Metal-X-linked Poly: 27, Metal-X-linked Poly: 28, Metal-Metal: 29, Ceramic-Ceramic: 30, Metal-UHMWPE TDA: 17, Metal-Metal TDA: 18.

degrade through 2 mechanisms, wear and corrosion. Wear is a mechanical/physical degradation of materials (abrasive, adhesive, etc), whereas corrosion is a chemical (electrochemical) form of degradation. Of these 2 degradation mechanisms, wear is the primary source of articulating implant debris.

Wear. The fiction is that wear-resistant newer materials, like highly cross-linked polyethylene and ceramic, do not wear and release debris. The fact is that all bearing surfaces wear to some degree. Different types of orthopedic materials and couples produce different amounts and kinds of wear debris. Hard-on-hard material couples, such as metal-on-metal articulations, generally produce less wear (weight loss) than metal-on-polymer (Fig. 2). These 2 basic types of articulating bearing designs are available in spine, knee, and hip arthroplasties.

Metal-on-polymer spine arthroplasty wear. In vitro analysis of wear has demonstrated wear rates of metal-on-polymer bearing lumbar total disc arthroplasty devices range from 2 to 20.8 mm³/million cycles,[17,18] where the size of the wear debris generally ranges from 0.1 to 100 μm in diameter UHMWPE.[17,19–21] This amount of debris is 10-fold less wear than THAs and TKAs that are composed of metal on highly-crosslinked polyethylene (x-UHMWPE) bearing surfaces.[22,23]

Metal-on-metal spinal arthroplasty wear. In general, the wear of metal-on-metal TJA is well below that of metal-on-polymer (Fig. 2).[22,24–30] The few published reports on the wear rates of metal-on-metal disc arthroplasty prostheses indicate a wear rate of 0.93–1.26 mm³/million cycles (Cobalt-alloy).[18,31] Another study of an all titanium-6%

Al-4%V alloy disc arthroplasty found wear rates to be as high as 3 mm³/million cycles.[32] These values are similar to those reported for metal-on-metal hip replacements, which have been shown to range from approximately 0.05–6 mm³/million cycles (Cobalt-alloy).[29,33,34] Long-term follow-up of patients undergoing total disc arthroplasty is required to assess how intimately wear will correlate with inflammation and poor implant performance.

Corrosion. The fiction is that some metals do not corrode in vivo. The fact is that all metals corrode in vivo. Corrosion can be defined as an electrochemical attack of a metal by its environment. Implant corrosion reduces structural integrity and causes the release of by-products that interact locally and systemically. Orthopedic alloys rely on the formation of passive films on their surface for corrosion protection. Some alloys are better than others at resisting this chemical degradation; for instance, stainless steel alloys generally corrode to a greater extent than either cobalt or titanium alloys.[35–37] Special types of corrosion, such as fretting, can take place, where a combination of chemical degradation is
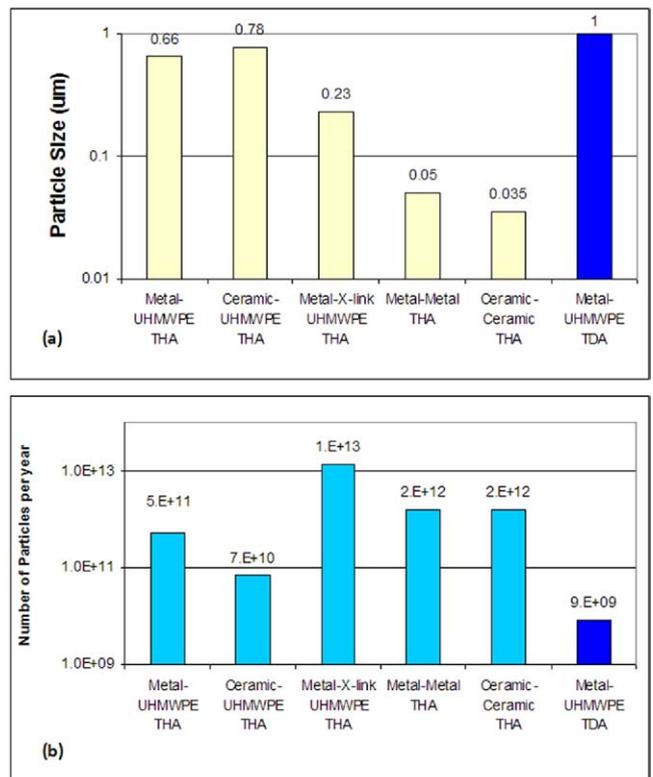

Fig. 3. A graphical comparison of data showing (a) the reported size of implant debris generated from different types of total joint arthplasties and (b) the amount of particles per year this results in using the gravimetric data shown in Figure 1. The smaller size of the particles reported in highly crosslinked polymer particles (copared to traditional poly) combined with the modest reductions in wear rate results in metal on Metal-X-linked Poly. Note: Figure References: Metal-Poly:24Ceramic-Poly:25, Metal-X-linked Poly: 22 Metal-X-linked Poly: 26, Metal-X-linked Poly: 27, Metal-X-linked Poly: 28, Metal-Metal: 29, Ceramic-Ceramic: 30, Metal-UHMWPE TDA: 17, Metal-Metal TDA: 18.

enhanced by mechanical factors such as a crevice and abrasive wear, as is common in the screw-plate junction of spine implants. In modern practice, gross evidence of corrosion in screw-plate interfaces is less common.[38] Corrosion products are typically oxides (Cr_2O_3, CoO, TiO_2, Al_2O_3, etc), metal phosphates, metal salts, metal-ions bound to proteins, or organometallic complexes.[39–43]

Implant debris types: particles and ions. The degradation products of all orthopedic implants are 1 of 2 basic types of debris: particles or soluble debris (metal ions). While there is typically a large distinction between the 2, this distinction becomes a gray area as the size of particles decreases into the nanometer range. Typically, particulate wear debris (metal, ceramic or polymer) exist from the submicron size up to thousands of microns (mm), while so-called "soluble debris" are limited to metal ions that are bound to plasma proteins.

Particulate debris. The fiction is that all implant debris are approximately 1 μm in size. The fact is that the easiest (most numerous) debris to measure is typically less than 1 μm in size. But all implant debris cover a range of sizes from nanometers to tenths of a millimeter (0.01 to hundreds of μm in diameter). Currently, there is a lack of comprehensive information regarding the debris retrieved from spinal implants. However, we do know that particles generated in simulator studies of articulating spinal implants match the sizes and types of particles produced from hip and knee arthroplasty (Fig. 3).[22,24–30] Generally, hard-on-hard material couples, such as metal-on-metal articulations, generally produce smaller-sized (nanometer and sub-micron), fairly round debris, whereas traditional metal-on-polymer bearings produce larger (micron-sized) debris that are more elongated in shape (Figs. 2 and 3)**.** The particles produced from articulating bearing in any metal-on-polymer bearing implants are dominated by polymer particles with little metallic debris, unless there are other sources of metal release such as corrosion at metal-metal connections. Polymeric particles produced from implants generally fall into the range from 0.23–1 μm (Fig. 3A). Past investigations, primarily of UHMWPE wear debris in peri-implant tissues, have shown that 70–90% of recovered particulates were submicron, with the mean size being approximately 0.2–1 μm.[43–45] Newer polymer implant debris from highly cross-linked polymers have demonstrated the production of smaller, more rounded debris in the submicron range as small as 0.1 μm in size.[29;46] Metal and ceramic particles have generally been characterized as an order of magnitude smaller than polymer particles (at approximately 0.05 μm in diameter, in the nanometer range). Given the relative wear rates in Fig. 2 and the average particle sizes in Fig. 3A, this translates to a theoretical increase in the yearly production of metal-on-metal particles of 1-3 orders of magnitude over that produced by metal-on-polymer articulating surfaces, even though the amount of mass loss is over an order of magnitude less for metal-on-metal bearings (Fig. 3B). Different types and sizes of particles have been found histo-
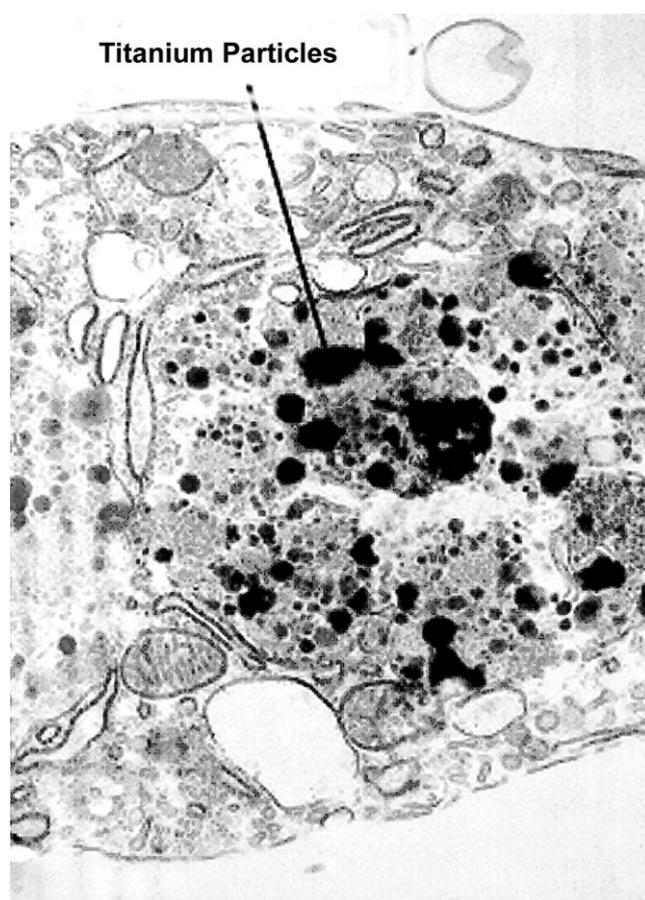

Fig. 4. Transmission Electron Photomicrographs: (a) Macrophage containing phagocytized titanium particles. (b) Endothelial cell lining with embedded titanium debris. These specimens were obtained from a tissue sample overlying the posterolateral fusion mass (sixteen-week autograft + titanium) (TEM magnification = 20,000×) (courtesy of Bryan Cunningham).

logically in peri-implant tissues.[19,35,47–51] Stainless steel: At steel screw-plate junctions, which contain particles of chromium compound ranging in size from 0.5 to 5.0 μm, stainless steel has been found in the peri-implant tissues as closely packed, plate-like particle aggregates.[52] Cobalt alloy: Cobalt alloy corrosion produces a chromium-phosphate ($Cr(PO_4)4H_2O$) hydrate rich material termed "orthophosphate", which ranges in size from sub-micron to aggregates of particles up to 500 μm.[52,53] Titanium alloy: The degradation products observed in histologic sections of tissues adjacent to titanium base alloys generally have the same elemental composition as the parent alloy (which often is detected as titanium oxide, the thick oxide layer that forms on all titanium implants and protects the bulk alloy), as opposed to precipitated corrosion products which occur with stainless steel and cobalt-chromium alloys (Fig. 4).

Particle characterization. The fiction is that scanning electron microscopy is the best way to analyze the size of particles. The fact is that newer techniques, such as low-angle laser light scattering (LALLS), can increase the number of counted and sized particles from hundreds to millions

or billions facilitating catching the one in a million large particle. Traditional particle-sizing techniques, such as SEM or TEM (number-based counting methods), indicated that the majority of the wear (mass loss) from an implant is comprised of particles in the nanometer to submicron range. This understanding largely stems from the relatively low numbers of particles (hundreds to thousands) used in traditional number-based analysis techniques such as SEM. Newer analytical techniques catch the one-in-a-million large particle that comprises a significant portion of the total mass loss (total debris). This contribution of large particles to the total debris mass, but insignificant contribution to the total number of particles, is made apparent in graphical representation of number and volume particle size distributions (Fig. 1). The counting of millions to billions of particles facilitates not only a number-based analysis, but because the one-in-a-million larger particle is also counted, a volume-based analysis is facilitated.

The ability to characterize accurately, and as comprehensively as possible, implant debris is critically important to the new generation of bearing surfaces used in novel spinal implants, where weight loss from the implant after a year of use (eg, less than 0.2 mm^3 volume loss after a million cycles of use) could be attributed to the loss of a relatively few large particles or hundreds of millions of small particles (200 particles of 100 μm diameter is equivalent mass to 200 million particles only 1 μm in diameter). This phenomenon is illustrated in Figure 1, where different samples of particles look demonstrably very different when viewed as a volume-based distribution, though they look very similar when analyzed using a number-based distribution. This shows how important it can be to have number- and volume-based distributions of the same particles to fully characterize the types of particles in the mix.

Metal ions (soluble debris). The fiction is that due to the smaller loads, spine arthroplasty implants release less metal ion into the body than hip or knee arthroplasties. The fact is that metal levels measured in people with disc arthroplasties have comparable levels of circulating metal ions as people with other TJA implants. There is continuing concern regarding the release of chemically active metal ions, which bind to proteins and remain in solution from which they can then disseminate into the surrounding tissues, bloodstream, and remote organs. Particulate metallic wear debris present an enormous surface area for electrochemical dissolution, which, in all likelihood, is a major factor contributing to observed systemic elevations in metals of patients with titanium implants.[35] Normal human serum levels of prominent implant metals are approximately: 1-10 ng/ml Al, 0.15 ng/ml Cr, <0.01 ng/ml V, 0.1-0.2 ng/ml Co, and <4.1 ng/ml Ti. Following total joint arthroplasty, levels of circulating metal have been shown to increase (Table 1). The values in this table show that following successful primary total joint replacement there are measurable elevations in serum and urine Co, Cr, and Ti. Transient elevations of

urine and serum Ni have also been noted immediately following surgery.

Recent studies of metal-on-metal TDA find serum levels of cobalt and chromium after TDA are elevated at concentrations of 3–4 ng/mL or parts per billion (ppb) for cobalt and 1–2 ng/mL or ppb for chromium, which were significantly elevated over control values.[54,55] The concentrations of circulating Cr/Co measured in the serum of people with a metal-on-metal TDA are similar to levels measured in well functioning metal-on-metal total hip arthroplasties. This is not true for nonarticulating implants, where recent studies have failed to detect elevated amounts of circulating Cr or Ni from stainless steel scoliosis rod fixation systems.[56] The long-term effects of presumably much higher elevations of metal proximal to the spinal implant remain unknown and are under careful surveillance by implant companies, the FDA and orthopedic researchers.[57]

There are subject dependent conditions that complicate using metal ion analysis as a diagnostic technique; eg, altered renal function has been reported to cause variability in circulating metal levels. Brodner et al have reported that renal failure is associated with highly elevated levels of serum Co and Cr (over 100-fold) in comparison with individuals with similar prostheses and normal renal function.[58] At this time, there is no established toxicity threshold for the degradation products of metal implants.

Particulate debris reactivity characterization. The fiction is that, generally, different types of implant debris elicit the same level of inflammation. The fact is that different types of implant debris elicit different types of biologic response. However, despite the large number of published studies examining the effect of metal, polymer and ceramic particles on peri-implant cells (eg, macrophages, fibroblasts, osteoblasts, and osteoclasts), there is surprisingly little consensus on what type of debris are most pro-inflammatory. That said, there are a few general particle characteristics on which local inflammation has been shown to depend: 1) particle load (particle size and total volume), 2) aspect ratio, and 3) chemical reactivity. Thus, theoretically, a bioreactivity index of particulate would take the mathematical form:

Particle Pro-inflammatory Index

$$\approx K_{Load}(\text{particle load}) \times K_{Shape}(\text{aspect ratio})$$
$$\times K_{Material}(\text{material type}) \times K_{unknown} \quad (1)$$

where *K*s are constants that depend on the testing environment and particle load is a function of both particle size and total debris volume.

Greater particle load: (size and volume) increases inflammation. The inflammatory response is proportional to the particle load (the concentration of phagocytosable particles per tissue volume, which is characterized by both the size and total volume).[59,60] If a given amount of debris (mass loss from an implant) is comprised of small diameter par-

Table 1

Approximate average concentrations of metal in human body fluids with and without total joint replacements. Note: where ranges were reported they are included here within parentheses, eg (1–4). All concentrations are reported in ppb (ng/mL)

Concentrations of metal in body fluids (ng/mL or ppb)

	Co	Cr	Mo	Ni	Ti	Al	V	References
Serum								
Normal	<0.2–0.6[109] (0.2–8.3)[109]	0.2[110] (0.1–0.7)[110]	0.42[110] (0.3–1.8)[110]	*	1.2–2.7[109;111] (1.1–7.9)	1.2–2.2[111] (1.1–6.4)	<0.8[111] <0.8	109;111
TKA-M/P	0.2 (<0.02–1.15)[112]	0.1 (<0.02–0.6)[112]	*	0.4 (0.05–1.5)[112]	3.2 (<2.1–6.3)[111]	6.5 (2.1–9.4)[111]	<0.8 <0.8[111]	111;112
TKA-F	*	*	*	*	135.6 (24.1–716.9)[111]	3.7 (0.8–6.2)[111]	0.9 (<0.8–2.6)[111]	111
THA-M/P	0.9 (<0.3–3.9)[113]	1.28 (0.1–2.4)[113]	*	*	1.4–4.1[6], 2.6[113] (<1.1–11.17)[109;113]	1.2–1.7[109] (0.2–2.46)[109]	*	40;109;113;114
THA-M-M	2.4 (0.6–7.9)[113]	3.5 (0.8–9.1)[113]	*	*	1.9[113] (1.1–6.0)[113]	*	*	113
TDA	1.9–4.8[54;55]	1.9–2.4[54;55]	*	*	*	*	*	54;55
Synovial fluid								
Normal	*	*	*	*	<0.1 (<0.1–7.6)[115]	7.3 (1.9–19)[115]	*	115;116
THA	5[116], 0.2 (<0.02–1.15)[112]	3[116], 0.1 (<0.02–0.6)[112]	21 ± 8[116]	4[116], 0.4 (0.05–1.5)[112]	13–556[116]	109–654[116]	5–62[116]	112;116
THA-F	588 ± 427[116]	385 ± 232[116]	58 ± 53[116]	32 ± 16[116]	86 ± 35[116]	256 ± 271[116]	25 ± 19[116]	116
Whole blood								
Normal	0.1–1.2[116]	2–6[116]	0.5–1.8[116]	2.9–7.0[116]	17 ± 60[116]	12 ± 4[116]	5.8 ± 4[116]	116
THA					67 ± 62[116]	218 ± 233[116]	23 ± 31[116]	116
THA-F	20 ± 25[116]	110 ± 150[116]	12 ± 9[116]	29 ± 29[116]	602 ± 927[116]	237 ± 307[116]	55 ± 63[116]	116

Human tissue (μg/g) (roughly equivalent to: 10^{-1} to 10^{-2} mM)

	Co	Cr	Mo	Ni	Ti	Al	V	References
Liver								
Normal	100	890	14	120	<14	*	*	117;118
TJA	560	680	22	15200	1130	*	*	117;118
Psuedocapsule								
Normal	<65	120	<9	50	150	*	*	116;117;119;120
TJA	39400	460	121	5490	3820	*	*	116;117;119;120
Lymphatic								
Normal	*	*	*	10	690	*	*	117
Tissue								
TJA	*	*	*	390	690	*	*	117

Abbreviations: Normal, subjects without any metallic prosthesis (not including dental); M/P, metal on polyarticulation; M/M, metal-on-metal articulation; F, subjects with a poorly functioning arthroplasty (loose or migratory osteolysis prior to surgical revision); THA, total hip arthroplasty; TKA, total knee arthroplasty; TJA, subjects with well functioning total joint arthroplasty (either knee or hip); TDA Spine, total disc arthroplasty (metal on metal).

* Data not available.

ticles, there will be far greater numbers than if that same mass of debris was composed of larger diameter particles.[60] The degree to which equal numbers (dose) of large versus small particles (eg, 10 μm vs 1 μm diameter) induce a inflammatory response on a per-particle basis in vivo has not been thoroughly investigated and remains an issue of debate. However, several past investigations have shown that for an equal amount of debris mass, smaller particles (eg, 0.4 μm) produce a greater inflammatory response than larger particles (eg, 7.5 μm).[60–62] In these studies, the challenge doses used generally contain many thousands more small particles per cell than larger particles; this is largely responsible for these responses and the popular misconception that smaller particles are always more pro-inflammatory regardless of dose.

Elongated (fibers) particles are more pro-inflammatory than round particles.[63,64] This phenomenon has been well established with the first such investigations over 30 years ago, involving asbestos fibers, which similarly cause inflammation through "danger signaling," inflammasome activation and production of IL-1beta, IL-18, IL-33, etc, and activation of general macrophage pathogen associated molecular pattern pathways (NFkb and p38 production of pro-inflammatory cytokines IL-6, TNFα and PGE2 through as yet unknown mechanism).[65,66] This is discussed further in the following section on local implant induced inflammation. However, it remains unknown at what point (aspect ratio: length/width) in the transition of round particles to fibers that elevated inflammation is generally initiated. Currently, fibers can be categorized as particles with aspect ratio greater than 3, as has been shown in metal and poly retrieved from tissues.[29,44,67]

More chemically-reactive particles are more pro-inflammatory. There is a growing evidence that metal particles are more proinflammatory to macrophages (in general) when compared to polymers (*ceteris paribas*) and that some metals are more reactive than other metal particles.[68] This opinion is not unanimous.[69] More complicated still, there have been reports that have shown no differences between similar sized metal and polymer particles.[70–72] Despite these reported differences, there is a growing consensus that metallic particles that are capable of corroding and releasing ions that have been associated with hypersensitivity responses, cytotoxicity, and DNA damage are thus more capable of eliciting proinflammatory responses when compared to relatively inert polymers and ceramics.[73–75]

Controversial particle characteristics. Does particle size matter? While there seems to be a large consensus that in vitro inflammatory responses require particles less than 10 μm in diameter, there continues to be debate on exactly what size particle produces the greatest inflammatory response.[60–62,76] Thus, to produce an in vitro inflammatory response, particles need to be less than 10 μm, that is, within a phagocytosable range. Purportedly, particles with a

mean size of 0.2–10μm are generally the most proinflammatory. Within this range there is no consensus as to which specific sizes and/or dose of particles (particles/cell or particles/tissue volume) are maximally inflammatory.[60,77–79]

Endotoxin (bacterial-derived lipopolysaccharides) on wear particles is presumably important because it has been found in periprosthetic tissue of failed implants, even in the absence of clinical signs of infection.[80] The relationship between bacteria and aseptic loosening has also been inferred, because antibiotic-eluting bone cement and systemically administered antibiotics reportedly reduce the frequency of aseptic loosening.[81]

Local and systemic bioreactivity of implant debris

The fiction is that implants generally "wear out" over time. The fact is that describing to patients that implants simply wear out over the long term mischaracterizes the main reason for long-term revision, aseptic loosening. Implant debris from wear cause local inflammation and granulomatous invasion of bone-implant contact that, over time, results in implant loosening and pain, necessitating revision arthroplasty.

Implant debris is known to cause inflammation, osteolysis, and, in some cases, hypersensitivity, and concerns about implant debris becoming carcinogenic and/or toxic persist. Macrophages are part of the innate immune system and, in the context of implant debris, are dedicated to phagocytosing debris, eliciting danger signals, and presenting antigen for T-cell recognition (ie, metal-protein complexes). Once debris is ingested by macrophages and other peri-implant cells, a host of pro-inflammatory reactions occur such as activation of metal-reactive T-cells through antigen presentation,[73] release of pro-inflammatory mediators,[60,82–84] cytotoxicity,[74] DNA damage,[74,85,86] and oxidative stress.[87] The central pro-inflammatory cells in this response are macrophages, which are generally responsible for mediating debris-induced inflammation leading to device loosening.

The following section will detail what is known of these different pathologies induced by implant debris and the primary suspects (kinds of implant debris for each pathology). Given that TJAs have been in use for over half a century with constant increases in biocompatibility and materials technology over that time frame, implant concerns about toxicity and carcinogenicity have been largely mitigated.

Debris-induced local effects. The fiction is that the amount of wear and corrosion debris produced from spine arthroplasty and modular spinal fixation implants are inconsequential and not likely to provoke a deleterious immune response. The fact is that biologic reactivity to spinal implant debris has been clinically observed with all the hallmarks of traditional particle-induced osteolysis; ie, granulomatous epithelioid membranes coating the metal implants have been reported, similar to the fibrous membranes associated with loose total hip replacements.[19,49,50,88–92]

Although few, case reports of painful granuloma associated with spinal implant debris[93,94] demonstrate that spinal implant debris induced inflammation can result in bone-destroying granuloma.[95] It is generally accepted that decreased wear and corrosion debris will lead to increased longevity of orthopedic implants. This rule of thumb has yet to be well established over the long term in newer types of articulating spinal implants; however, it is well established that debris induced inflammation and pain can be caused by spine implant debris.[49,94,96–99]

Macrophages are the major cell type responsible for mediating the pro-inflammatory response to implant debris that leads to inflammation and device loosening over time. Once implant debris is ingested by macrophages and other peri-implant cells, a host of biologic reactions can occur such as activation of T-cells through antigen presentation,[73] release of pro-inflammatory mediators,[60,82–84,100] cytotoxicity,[74] DNA damage,[74,85,86] and oxidative stress.[87] Of these reactivity types, it is the pro-inflammatory response to wear debris in the local environment that has been the only known correlate of implant performance.[11]

In the relatively few reports of human retrieval studies of loose spinal implants, granulomatous epithelioid membranes coating the metal implants have been shown similar to the fibrous membranes associated with loose total hip replacements.[19,49,50,89–92] However, before this phenomenon of wear debris can be well established in disc arthroplasty, larger series of implant retrievals will be needed to characterize the biologic responses to increased particle generation. When osteolysis or granulomas occur in the presence of metal debris, it is termed particle disease. In the case of metal debris, this is often accompanied by metallosis (aseptic black staining). Metallosis often accompanies metal implant debris-related osteolysis, aseptic fibrosis, local necrosis, or loosening. In a cohort of 12 loosened spinal implant cases, metallosis of the internal membrane was

Fig. 6. TNF-α Cytokine Expressing Macrophages: Membrane-bound or intracellular TNF-α, contained in the tissue layer overlying the posterolateral sites, produced yellow to brown chromagen label as shown in this sixteen-week autograft + stainless steel particles in a rabbit model. (Avitan-Biotin Complex horseradish peroxidase technique for TNF-α, magnification 40×). (Courtesy of Bryan Cunningham.)

associated with the outer layer of membrane containing an infiltrate of leukocytes and macrophages (see Fig. 5). All 12 patients had radiolucency around part of the spinal instrumentation. Seven of the patients had titanium implants and 5 of the patients had stainless steel implants, showing this phenomenon is not limited to 1 type of material. Eleven of 12 clinical cases demonstrated elevated TNFα levels and an increased osteoclastic response in the vicinity of wear debris caused by dry frictional wear particles of titanium or stainless steel (see Fig. 6). The focal areas of osteolysis most commonly involved loose transverse connectors. Resection of the wear debris stained tissue and surrounding fibro-inflammatory zones resulted in resolution of clinical symptoms in all 12 cases.[88]

Particle-induced proinflammatory responses. The fiction is that implant debris looks like a pathogen and is recognized by the immune system through pathogen receptors. The fact is that implant debris elicits both general and "danger" signals in immune cells similarly to UV light, stress, and particulate adjuvants used in vaccines. The hallmark of implant debris in tissues[101] is that it disrupts bone homeostasis through a number of pro-inflammatory responses. Particles activate macrophages that secrete TNFα, IL-1β, IL-6, and PGE2, stimulating differentiation of osteoclast precursors into mature osteoclasts and increasing peri-prosthetic bone resorption (see Fig. 7).[102] Wear debris particles have also been shown to compromise mesenchymal stem cell differentiation into functional osteoblasts,[103] and particles can directly inhibit collagen synthesis by mature osteoblasts[104] and induce apoptosis of osteoblasts.[105] Thus, it is not surprising that over time debris particles induce a net bone loss around implants that precipitates implant loosening.

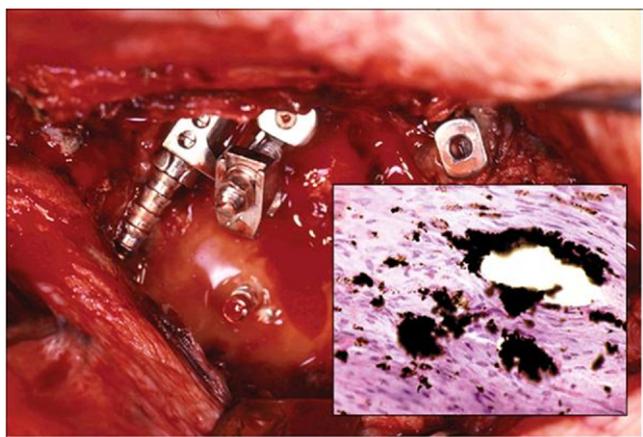Only recently have we learned how sterile, nonpatho-

Fig. 5. At surgical exploration the broken and dislodged instrumentation was accompanied by stainless steel particulate debris. Anteroposterior radiograph in a patient with breakage of a longitudinal rod connecting pedicle screws two years post-operatively. (Courtesy of Bryan Cunningham.)
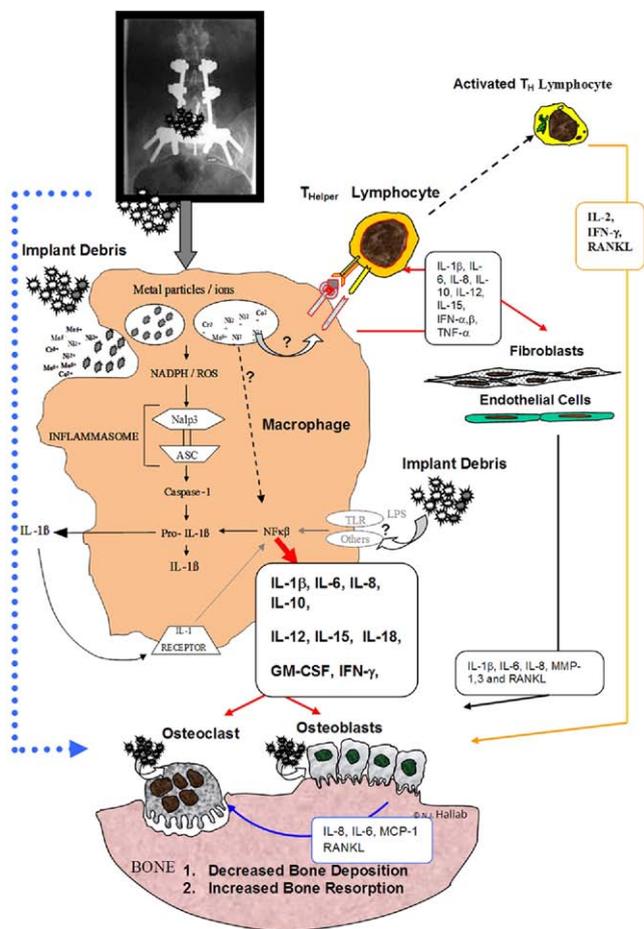
Fig. 7. This schematic shows the numerous pro-inflammatory mediators produced by peri-implant tissue and immune cells reacting to implant debris, which can negatively affect bone turnover. The pro-inflammatory cytokines IL-1, IL-6, and TNF-alpha are thought to be some of the most potent cytokines in this cascade of signaling. The inflammasome pathway within cells such as macrophages has recently been reported to be central to implant debris mediated pro-inflammatory reactivity. Ingestion of the debris phagocytosis results in the release of pro-inflammatory cytokines that affect local cell types and induce a widening zone of soft-tissue damage and inflammation. (Courtesy of BioEngineering Solutions Inc)

genic stimuli, such as implant debris, can elicit an immune response. Immunologic reactivity responses can be divided into 2 categories: pathogenic stimuli and nonpathogenic stimuli, which act as "sterile" danger signals such as UV light and asbestos particles. In the constant battle with pathogens, we have evolved pattern recognition receptors (PRRs) in cell membranes and cytosol of immune cells that selectively detect pathogen-associated molecular patterns (PAMPs).[106,107]

Sterile challenges, such as implant debris, produce DAMPs (danger-associated molecular patterns) which are different than PAMPs. Implant debris was first identified as DAMPs in 2008, and acts through the inflammasome pathway which leads to the release of IL-1β, a powerful pro-inflammatory cytokine.[108] Cobalt, chromium, molybdenum, nickel ions, and Co-Cr-Mo alloy particles were found to activate the inflammasome pathway in part through

NADPH-mediated monocyte/macrophage production of reactive oxygen species,[65,108] which suggests that metal-induced ROS is involved in inflammasome activation and IL-1β secretion. This is important to spinal implants debris, because activation of the inflammasome leads to cleavage of intracellular pro-IL-1β and pro-IL-18 into their mature forms, ultimately leading to their secretion and induction of a broad array of pro-inflammatory responses through autocrine and paracrine activation of NF$\kappa\beta$ that initiates a powerful pro-inflammatory response (Fig. 7).[106] Identification of inflammasome involvement in particle- and metal ion-induced inflammation will likely provide new therapeutic strategies to pharmacologically treat implant debris-induced inflammation and hypersensitivity by specifically interrupting the initiation of the inflammatory response that leads to aseptic osteolysis.

Debris-induced systemic effects. Homogenates of remote organs and tissue obtained postmortem from subjects with Co base alloy total joint replacement components have indicated that significant increases in Co and Cr concentrations occur in the heart, liver, spleen, and lymphatic tissue (Table 1). However, these values have yet to be well established. Elements used in modern orthopedic implant alloys, including disc arthroplasty implants, are theoretically bioreactive through: metabolic alterations; alterations in host/parasite interactions; immunologic interactions of metal moieties by virtue of their ability to act as haptens (specific immunological activation) or anti-chemotactic agents (nonspecific immunological suppression), and chemical carcinogenesis. Implant metals such as Co, Cr, V, and possibly Ni are essential trace metals required for normal homeostasis. In nonorthopedic contexts of excessive exposure, all these metals have been linked to specific pathologies such as polycythemia, cardiomyopathy, carcinogenesis, and nephropathy. However, toxicity associated with any orthopedic alloy materials has not been reported. Also, it is important to note that despite the potential toxicologic possibilities, the association of metal release from orthopedic implants with any metabolic, bacteriologic, immunologic, or carcinogenic toxicity remains speculative; cause and effect have not been well-established in humans with knee and hip TJAs.[118] The following discussion of the systemic effects of implant debris are divided into 4 areas: neuoropathic effects, hypersensitivity effects, carcinogenicity, and general toxicity.

Neuropathic effects of spinal implant debris. The fiction is that direct neuropathic effects of implant debris have been observed clinically. The fact is that neuropathies have been reported around both well-functioning and failing articulating implants, but were generated from a granulomatus (immune) response to implant debris, not directly from the implant debris.[121–123] Patients have been reported to develop pain and inflammation of unknown etiology associated with spinal implants (screws) and shown resolution after implant removal.[94,95] However, adjacent tissues in

these case studies of spinal implants have shown the presence of synovial-like granulomatous tissue, osteolysis, and elevated inflammatory mediators such as PGE2 speculated to be produced by the micromotion or debris of implants, such as a loose pedicle screw.[94,95] Thus, granulomatous inflammatory responses and not direct neuropathic effects were likely. Similarly, animal models of peri-spinal implant osteolysis using large amounts of particulate debris (>4 mg) have not resulted in observable neuropathy.[84,124] Conclusions from such studies remain guardedly optimistic, where observable debris induced inflammation was reportedly limited to the epidural space around injected (or placed) particles.[125]

Hypersensitivity to implant debris: Metal allergy. The fiction is that issues of metal sensitivity are not applicable to spine implants. The fact is that although rare, spinal implants have been implicated in case and group studies of hypersensitivity.[126] Implant-related metal sensitivity is well documented in case and group studies, though overall it remains a relatively unpredictable and poorly-understood phenomenon in the context of orthopedic implant materials.[127–129] Metal-protein complexes are considered to be candidate antigens (or more loosely termed, allergens) for eliciting hypersensitivity responses. The terms "metal sensitivity," "metal allergy," and "metal hypersensitivity" all refer to the same adaptive immune response to metal antigens by lymphocytes, typically characterized as a type IV delayed type hypersensitivity response. However, the specific T-cell subpopulations, the cellular mechanism of recognition and activation, and the antigenic metal-protein determinants created by these metals remain incompletely characterized.[130–132]

Metals known as sensitizers (haptenic moieties in antigens) are beryllium,[133] nickel,[133–136] cobalt,[133] and chromium,[133] while occasional responses have been reported to tantalum,[137] titanium,[138,139] and vanadium.[137] Nickel is the most common metal sensitizer in humans followed by cobalt and chromium.[127,134–136] The prevalence of metal sensitivity among the general population is approximately 10-15% (Fig. 8), with nickel sensitivity the highest (approximately 14%).[127] The amounts of these metals found in medical grade alloys are shown in Table 1. Nonbiodegradable polymeric biomaterials used for load bearing in TJA are not easily chemically degraded in vivo and have not been intensely investigated or implicated in case or group studies as sources of hypersensitivity type immune responses.

Testing for metal sensitivity. The fiction is that the only kind of testing for metal allergy is patch testing. The fact is that proliferation testing has been well established as a method for testing metal sensitivity in a variety of clinical settings.[73,140,140–149] While patch testing and metal-LTT testing generally yield the same results, LTT testing may be equally or better suited for the testing of implant related sensitivity, because there is no risk of inducing metal sensitization using skin exposure; metal-LTT is highly quanti-
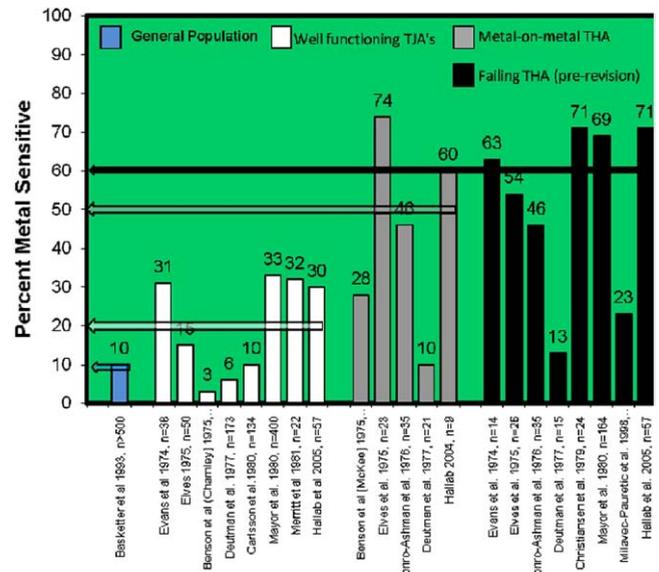

Fig. 8. A compilation of investigations showing the averaged incidence percentages of metal sensitivity for nickel, cobalt or chromium among 1) the general population, 2) patients after receiving a metal containing TJA, 3) patients with metal-on-metal bearing arthroplasty and 4) patient populations with significant osteolysis or due to be revised. Note: Studies by Hallab et al used LTT to measure hypersensitivity, all other used dermal patch testing.

tative and thus less dependent on the expertise of an observer to grade a response from +1 to +3; and the test is less costly, involves less patient discomfort, and is not subject to the same environmental susceptibility as patches that must be kept dry for 2-3 days.[148,150–152]

Clinical studies of metal implant-related metal sensitivity. The fiction is that there are only a few case reports of this relatively rare phenomenon. The fact is that over the past 25 years, growing numbers of case reports link immunogenic reactions with adverse performance of metallic cardiovascular,[153–155] orthopedic,[128,156–160] plastic surgical,[161] and dental[162–168] implants, which have sometimes required device removal.[153,156,158–160,169] Some of these reactions of severe dermatitis,[139,155,158,170] urticaria (intensely sensitive and itching red round wheels on the skin),[154,169] and/or vasculitis (patch inflammation of the walls of small blood vessels) have been linked with the relatively more general phenomena of metallosis, excessive periprosthetic fibrosis, and muscular necrosis.[160,171,172] Generally, there are more case reports of hypersensitivity reactions associated with stainless steel and cobalt alloy implants than with titanium alloy components.[128,157–159,169,170,173,174]

Cohort studies over the past 30+ years have generally indicated a correlation between metal implants and metal sensitivity.[73] Data (from these different investigations) regarding the prevalence of metal sensitivity are compiled in Figure 8. The average prevalence of metal sensitivity among patients with a failed or poorly functioning implant (as judged by a variety of criteria) using the 7 investigations is

approximately 60%.[173,175–178] Overall, the prevalence of metal sensitivity in patients with failed or failing implants is approximately 6 times that of the general population and approximately 2-3 times that of all patients with metal implants.

Despite the association of implant debris release from implants with adverse immunologic response, cause and effect have not been established in symptomatic patients with spine implants. Specific types of implants with a greater propensity to release metal in vivo may be more prone to induce metal sensitivity, as has been shown in total hip prostheses with metal-on-metal bearing surfaces (Fig. 8).[176,179] Metal sensitivity can be a contributing factor to implant failure.[13,157,180] Spinal implants have been only rarely implicated in case or group studies of hypersensitivity.[126] Thus metal-LTT may be warranted for people with a history of metal allergy prior to receiving an implant. The importance of this line of investigation is growing, as the use of metallic spinal implants is increasing and as expectations of implant durability and performance increase.[36,181]

Carcinogenicity. The fiction is that there have been documented cases of etiologically linked implant debris and cancer. The fact is that the carcinogenic potential of the metallic elements used in TJA remains an area of concern, but one that has not been verified by any etiological evidence.[182] Animal studies have documented the carcinogenic potential of orthopedic implant materials. Small increases in rat sarcomas were noted to correlate with high serum cobalt, chromium, or nickel content from metal implants. Furthermore, lymphomas with bone involvement were also more common in rats with metallic implants. Implant site tumors in dogs and cats (primarily osteosarcoma and fibrosarcoma) have been associated with stainless steel internal fixation devices.

The association of metal release from orthopedic implants with carcinogenesis remains conjectural, as causality has not been definitely established in human subjects. The actual number of cases of tumors associated with orthopedic implants is likely under-reported. However, with respect to the number of devices implanted on a yearly basis, the incidence of cancer at the site of implantation is relatively rare. Continued surveillance and longer-term epidemiological studies are required to fully address these issues.[182–186]

Toxicity. The fiction is that metals released from implants are not toxic to peri-implant cells. The fact is that previous nonclinical investigations of implant alloys using selected metals and selected cell lines show that high concentrations of metals can negatively impact cellular function.[74,187] However, the degree to which this occurs clinically is not known. Past investigations of implant-related metal toxicity include a variety of cell types (fibroblasts, endothelial cells, and nonhuman osteoblast-like cells),[188,189] but have, generally, been limited to in vitro studies and animal studies.[190–192] Thus toxicity effects of implant debris around spinal implants remain speculative. However, given past in vitro and

animal studies previously discussed, it is likely that metal toxicity effects can contribute to osteolysis in the peri-implant area if present in sufficient concentration. However, the concentrations at which this will occur are not known and the degree to which soluble metals are able to contribute to clinical pathology is not well understood. However, metal induced toxic effects will likely be difficult to distinguish from well-established pro-inflammatory effects of metal particles.

The use of animal models to evaluate host biological response to spinal implant debris. The fiction is that there are strict definite limits to the amount of implant debris allowed by federal agencies. The fact is that there is no single limit for the amount debris generation from spinal implants. Each implant is put through a series of tests to determine the amount of debris expected, then a relative amount of similar debris is evaluated in an animal model. The evaluation of the biologic response to implant debris has been traditionally conducted using mice, rats, rabbits, and sheep animal models under such standards as *ASTM F981-04 Standard Practice for Assessment of Compatibility of Biomaterials for Surgical Implants with Respect to Effect of Materials on Muscle and Bone*. Larger animal models, such as primates, that may more closely approximate human responses to implant debris have prohibitively high costs and have been generally limited in use.[84,88,193] Thus much of what we know of debris induced in vivo mechanisms/pathways of inflammation comes from small animal (mouse, rat, and rabbit) models[194–197] and human clinical observations.[19,49,50,88–92] Small models have been used to investigate particulate debris of many different kinds and sizes.[194–197] Generally, mouse and rat models have been used to assess inflammatory reaction and bone loss in calvaria, where particles are placed on the top of skull and the resulting inflammatory responses and bone loss are measured.[196,198–207] Rabbit models are typically used to assess new implant-related forms of particulate implant debris prior to FDA approval and the start of clinical studies. In these investigations, debris is injected or placed at the site of implantation.

Generally, the methods of testing particles in animals for the purposes of evaluating the biocompatibility of spinal implants involves: ascertaining the size and amount of debris that can be expected under implant appropriate loading conditions using mechanical simulator studies; producing similar-sized particulate debris in vitro; dosing animals with a bolus amount of debris equivalent to 10–50 years of implant use by placing debris onto the site of interest; and sacrificing the animals at 3 and 6 months to histologically examine peri-implant tissue either qualitatively or by quantitative immunohistochemical analysis, where tissue sections are stained for specific proinflammatory mediators (eg IL-6 and TNFα) and quantitatively compared to control animals with sham operations.[84]

The concentrations of powder typically implanted at the implant sites to induce osteolysis require using 1–30 mg

particulate challenge (with a average particle size of 1–5 μm diameter) for a mouse of 25 g (0.0004–0.12% body weight),[202,208] where the debris (dry delivery to the implant site) is spread over a calvarial defect measuring 1 cm². For rabbits, typically 0.01–200 mg of powder for a rabbit of 4.0 kg (<0.005% body weight) is typically used[84,193] and spread over implant sites at a concentration of 100 mg/6 cm². The weight of a 50-kg human is 12.5 times that of a rabbit, and thus the 1–4 mg of mass loss typical of an articulating human spinal implant is roughly equivalent to 50–200 mg of debris over 50 years of implant use. This 50–200 mg of debris in a 50-kg human scales down to 4–16 mg of debris for a 4-kg rabbit for a 50 years of implant use. However, bolus injection testing challenges the animal with years of implant debris at a single time point, and using a 50 years worth of debris may erroneously elicit non-physiologically representative inflammation. Thus debris amounts equivalent to 10 years of implant use (approximately 10 million loading cycles) have been recommended as an appropriate proxy for small animal studies. This amount of debris is generally far above that required by the FDA for bolus injection studies in rabbits for simulated testing to 10 million cycles (10 years) of use (*Guidance for Industry and FDA / Staff Preparation and Review of Investigational Device Exemption Applications (IDEs) for Total Artificial Discs, Document issued on: April 11, 2008:* http://www.fda.gov/cdrh/ode/guidance/1637.html). However, the possible synergistic pro-inflammatory effects of multiple types of debris produced in modern spinal implants (eg, polyurethane + cobalt-alloy + titanium alloy) have not been tested together and the outcome of these types of challenge conditions remains unknown.

Discussion and conclusion

Given the reality of pro-inflammatory responses to debris produced from articulating spinal implants, 2 things are certain: 1) implant longevity will be limited by implant debris inflammation where eventual revision is likely in younger individuals, and 2) regular follow-up is necessary to ascertain the yearly extent of debris-induced bioreactivity. New techniques can be used to aid follow-up evaluations; for example, reliably measurement metal ion levels in low ranges (parts per billion) have shown clinical utility and can be used to indicate excessive implant wear. However, basic contamination precautions must be adhered to (eg, verifying all processing containers used for ICP-MS analysis are metal ion free). While several centers now have the capability of performing this testing routinely (eg, Mayo Clinic, Rochester MN), most hospitals and medical centers do not have this testing available.

The potential of released spinal implant debris to induce inflammation and osteolysis in the spine is well accepted, yet it remains unknown how to determine what tolerable thresholds are for each individual. It is generally accepted that the most important determinant of inflammation is particle dose (assuming particles are in the range of <10 μm and able to be phagocytosed by cells).[79] However, not all types of particles are equally bioreactive. Particle bioreactivity general rules of thumb are: greater numbers of particles are more pro-inflammatory, and this inflammatory response is proportional to the particle load (the concentration of phagocytosable particles per tissue volume, which is characterized by both the size and total volume)[59,60]; elongated particles (fibers) are more pro-inflammatory than round particles[63,64]; and more chemically reactive (degradable and bioavailable) particles are more pro-inflammatory (ie, metals). There is a growing consensus of investigations that have shown metal particles are more proinflammatory when compared to polymers.[68]

The central hallmark of particle induced inflammation is innate immune cell (macrophages) secretion of TNFα, IL-1β, IL-6, and PGE2, which stimulate differentiation of osteoclast precursors into mature osteoclasts and increase peri-prosthetic bone resorption.[102]

With the growing number of people receiving spine arthroplasty implants and the issue of biologic reactivity looming, there is a growing need for more comprehensive diagnosis and intervention of untoward inflammation. Given that some versions of modern spinal arthroplasty designs have been in use for over 20 years internationally, implant concerns about neuropathology, toxicity, and carcinogenicity have been somewhat mitigated, yet remain incompletely addressed. New discoveries of how sterile nonpathogen implant debris lead to immune activation continue to be discovered, such as the inflammasome "danger signaling" pathway.[108] Consequently, new therapies (such as Anti-TNF-Infliximab, Anti-IL-1β [IL-1β-receptor-antagonist Anakinra] etc) and diagnostic testing (metal-LTT and metal ion analysis) are continually being developed to help mitigate the subtle low-grade local inflammation which leads to eventual poor implant performance in some people more than others.

References

1. Willert HG, Semlitsch M. Reactions of the articular capsule to wear products of artificial joint prostheses. *J Biomed Mater Res* 1977;11:157–64.
2. Holt G, Murnaghan C, Reilly J, Meek RM. The biology of aseptic osteolysis. *Clin Orthop Relat Res* 2007;460:240–52.
3. Jacobs JJ, Hallab NJ. Loosening and osteolysis associated with metal-on-metal bearings: A local effect of metal hypersensitivity? *J Bone Joint Surg Am* 2006;88:1171–2.
4. Korovessis P, Petsinis G, Repanti M, Repantis T. Metallosis after contemporary metal-on-metal total hip arthroplasty. Five to nine-year follow-up. *J Bone Joint Surg Am* 2006;88:1183–91.
5. Milosev I, Trebse R, Kovac S, Cor A, Pisot V. Survivorship and retrieval analysis of Sikomet metal-on-metal total hip replacements at a mean of seven years. *J Bone Joint Surg Am* 2006;88:1173–82.
6. Goodman SB. Wear particles, periprosthetic osteolysis and the immune system. *Biomater* 2007;28:5044–8.
7. Jacobs JJ, Hallab NJ. Loosening and osteolysis associated with metal-on-metal bearings: A local effect of metal hypersensitivity? *J Bone Joint Surg Am* 2006;88:1171–2.

8. Ren W, Wu B, Peng X, Hua J, Hao HN, Wooley PH. Implant wear induces inflammation, but not osteoclastic bone resorption, in RANK(-/-) mice. *J Orthop Res* 2006;24:1575–86.

9. Shanbhag AS, Kaufman AM, Hayata K, Rubash HE. Assessing osteolysis with use of high-throughput protein chips. *J Bone Joint Surg Am* 2007;89:1081–9.

10. Fritz EA, Glant TT, Vermes C, Jacobs JJ, Roebuck KA. Chemokine gene activation in human bone marrow-derived osteoblasts following exposure to particulate wear debris. *J Biomed Mater Res A* 2006;77: 192–201.

11. Kerboull L, Hamadouche M, Courpied JP, Kerboull M. Long-term results of Charnley-Kerboull hip arthroplasty in patients younger than 50 years. *Clin Orthop* 2004;418:112–8.

12. Hensten-Pettersen A. Allergy and hypersensitivity. In: Morrey BF, editor. Biological, material, and mechanical considerations of joint replacements. New York: Raven Press; 1993. p. 353–60.

13. Rooker GD, Wilkinson JD. Metal sensitivity in patients undergoing hip replacement. A prospective study. *J Bone Joint Surg* 1980;62-B: 502–5.

14. Kuby J. Immunology. 2nd ed. New York: W.H. Freeman and Company; 1991.

15. Korenblat PE. Contact Dermatitis. 2nd ed. Philidelphia: W.B. Saunders Company; 1992.

16. Merritt K, Brown S. Tissue reaction and metal sensitivity. *Acta Orthop Scand* 1980;51:403–4111.

17. Popoola OO, Shen M, Heller, M, Seebeck J. IN vitro wear of UHMWPE inlays in Dynardi and Prodisc spine disc replacment implants. Trans 7th Annual Meeting Spine Arthroplasty Society 2007;May14(Berlin):49.

18. Pare PE, Chan F, Powell ML, Mathews HH. Wear characterization of the MAVERICK total disc replacment. Trans 7th Annual Meeting Spine Arthroplasty Society 2007;May14:59.

19. van OA, Kurtz SM, Stessels F, Noten H, van Rhijn L. Polyethylene wear debris and long-term clinical failure of the Charite disc prosthesis: a study of 4 patients. *Spine* 2007;32:223–9.

20. Anderson PA, Rouleau JP, Bryan VE, Carlson CS. Wear analysis of the Bryan Cervical Disc prosthesis. *Spine* 2003;28:S186–S94.

21. Hallab NJ, Khandha A, Malcolmson G, Timm JP. In vitro assessment of serum-saline ratios for fluid simulator testing of highly modular spinal implants with articulating surfaces. *SAS Journal* 2008;2:171–83.

22. Kurtz SM, Hozack W, Turner J, Purtill J, MacDonald D, Sharkey P, et al. Mechanical properties of retrieved highly cross-linked crossfire liners after short-term implantation. *J Arthroplasty* 2005;20:840–9.

23. Greenwald AS, Garino JP. Alternative bearing surfaces: the good, the bad, and the ugly. *J Bone Joint Surg Am* 2001;83-A(Suppl 2 Pt 2):68-72.

24. Callaghan JJ, Rosenberg A, Rubash H. The adult hip. New York: Lippincott Williams & Wilkins; 2007.

25. Minoda Y, Kobayashi A, Iwaki H, Miyaguchi M, Kadoya Y, Ohashi H, Takaoka K. Polyethylene wear particle generation in vivo in an alumina medial pivot total knee prosthesis. B*iomate.* 2005;26:6034–40.

26. Heisel C, Silva M, la Rosa MA, Schmalzried TP. Short-term in vivo wear of cross-linked polyethylene. *J Bone Joint Surg Am* 2004;86-A(4):748-51.

27. Wroblewski BM, Siney PD, Dowson D, Collins SN. Prospective clinical and joint simulator studies of a new total hip arthroplasty using alumina ceramic heads and cross-linked polyethylene cups. *J Bone Joint Surg Br* 1996;78:280–5.

28. Saikko V, Calonius O, Keranen J. Wear of conventional and cross-linked ultra-high-molecular-weight polyethylene acetabular cups against polished and roughened CoCr femoral heads in a biaxial hip simulator. *J Biomed Mater Res* 2002;63:848–53.

29. Catelas I, Medley JB, Campbell PA, Huk OL, Bobyn JD. Comparison of in vitro with in vivo characteristics of wear particles from metal-metal hip implants. *J Biomed Mater Res B Appl Biomater* 2004;70:167–78.

30. Tipper JL, Hatton A, Nevelos JE, Ingham E, Doyle C, Streicher R, et al. Alumina-alumina artificial hip joints. Part II: characterisation of the wear debris from in vitro hip joint simulations. *Biomater* 2002; 23:3441–8.

31. Firkins PJ, Tipper JL, Saadatzadeh MR, Ingham E, Stone MH, Farrar R, et al. Quantitative analysis of wear and wear debris from metal-on-metal hip prostheses tested in a physiological hip joint simulator. *Biomed.Mater.Eng* 2001;11:143–57.

32. Hellier WG, Hedman TP, Kostuik JP. Wear studies for development of an intervertebral disc prosthesis. *Spine* 1992;17(6 Suppl):S86–S96.

33. Clarke IC, Good V, Williams P, Schroeder D, Anissian L, Stark A, et al. Ultra-low wear rates for rigid-on-rigid bearings in total hip replacements. *Proc.Inst.Mech.Eng [H.]* 2000;214:331–47.

34. McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, et al. In vivo wear of three types of metal on metal hip prostheses during two decades of use. *Clin Orthop* 1996;329(Suppl):S128–S40.

35. Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am* 1998;80:268–82.

36. Black J. Prosthetic materials. New York: VCH Publishers, Inc.; 1996. p. 141–62.

37. Breme J, Biehl V. Metallic biomaterials. In: Black J, Hastings G, editors. Handbook of biomaterial properties. London: Chapman and Hall; 2001. p. 135–214.

38. Cohen J, Lindenbaum B. Fretting corrosion in orthopedic implants. *Clin Orthop* 1968;61:167–75.

39. Ballard WT, Jacobs JJ, Skipor AK, Patterson LM, Black J. Serum chromium levels in total hip arthroplasty patients with CoCr femoral components revised for aseptic loosening. AAOS 64th Annual Meeting, San Fransisco, CA; 1997.

40. Jacobs JJ, Skipor AK, Doorn PF, Campbell P, Schmalzried TP, Black J, et al. Cobalt and chromium concentrations in patients with metal on metal total hip replacements. *Clin Orthop* 1996;329(Suppl):S256–S63.

41. Jacobs JJ, Skipor AK, Patterson LM, Black J, Galante JO. Serum titanium concentration in patients with cementless TKR: a 5-year prospective study. *Trans ORS* 1997;22:235.

42. Jacobs JJ, Skipor AK, Patterson LM, Paprosky WG, Black J, Galante JO. A prospective, controlled, longitidunal study of metal release in patients undergoing primary total hip arthroplasty. *J.Bone Joint Surg* 2001;80:1447–58.

43. Jacobs JJ, Shanbhag A, Glant TT, Black J, Galante JO. Wear debris in total joint replacements. *J Am Acad Orthop Surg* 1994;2:212–20.

44. Campbell P, Ma S, Yeom B, McKellop H, Schmalzried TP, Amstutz HC. Isolation of predominantly submicron-sized UHMWPE wear particles from periprosthetic tissues. *J Biomed Mater Res* 1995;29: 127–31.

45. Maloney WJ, Smith RL, Castro F, Schurman DJ. Fibroblast response to metallic debris in vitro. Enzyme induction cell proliferation, and toxicity. *J Bone Joint Surg Am* 1993;75:835–44.

46. Scott M, Morrison M, Mishra SR, Jani S. Particle analysis for the determination of UHMWPE wear. *J Biomed Mater Res B Appl Biomater* 2005;73:325–37.

47. Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M. Dissemination of Wear Particles to the Liver, Spleen, and Abdominal Lymph Nodes of Patients with Hip or Knee Replacement. *J Bone Joint Surg* 2000;82-A:457–77.

48. Urban RM, Jacobs JJ, Tomlinson MJ, Gavrilovic J, Black J, Peoc'h M. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J. Bone Joint Surg Am* 2000;82:457–76.

49. Punt IM, Cleutjens JP, de BT, Willems PC, Kurtz SM, van Rhijn LW, et al. Periprosthetic tissue reactions observed at revision of total intervertebral disc arthroplasty. *Biomater* 2009;30:2079–84.

50. Choma TJ, Miranda J, Siskey R, Baxter R, Steinbeck MJ, Kurtz SM. Retrieval analysis of a ProDisc-L total disc replacement. *J Spinal Disord Tech* 2009;22:290–6.

51. Punt IM, Visser VM, van Rhijn LW, Kurtz SM, Antonis J, Schurink GW, et al. Complications and reoperations of the SB Charite lumbar disc prosthesis: experience in 75 patients. *Eur Spine J* 2008;17:36–43.

52. Urban RM, Jacobs JJ, Sumner DR, Peters CL, Voss FR, Galante JO. The bone-implant interface of femoral stems with non- circumferential porous coating: a study of specimens retrieved at autopsy. *J Bone Joint Surg Am* 1996;78-A:1068–81.

53. Urban RM, Jacobs J, Gilbert JL, Rice SB, Jasty M, Bragdon CR, Galante GO. Characterization of solid products of corrosion generated by modular-head femoral stems of different designs and materials. In: Marlowe DE, Parr JE, Mayor MB, editors. STP 1301 Modularity of orthopedic implants.Philadelphia, PA: ASTM; 1997. p. 33–44.

54. Zeh A, Planert M, Siegert G, Lattke P, Held A, Hein W. Release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick-type artificial lumbar disc (Medtronic Sofamor Danek). *Spine* 2007;32:348–52.

55. Zeh A, Becker C, Planert M, Lattke P, Wohlrab D. Time-dependent release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick type artificial lumbar disc (Medtronic Sofamor Danek). *Arch Orthop Trauma Surg* 2009 ;129: 741–6.

56. McPhee IB, Swanson CE. Metal ion levels in patients with stainless steel spinal instrumentation. *Spine* 2007;32:1963–8.

57. Skipor A, Harper M, Gornet M, Burkus J, Chan F, Jacobs J. Serum metal levels in a metal-on-metal lumbar disc arthroplasty. *Trans ORS* 2009;23:1847.

58. Brodner W, Grohs JG, Bitzan P, Meisinger V, Kovarik J, Kotz R. [Serum cobalt and serum chromium level in 2 patients with chronic renal failure after total hip prosthesis implantation with metal-metal gliding contact]. *Z Orthop Ihre Grenzgeb* 2000;138:425–9.

59. González O, Smith RL, Goodman SB. Effect of size, concentration, surface area, and volume of polymethylmethacrylate paticles on human macrophages *in vitro*. *J Biomed Mater Res* 1996;30:463–73.

60. Matthews JB, Besong AA, Green TR, Stone MH, Wroblewski BM, Fisher J, et al. Evaluation of the response of primary human peripheral blood mononuclear phagocytes to challenge with in vitro generated clinically relevant UHMWPE particles of known size and dose. *J Biomed Mater Res* 2000;52:296–307.

61. Matthews JB, Green TR, Stone MH, Wroblewski BM, Fisher J, Ingham E. Comparison of the response of primary murine peritoneal macrophages and the U937 human histiocytic cell line to challenge with in vitro generated clinically relevant UHMWPE particles. *Biomed Mater Eng* 2000;10:229–40.

62. Green TR, Fisher J, Matthews JB, Stone MH, Ingham E. Effect of size and dose on bone resorption activity of macrophages by in vitro clinically relevant ultra high molecular weight polyethylene particles. *J Biomed Mater Res* 2000;53:490–7.

63. Laquerriere P, Grandjean-Laquerriere A, Jallot E, Balossier G, Frayssinet P, Guenounou M. Importance of hydroxyapatite particles characteristics on cytokines production by human monocytes in vitro. *Biomater* 2003;24:2739–47.

64. Sieving A, Wu B, Mayton L, Nasser S, Wooley PH. Morphological characteristics of total joint arthroplasty-derived ultra-high molecular weight polyethylene (UHMWPE) wear debris that provoke inflammation in a murine model of inflammation. *J Biomed Mater Res* 2003;64A(3):457–64.

65. Dostert C, Petrilli V, Van BR, Steele C, Mossman BT, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. *Science* 2008;320:674–7.

66. Bruch J. Response of cell cultures to asbestos fibers. *Environ Health Perspect* 1974;9:253–4.

67. Schmalzried TP, Campbell P, Schmitt AK, Brown IC, Amstutz HC. Shapes and dimensional characteristics of polyethylene wear particles generated in vivo by total knee replacements compared to total hip replacements. *J Biomed Mater Res* 1997;38:203–10.

68. Ramachandran R, Goodman SB, Smith RL. The effects of titanium and polymethylmethacrylate particles on osteoblast phenotypic stability. *J Biomed Mater Res A* 2006;77:512–7.

69. von Knoch M, Engh CAS, Sychterz CJ, Engh CAJ, Willert HG. Migration of polyethylene wear debris in one type of uncemented femoral component with circumferential porous coating: an autopsy study of 5 femurs. *J Arthroplasty* 2000;15:72–8.

70. Baumann B, Rader CP, Seufert J, Noth U, Rolf O, Eulert J, Jakob F. Effects of polyethylene and TiAlV wear particles on expression of RANK, RANKL and OPG mRNA. *Acta Orthop Scand* 2004;75:295–302.

71. Baumann B, Seufert J, Jakob F, Noth U, Rolf O, Eulert J, Rader CP. Activation of NF-kappaB signalling and TNFalpha-expression in THP-1 macrophages by TiAlV- and polyethylene-wear particles. *J Orthop Res* 2005;23:1241–8.

72. Baumann B, Rolf O, Jakob F, Goebel S, Sterner T, Eulert J, et al. Synergistic effects of mixed TiAlV and polyethylene wear particles on TNFalpha response in THP-1 macrophages. *Biome Tech* (Berl) 2006;51:360–6.

73. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001;83-A:428–36.

74. Hallab NJ, Anderson S, Caicedo M, Brasher A, Mikecz K, Jacobs JJ. Effects of soluble metals on human peri-implant cells. *J Biomed Mater Res.A* 2005;74:124–40.

75. Caicedo M, Reddy A, Samee I, Jacobs JJ, Hallab N. Cobalt Ions and Co-Cr-Mo alloy particles induce human monocyte co-stimulatory molecules CD-86, ICAM-1 and the cytokine IL-8: Implications for innate activation of adaptive immune responses. 6th Combined Meeting of the Orthopaedic Research Societies 2007;6:535.

76. Green TR, Fisher J, Stone M, Wroblewski BM, Ingham E. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. *Biomater* 1998;19:2297–302.

77. Ingram J, Matthews JB, Tipper J, Stone M, Fisher J, Ingham E. Comparison of the biological activity of grade GUR 1120 and GUR 415HP UHMWPE wear debris. *Biomed Mater Eng* 2002;12:177–88.

78. Rader CP, Sterner T, Jakob F, Schutze N, Eulert J. Cytokine response of human macrophage-like cells after contact with polyethylene and pure titanium particles. *J Arthroplasty* 1999;14:840–8.

79. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Human monocyte response to particulate biomaterials generated in vivo and in vitro. *J Orthop Res* 1995;13:792–801.

80. Nalepka JL, Lee MJ, Kraay MJ, Marcus RE, Goldberg VM, Chen X, et al. Lipopolysaccharide found in aseptic loosening of patients with inflammatory arthritis. *Clin Orthop Relat Res* 2006;451:229–35.

81. Espehaug B, Engesaeter LB, Vollset SE, Havelin LI, Langeland N. Antibiotic prophylaxis in total hip arthroplasty. Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995. *J Bone Joint Surg Br* 1997;79: 590–5.

82. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Macrophage/particle interactions. Effect of size, composition and surface area. *J Biomed Mater Res* 1994;28:81–90.

83. Ingham E, Green TR, Stone MH, Kowalski R, Watkins N, Fisher J. Production of TNF-alpha and bone resorbing activity by macrophages in response to different types of bone cement particles. *Biomater* 2000;21:1005–13.

84. Cunningham BW, Orbegoso CM, Dmitriev AE, Hallab NJ, Sefter JC, McAfee PC. The effect of titanium particulate on development and maintenance of a posterolateral spinal arthrodesis: an in vivo rabbit model. *Spine* 2002 ;27:1971–81.

85. Savarino L, Stea S, Granchi D, Visentin M, Ciapetti G, Donati ME, et al. Sister chromatid exchanges and ion release in patients wearing fracture fixation devices. *J Biomed Mater Res* 50:21–6.

86. Nagaya T, Ishikawa N, Hata H. Sister chromatid exchange analysis in lymphocytes of workers exposed to hexavalent chromium. *Br J Ind Med* 1989;46:48–51.

87. Soloviev A, Schwarz EM, Darowish M, O'Keefe RJ. Sphingomyelinase mediates macrophage activation by titanium particles independent of phagocytosis: a role for free radicals, NFkappaB, and TNFalpha. *J Orthop Res* 2005;23:1258–65.

88. Hallab NJ, Cunningham BW, Jacobs JJ. Spinal Implant Debris-Induced Osteolysis. *Spine* 2003;28:S125–S38.

89. Doorn PF, Mirra JM, Campbell PA, Amstutz HC. Tissue reaction to metal on metal total hip prostheses. *Clin Orthop* 1996;329(Suppl):S187–S205.

90. Berger RA, Quigley LR, Smink D, Sheinkop M, Jacobs JJ, Rosenberg AG, et al. Factors contributing to osteolysis and failure in primary cementless THA. *Orthop Trans* 1999;22:129.

91. Inoue S, Kubo T, Suehara H, Yamazoe S, Nakamura M, Miyaoka H, Hirasawa Y. A 10- to 13-year follow-up study of Harris-Galante type prosthesis in total hip arthroplasty. *J Orthop Sci* 2000;5:561–6.

92. Jacobs JJ, Roebuck KA, Archibeck M, Hallab NJ, Glant TT. Osteolysis: basic science. *Clin Orthop* 2001;393:71–7.

93. Gaine WJ, Andrew SM, Chadwick P, Cooke E, Williamson JB. Late operative site pain with isola posterior instrumentation requiring implant removal: infection or metal reaction? *Spine* 2001;26:583–7.

94. Johnson D, Tucci M, McGuire R, Hughes J. Evaluation of the biomaterial-interface of screw threads in patients having clinical pain. *Biomed Sci Instrum* 1996;32:127–33.

95. Mody DR, Esses SI, Heggeness MH. A histologic study of soft-tissue reactions to spinal implants. *Spine* 1994;19:1153–6.

96. Kurtz SM, van OA, Ross R, de Waal MJ, Peloza J, Ciccarelli L, et al. Polyethylene wear and rim fracture in total disc arthroplasty. *Spine J* 2007;7:12–21.

97. Kurtz SM, Peloza J, Siskey R, Villarraga ML. Analysis of a retrieved polyethylene total disc replacement component. *Spine J* 2005;5:344–50.

98. McAfee PC, Fedder IL, Saiedy S, Shucosky EM, Cunningham BW. SB Charite disc replacement: report of 60 prospective randomized cases in a US center. *J Spinal Disord Tech* 2003;16:424–33.

99. Denaro V, Papapietro N, Sgambato A, Barnaba SA, Ruzzini L, Paola BD, et al. Periprosthetic electrochemical corrosion of titanium and titanium-based alloys as a cause of spinal fusion failure. *Spine* 2008;33:8–13.

100. Glant TT, Jacobs JJ. Response of three murine macrophage populations to particulate debris: bone resorption in organ cultures. *J Orthop Res* 1994;12:720–32.

101. Jacobs JJ, Hallab NJ, Urban RM, Wimmer MA. Wear particles. *J Bone Joint Surg Am* 2006;88(Suppl 2):99–102.

102. Sabokbar A, Kudo O, Athanasou NA. Two distinct cellular mechanisms of osteoclast formation and bone resorption in periprosthetic osteolysis. *J Orthop Res* 2003;21:73–80.

103. Wang ML, Nesti LJ, Tuli R, Lazatin J, Danielson KG, Sharkey PF, et al. Titanium particles suppress expression of osteoblastic phenotype in human mesenchymal stem cells. *J Orthop Res* 2002;20:1175–84.

104. Vermes C, Chandrasekaran R, Jacobs JJ, Galante JO, Roebuck KA, Glant TT. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J Bone Joint Surg Am* 2001;83:201–11.

105. Pioletti DP, Leoni L, Genini D, Takei H, Du P, Corbeil J. Gene expression analysis of osteoblastic cells contacted by orthopedic implant particles. *J Biomed Mater Res* 2002;61:408–20.

106. Mariathasan S, Monack DM. Inflammasome adaptors and sensors: intracellular regulators of infection and inflammation. *Nat Rev Immunol* 2007;7:31–40.

107. Mariathasan S, Newton K, Monack DM, Vucic D, French DM, Lee WP, et al. Differential activation of the inflammasome by caspase-1 adaptors ASC and Ipaf. *Nature* 2004;430:213–8.

108. Caicedo MS, Desai R, McAllister K, Reddy A, Jacobs JJ, Hallab NJ. Soluble and particulate Co-Cr-Mo alloy implant metals activate the inflammasome danger signaling pathway in human macrophages: A novel mechanism for implant debris reactivity. *J Orthop Res* 2008;27:847–54.

109. Jacobs JJ, Skipor AK, Patterson LM, Hallab NJ, Paprosky WG, Black J, et al. Metal release in patients who have had a primary total hip arthroplasty. A prospective, controlled, longitudinal study. *J Bone Joint Surg Am* 1998;80:1447–58.

110. Savarino L, Granchi D, Ciapetti G, Cenni E, Nardi PA, Rotini R, et al. Ion release in patients with metal-on-metal hip bearings in total joint replacement: a comparison with metal-on-polyethylene bearings. *J Biomed Mater Res* 2002;63:467–74.

111. Jacobs JJ, Silverton C, Hallab NJ, Skipor AK, Patterson L, Black J, et al. Metal release and excretion from cementless titanium alloy total knee replacements. *Clin Orthop* 1999;358:173–80.

112. Sunderman FW, Hopfer SM, Swift T, Rezuke WN, Ziebka L, Highman P, et al. Cobalt, chromium, and nickel concentrations in body fluids of patients with porous-coated knee or hip prostheses. *J Orthop Res* 1989;7:307–15.

113. Rasquinha VJ, Ranawat CS, Weiskopf J, Rodriguez JA, Skipor AK, Jacobs JJ. Serum metal levels and bearing surfaces in total hip arthroplasty. *J Arthroplasty.* 2006;21(6 Suppl 2):47–52.

114. Silva M, Heisel C, Schmalzried TP. Metal-on-metal total hip replacement. *Clin Orthop Relat Res* 2005;430:53–61.

115. Karrholm J, Frech W, Nilsson KG, Snorrason F. Increased metal release from cemented femoral components made of titanium alloy. 19 hip prostheses followed with radiostereometry (RSA). *Acta Orthop Scand* 1994;65:599–604.

116. Dorr LD, Bloebaum R, Emmanual J, Meldrum R. Histologic, biochemical and ion analysis of tissue and fluids retrieved during total hip arthroplasty. *Clin Orthop Relat Res* 1990;261:82–95.

117. Jacobs JJ, Skipor AK, Urban RM, Black J, Manion LM, Starr A, et al. Systemic distribution of metal degradation products from titanium alloy total hip replacements: an autopsy study. *Trans Orthop Res Soc New Orleans* 1994;838.

118. Michel R, Nolte M, Reich M, Loer F. Systemic effects of implanted prostheses made of cobalt-chromium alloys. *Arch OrthopTrauma Surg* 1991;110:61–74.

119. Stulberg BN, Merritt K, Bauer T. Metallic wear debris in metal-backed patellar failure. *J Biomed Mat Res Appl Bio* 1994;5:9–16.

120. Betts F, Wright T, Salvati EA, Boskey A, Bansal M. Cobalt-alloy metal debris in periarticular tissues from total hip revision arthroplasties. Metal contents and associated histologic findings. *Clin Orthop* 1992;276:75–82.

121. Crawford JR, Van RL, Marx C. Compression of the sciatic nerve by wear debris following total hip replacement: a report of three cases. *J Bone Joint Surg Br* 2003;85:1178–80.

122. Fischer SR, Christ DJ, Roehr BA. Sciatic neuropathy secondary to total hip arthroplasty wear debris. *J Arthroplasty* 1999;14:771–4.

123. Waite J, Marks P, Young D. Acute sciatic nerve palsy caused by a polyethylene granuloma arising from a well-fixed total knee arthroplasty. *J Arthroplasty* 2006;21:907–10.

124. Chang BS, Brown PR, Sieber A, Valdevit A, Tateno K, Kostuik JP. Evaluation of the biological response of wear debris. *Spine J* 2004;4(6 Suppl):239S–44S.

125. Rhalmi S, Charette S, Assad M, Coillard C, Rivard CH. The spinal cord dura mater reaction to nitinol and titanium alloy particles: a 1-year study in rabbits. *Eur Spine J* 2007;16:1063–72.

126. Cavanaugh DA, Nunley PD, Kerr EJ III, Werner DJ, Jawahar A. Delayed hyper-reactivity to metal ions after cervical disc arthroplasty: a case report and literature review. *Spine* 2009;34:E262–E5.

127. Basketter DA, Briatico-Vangosa G, Kaestner W, Lally C, Bontinck WJ. Nickel, cobalt and chromium in consumer products: a role in allergic contact dermatitis? *Contact Dermatitis* 1993;28:15–25.

128. Cramers M, Lucht U. Metal sensitivity in patients treated for tibial fractures with plates of stainless steel. *Acta Orthop Scand* 1977;48:245–9.

129. Fisher AA. Allergic dermatitis presumably due to metallic foreign bodies containing nickel or cobalt. *Current Contact News* 1977;19:285–95.

130. Silvennoinen-Kassinen S, Poikonen K, Ikaheimo I. Characterization of nickel-specific T cell clones. *Scand J Immunol* 1991;33:429–34.

131. Moulon C, Vollmer J, Weltzien HU. Characterization of processing requirements and metal cross- reactivities in T cell clones from patients with allergic contact dermatitis to nickel. *Eur J Immunol* 1995;25:3308–15.

132. Saito K. [Analysis of a genetic factor of metal allergy—polymorphism of HLA-DR, -DQ gene]. *Kokubyo Gakkai Zasshi* 1996;63:53–69.

133. Liden C, Maibach HI, Howard I, Wahlberg JE. Skin. In: Goyer RA, Klaasen CD, Waalkes M, editors. New York, NY: Academic Press; 1995. p. 447–64.

134. Kanerva L, Sipilainen-Malm T, Estlander T, Zitting A, Jolanki R, Tarvainen K. Nickel release from metals, and a case of allergic contact dermatitis from stainless steel. *Contact Dermatitis* 1994;31:299–303.

135. Haudrechy P, Foussereau J, Mantout B, Baroux B. Nickel release from nickel-plated metals and stainless steels. *Contact Dermatitis* 1994;31:249–55.

136. Gawkrodger DJ. Nickel sensitivity and the implantation of orthopaedic prostheses. *Contact Dermatitis* 1993;28:257–9.

137. Angle C, Organ-specific therapeutic intervention. In: Goyer RA, Klaassen CD, Waalkes MP, editors. Metal toxicology. New York, NY: Academic Press; 1995. p. 71–110.

138. Lalor PA, Revell PA, Gray AB, Wright S, Railton GT, Freeman MA. Sensitivity to titanium. A cause of implant failure. *J Bone Joint Surg* 1991;73-B:25–8.

139. Parker AW, Drez D Jr, Jacobs JJ. Titanium dermatitis after failure of a metal-backed patellas. *Am J Knee Surg* 1993;6:129–31.

140. Veien NK, Svejgaard E. Lymphocyte transformation in patients with cobalt dermatitis. *Br J Dermatol* 1978;99:191–6.

141. Svejgaard E, Morling N, Svejgaard A, Veien NK. Lymphocyte transformation induced by nickel sulphate: an in vitro study of subjects with and without a positive nickel patch test. *Acta Derm Venereol* 1978;58:245–50.

142. Veien NK, Svejgaard E, Menne T. In vitro lymphocyte transformation to nickel: a study of nickel-sensitive patients before and after epicutaneous and oral challenge with nickel. *Acta Derm Venereol* 1979;59:447–51.

143. Svejgaard E, Thomsen M, Morling N, Hein CA. Lymphocyte transformation in vitro in dermatophytosis. *Acta Pathol Microbiol Scand C* 1976;84C:511–23.

144. Everness KM, Gawkrodger DJ, Botham PA, Hunter JA. The discrimination between nickel-sensitive and non-nickel-sensitive subjects by an in vitro lymphocyte transformation test. *Br J Dermatol* 1990;122:293–8.

145. Hallab NJ. Lymphocyte transformation testing for quantifying metal-implant-related hypersensitivity responses. *Dermatitis* 2004;15:82–90.

146. Hallab NJ, Anderson S, Caicedo M, Skipor A, Campbell P, Jacobs JJ. Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. *J Arthroplasty* 2004;19(8 Suppl 3):88–93.

147. Kwon YM, Thomas P, Summer B, Pandit H, Taylor A, Beard D, et al. Lymphocyte proliferation responses in patients with pseudotumors following metal-on-metal hip resurfacing arthroplasty. *J Orthop Res* 2009 (epub ahead of print).

148. Thomas P, Braathen LR, Dorig M, Aubock J, Nestle F, Werfel T, et al. Increased metal allergy in patients with failed metal-on-metal hip arthroplasty and peri-implant T-lymphocytic inflammation. *Allergy* 2009;64:1157–65.

149. Lindemann M, Rietschel F, Zabel M, Grosse-Wilde H. Detection of chromium allergy by cellular in vitro methods. *Clin.Exp. Allergy* 2008;38:1468–75.

150. Carando S, Cannas M, Rossi P, Portigliatti-Barbos M. The lymphocytic transformation test (L.T.T.) in the evaluation of intolerance in prosthetic implants. *Ital.J Orthop Traumatol* 1985;11:475–81.

151. Granchi D, Ciapetti G, Stea S, Cavedagna D, Bettini N, Bianco T, et al. Evaluation of several immunological parameters in patients with aseptic loosening of hip arthroplasty. *Chir Organi Mov* 1995;80:399–408.

152. Granchi D, Ciapetti G, Savarino L, Cavedagna D, Donati ME, Pizzoferrato A. Assessment of metal extract toxicity on human lymphocytes cultured in vitro. *J Biomed Mater Res* 1996;31:183–91.

153. Abdallah HI, Balsara RK, O'Riordan AC. Pacemaker contact sensitivity: Clinical recognition and management. *Ann Thorac Surg* 1994;57:1017–8.

154. Buchet S, Blanc D, Humbert P, Girardin P, Vigan M, Anguenot T, et al. Pacemaker dermatitis. *Contact Dermatitis* 1992;26:46–7.

155. Peters MS, Schroeter AL, Hale HM, Broadbent JC. Pacemaker contact sensitivity. *Contact Dermatitis* 1984;11:214–8.

156. Barranco VP, Solloman H. Eczematous dermatitis from nickel. *JAMA* 1972;220:1244.

157. Rostoker G, Robin J, Binet O, Blamutier J, Paupe J, Lessana-Liebowitch M, et al. Dermatitis due to orthopaedic implants. A review of the literature and report of three cases. *J Bone Joint Surg* 1987;69-A:1408–12.

158. Thomas RH, Rademaker M, Goddard NJ, Munro DD. Severe eczema of the hands due to an orthopaedic plate made of Vitallium. *Br Med J* 1987;294:106–7.

159. Merle C, Vigan M, Devred D, Girardin P, Adessi B, Laurent R. Generalized eczema from vitallium osteosynthesis material. *Contact Dermatitis* 1992;27:257–8.

160. Halpin DS. An unusual reaction in muscle in association with a vitallium plate: A report of possible metal hypersensitivity. *J Bone Joint Surg* 1975;57-B:451–3.

161. Holgers KM, Roupi G, Tjellstrom A, Bjurstem LM. Clinical, immunological and bacteriological evaluation of adverse reactions to skin-penetrating titanium implants in the head and neck region. *Contact Dermatitis* 1992;27:1–7.

162. Spiechowitz E, Glantz PO, Axell T, Chmieleweski W. Oral exposure to a nickel-containing dental alloy of persons with hypersensitive skin reactions to nickel. *Contact Dermatitis* 1984;10:206–11.

163. Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria. *J Am Acad Dermatol* 1994;31:205.

164. Vilaplana J, Rmoaguera C, Cornellana F. Contact dermatitis and adverse oral mucus membrane reactions related to the use of dental prosthesis. *Contact Dermatitis* 1994;30:80–4.

165. Guimaraens D, Gonzalez MA, Conde-Salazar L. Systemic contact dermatitis from dental crowns. *Contact Dermatitis* 1994;30:124–5.

166. Hubler WJ, Hubler WS. Dermatitis from a chromium dental plate. *Contact Dermatitis* 1983;9:377–83.

167. Bruze, Edman B, Bjorkner B, Moller H. Clinical relevance of contact allergy to gold sodium. *J Am Acad Dermatol* 1994;31:579–83.

168. Laeijendecker R, vanJoost T. Oral manifestations ofgold allergy. *J Am Acad Dermatol* 1994;30:205–9.

169. King J, Fransway A, Adkins RB. Chronic urticaria due to surgical clips. *N Engl J Med* 1993;329:1583–4.

170. Gordon PM, White MI, Scotland TR. Generalized sensitivity from an implanted orthopaedic antibiotic minichain containing nickel. *Contact Dermatitis* 1994;30:181–2.

171. Nakamura S, Yasunaga Y, Ikutu Y, Shimogaki K, Hamada N, Takata N. Autoantibodies to red cells associated with metallosis-a case report. *Acta Orthop Scand* 1997;68:495–6.

172. Black J, Sherk H, Bonini J, Rostoker WR, Schajowicz F, Galante JO. Metallosis associated with a stable titanium-alloy femoral component in total hip replacement. *J Bone Joint Surg* 1990;72A:126–30.

173. Elves MW, Wilson JN, Scales JT, Kemp HB. Incidence of metal sensitivity in patients with total joint replacements. *Br Med J* 1975; 4:376–8.

174. Burt CF, Garvin KL, Otterberg ET, Jardon OM. A femoral component inserted without cement in total hip arthroplasty. A study of the Tri-Lock component with an average ten-year duration of follow-up. *J Bone Joint Surg Am* 1998;80:952–60.

175. Deutman R, Mulder TH, Brian R, Nater JP. Metal sensitivity before and after total hip arthroplasty. *J Bone Joint Surg Am* 1977;59-A:862–5.

176. Evans EM, Freeman MA, Miller AJ, Vernon-Roberts B. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg* 1974;56-B:626–42.

177. Mayor MB, Merritt K, Brown SA. Metal allergy and the surgical patient. *Am J Surg* 1980;139:477–9.

178. Munro-Ashman D, Miller AJ. Rejection of metal to metal prosthesis and skin sensitivity to cobalt. *Contact Dermatitis* 1976;2:65.

179. Benson MK, Goodwin PG, Brostoff J. Metal sensitivity in patients with joint replacement arthroplasties. *Br Med J* 1975;4:374–5.

180. Merritt K, Rodrigo JJ. Immune response to synthetic materials. Sensitization of patients receiving orthopaedic implants. *Clin Orthop Rel Res* 1996;326:71–9.

181. Jacobs JJ, Goodman SL. What in vitro, in vivo and combined approaches can be used to investigate the biologic effects of particles? In: Wright TMGoodman SB, editors. Implant wear: The future of total joint replacement. Rosemont, IL: American Academy of Orthopedic Surgeons; 1996. p. 41–4.

182. Tharani R, Dorey FJ, Schmalzried TP. The risk of cancer following total hip or knee arthroplasty. *J Bone Joint Surg Am* 2001;83-A:774–80.

183. Nyren O, Mclaughlin JK, Anders-Ekbom GG, Johnell O, Fraumeni, Adami H. Cancer risk after hip replacement with metal implants: a population-based cohort study in Sweden. *J Natl Cancer Inst* 1995;87:28–33.

184. Matheisen EB, Ahlbom A, Bermann G, Lindgren JU. Total hip replacement and cancer. *J Bone Joint Surg Br* 1995;77-B:345–50.

185. Visuri T, Koskenvuo M. Cancer risk after Mckee-Farrar total hip replacement. *Orthopedics* 1991;14:137–42.

186. Gillespie WJ, Frampton CM, Henderson RJ, Ryan PM. The incidence of cancer following total hip replacement. *J Bone Joint Surg Br* 1988;70:539–42.

187. Caicedo M, Jacobs JJ, Reddy A, Hallab NJ. Analysis of metal ion-induced DNA damage, apoptosis, and necrosis in human (Jurkat) T-cells demonstrates Ni(2+) and V(3+) are more toxic than other metals: Al(3+), Be(2+), Co(2+), Cr(3+), Cu(2+), Fe(3+), Mo(5+), Nb(5+), Zr(2+). *J Biomed Mater Res A* 2007;15;86:905–13.

188. Edwards DL, Wataha JC, Hanks CT. Uptake and reversibility of uptake of nickel by human macrophages. *J Oral Rehabil* 1998;25:2–7.

189. Wang JY, Wicklund BH, Gustilo RB, Tsukayama DT. Prosthetic metals interfere with the functions of human osteoblast cells in vitro. *Clin Orthop* 1997;339:216–26.

190. Sun ZL, Wataha JC, Hanks CT. Effects of metal ions on osteoblast-like cell metabolism and differentiation. *J Biomed Mater Res* 1997; 34:29–37.

191. Thompson GJ, Puleo DA. Ti-6Al-4V ion solution inhibition of osteogenic cell phenotype as a function of differentiation timecourse in vitro. *Biomater* 1996;17:1949–54.

192. Thompson GJ, Puleo DA. Effects of sublethal metal ion concentrations on osteogenic cells derived from bone marrow stromal cells. *J Appl Biomater* 1995;6:249–58.

193. Cunningham BW. Basic scientific considerations in total disc arthroplasty. *Spine J* 2004;4(6 Suppl):219S–30S.

194. Howie DW, Vernon-Roberts B, Oakeshott R, Manthey B. A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles. *J Bone Joint Surg Am* 1988;70:257–63.

195. Iwase M, Kim KJ, Kobayashi Y, Itoh M, Itoh T. A novel bisphosphonate inhibits inflammatory bone resorption in a rat osteolysis model with continuous infusion of polyethylene particles. *J Orthop Res* 2002;20:499–505.

196. Warashina H, Sakano S, Kitamura S, Yamauchi KI, Yamaguchi J, Ishiguro N, et al. Biological reaction to alumina, zirconia, titanium and polyethylene particles implanted onto murine calvaria. *Biomater* 2003;24:3655–61.

197. von Knoch M, Jewison DE, Sibonga JD, Sprecher C, Morrey BF, Loer F, et al. The effectiveness of polyethylene versus titanium particles in inducing osteolysis in vivo. *J Orthop Res* 2004;22:237–43.

198. Yokohama Y, Matsumoto T, Hirakawa M, Kuroki Y, Fujimoto N, Imai K, et al. Production of matrix metalloproteinases at the bone-implant interface in loose total hip replacements. *Lab Invest* 1995; 73:899–911.

199. Horowitz SM, Algan SA, Purdon MA. Pharmacologic inhibition of particulate-induced bone resorption. *J Biomed Mater Res* 1996;31: 91–6.

200. Garcia C, Boyce BF, Gilles J, Dallas M, Qiao M, Mundy GR, et al. Leukotriene B4 stimulates osteoclastic bone resorption both in vitro and in vivo. *J Bone Miner Res* 1996;11:1619–27.

201. Liao H, Wurtz T, Li J. Influence of titanium ion on mineral formation and properties of osteoid nodules in rat calvaria cultures. *J Biomed Mater Res* 1999;47:220–7.

202. Schwarz EM, Benz EB, Lu AP, Goater JJ, Mollano AV, Rosier RN, et al. Quantitative small-animal surrogate to evaluate drug efficacy in preventing wear debris-induced osteolysis. *J Orthop Res* 2000;18: 849–55.

203. Wang KY, Horne JG, Devane PA, Miller JH. Polyethylene particles from a hip simulator cause (45)Ca release from cultured bone. *J Orthop Surg (Hong Kong)* 2001;9:23–30.

204. von Knoch M, Jewison DE, Sibonga JD, Turner RT, Morrey BF, Loer F, et al. Decrease in particle-induced osteolysis in obese (ob/ob) mice. *Biomater* 2004;25:4675–81.

205. Ingram JH, Kowalski R, Fisher J, Ingham E. The osteolytic response of macrophages to challenge with particles of simplex P, endurance, palacos R, and vertebroplastic bone cement particles in vitro. *J Biomed Mater Res B Appl Biomater* 2005;75:210–20.

206. Ren WP, Markel DC, Zhang R, Peng X, Wu B, Monica H, et al. Association between UHMWPE particle-induced inflammatory osteoclastogenesis and expression of RANKL, VEGF, and Flt-1 in vivo. *Biomater* 2006;27:5161–9.

207. Clohisy JC, Yamanaka Y, Faccio R, Abu-Amer Y. Inhibition of IKK activation, through sequestering NEMO, blocks PMMA-induced osteoclastogenesis and calvarial inflammatory osteolysis. *J Orthop Res* 2006;24:1358–65.

208. Pioletti DP, Takei H, Kwon SY, Wood D, Sung KL. The cytotoxic effect of titanium particles phagocytosed by osteoblasts. *J Biomed Mater Res* 1999;46:399–407.