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Resources from the Societies

- Patient Information at OrthoInfo.org
- Technology Overview
- Participation in ASTM and ISO
- Member education

- ORS.org – Clinical Research symposia and forums
- Patient Information
- Educational programs

Presenting on behalf of AAOS, AAHKS, ORS and the Hip Society

Paul Manner, MD – Opening remarks, history of metal on metal with current clinical outcomes, results of the AAOS Technology Overview

Markus Wimmer, PhD – preclinical testing, implant retrieval analysis, and tribology/tribocorrosion

Young-Min Kwon, MD, PhD – local and systemic effects, management strategies, and algorithm

The safety of every orthopaedic patient is always our number one concern. We welcome the publication of updated evidence and we will continue to work with the FDA to provide further advice as new information and evidence becomes available.

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FDA Orthopaedic Rehabilitation Devices Panel
Medical Devices Advisory Committee Meeting
Wednesday June 27th 2012

MODERN METAL-ON-METAL HIP IMPLANTS: A CLINICIAN'S PERSPECTIVE AND A TECHNOLOGY OVERVIEW

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Disclosure

- No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this testimony.

Clinician's Dilemma

"Objectives must be reasonable. Neither surgeon nor engineers can ever make an artificial hip-joint that will last thirty years and at some time in this period enable the patient to play football."

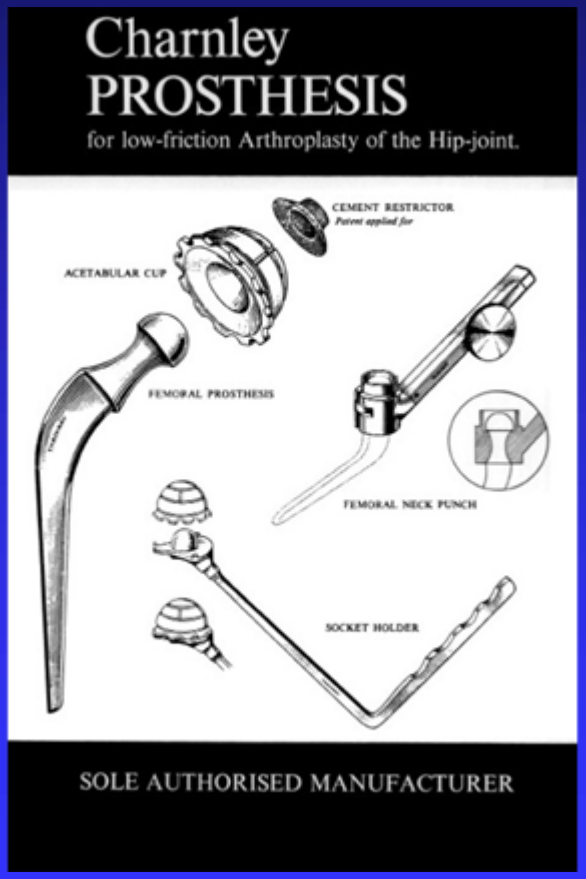
- John Charnley

Clinical Goals for a Total Joint

Primary goal
- Relieve pain
- Restore function

Secondary goals
- Simple
- Be good to soft tissue
- Manufacturability
- Safety
- Durability
- Fixable
- Cheap

Defining the current standard and clinical expectation



- What did we expect in the 1960s?
  - Initially restricted to patients >65 yo
  - Severe RA or OA
  - Occasional middle-aged patient with bilateral disease

What do we expect now?

AAHKS members allow:

Walking/hiking	98%
Biking	80%
Skiing	21%
	56% with experience
Martial arts	9%
Running	6%
Contact sports	2%

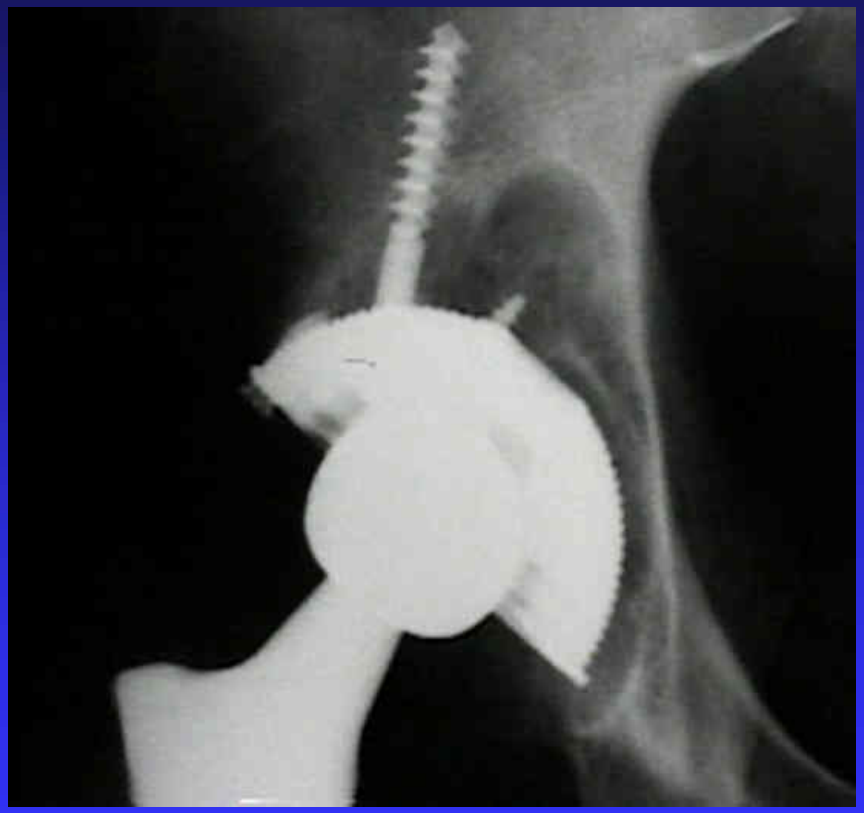
Klein et al, J Arthroplasty 2007

What do patients expect?

"I want to do what I was doing before my hip hurt!"

But reality intrudes….

"…the principal culprit of long-term implant failures has been identified as the ultra high molecular weight polyethylene (UHMWPE) wear debris generated at the articulating surface of the polymer component"



AAOS Monograph 2001

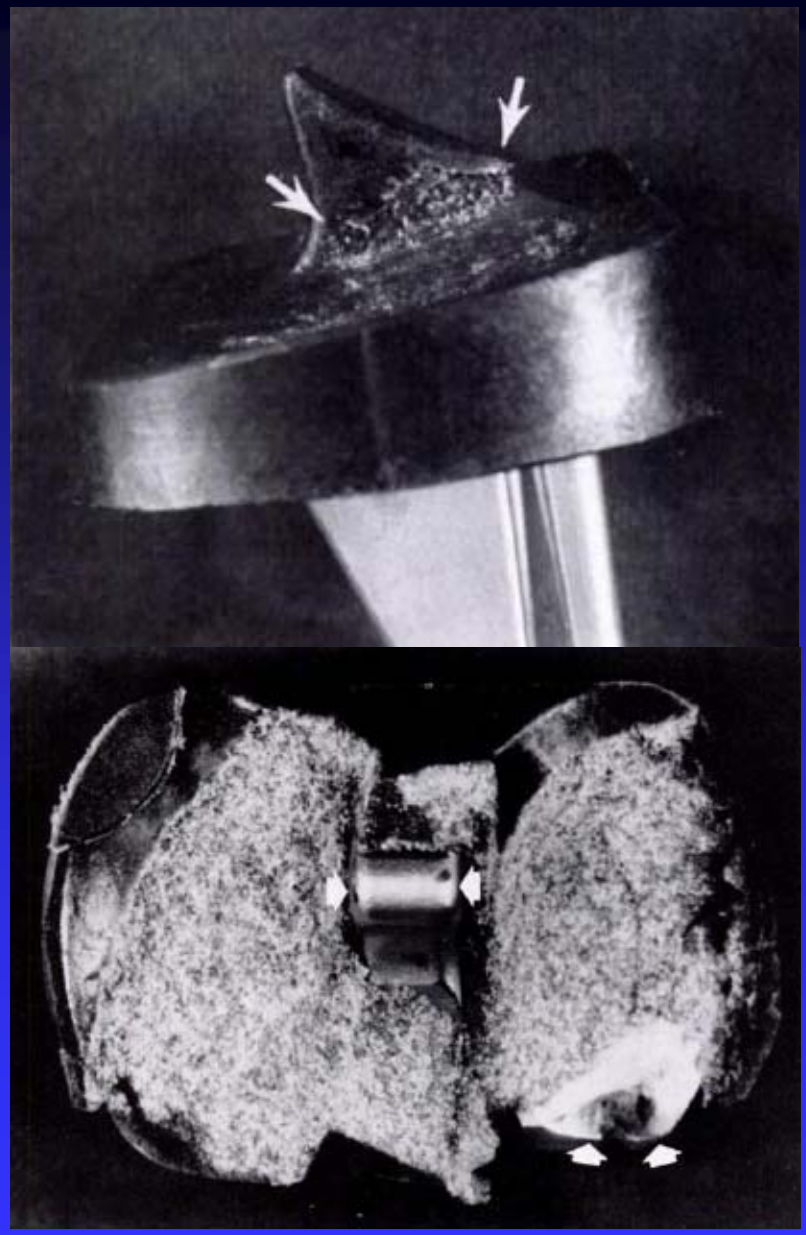
Two main approaches to wear reduction

- Decrease opportunities for wear
  - Increase contact area with more conforming surfaces by prosthesis design (macro)
  - Avoid technical errors/malalignment (macro)
  - Increase contact area by tighter tolerances in manufacture (micro)
  - Amelioration/elimination of backside wear (nano)
- Create better bearing surface
  - Change polyethylene
  - Eliminate polyethylene

Poly-II

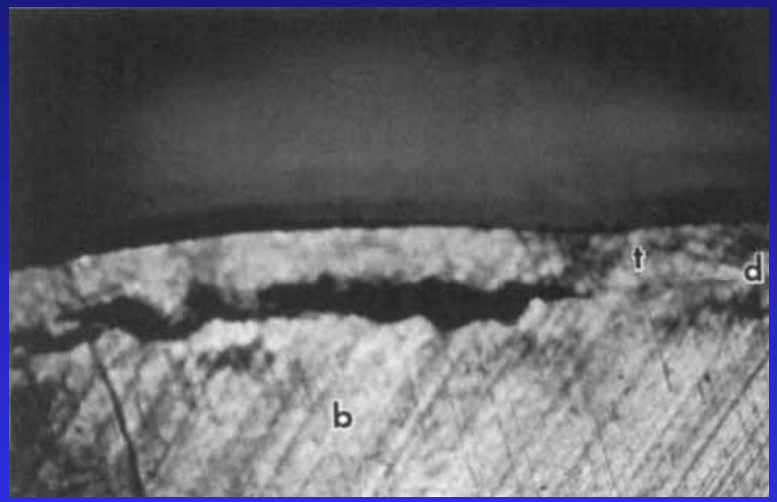
- Withdrawn from market, after reports of catastrophic failure, 7 years after introduction

Wright et al JBJS 1988



Heat-pressed Polyethylene

- High incidence of delamination
- Surface layer separated from insert by clear line of demarcation 250-580 µm below surface
- 17/33 retrieval specimens showed delamination at 4 years

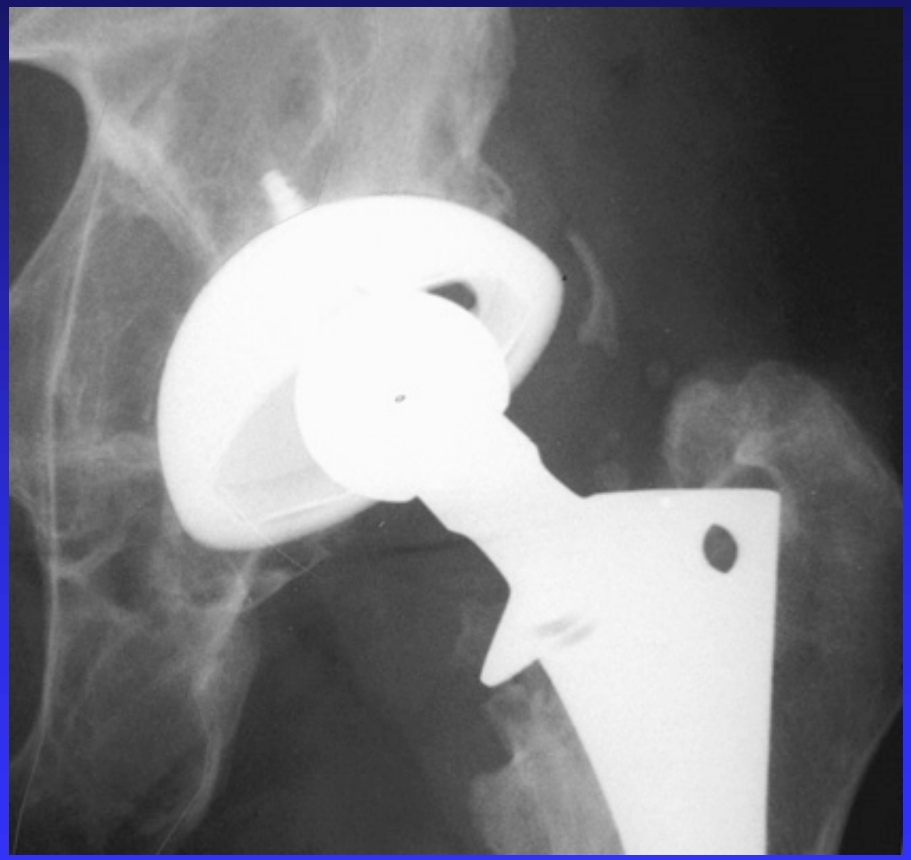


Bloebaum et al Clin Orthop 1991

Hylamer at 10 years

- "…number of pelvic osteolytic lesions and their size detected on plain radiographs were significantly greater for Hylamer liners"

Huddleston et al 2010



Patients are different….

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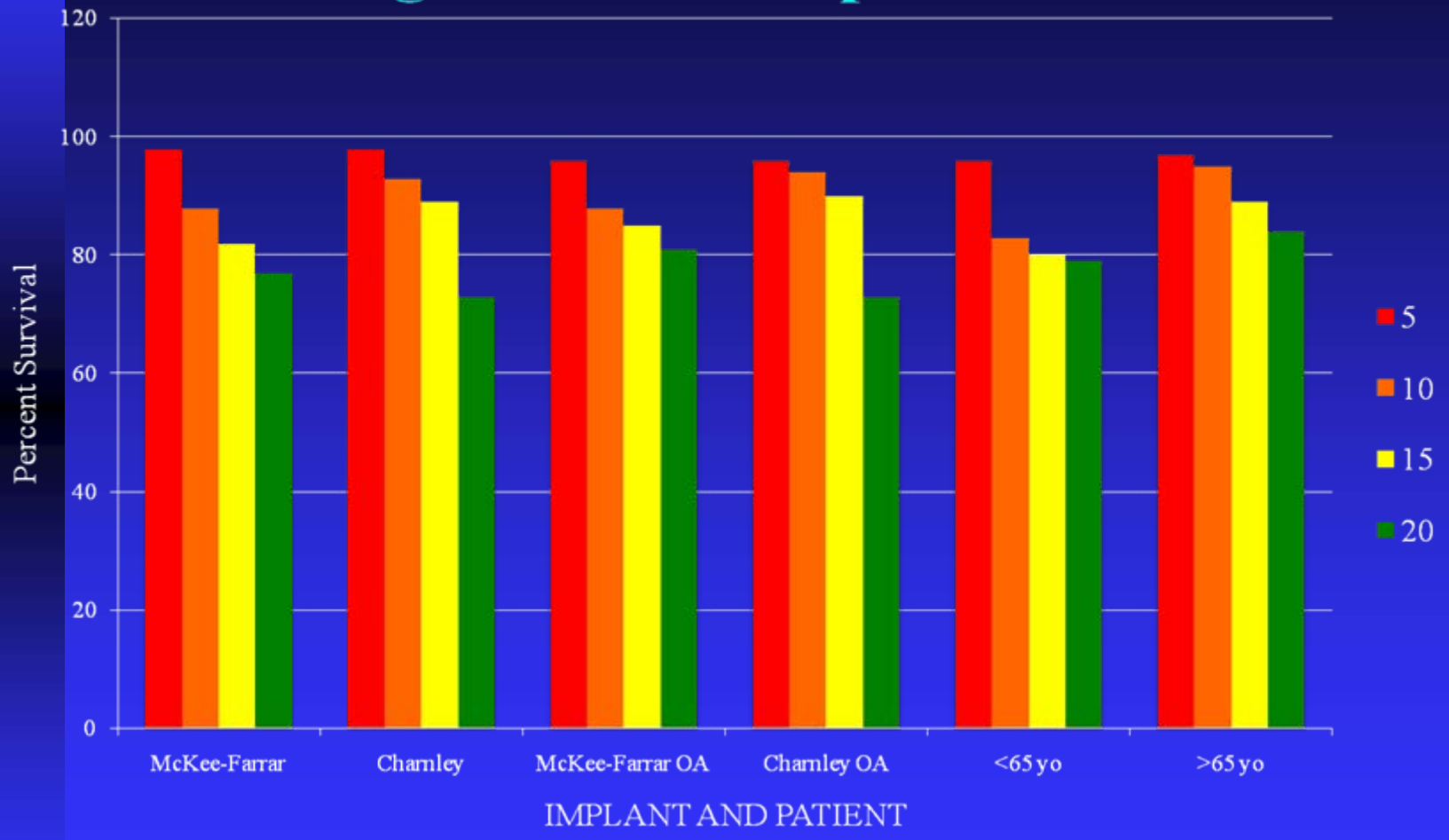
McKee-Farrar

- Poor stem geometry
  - Sharp angles
  - Not enough offset
- Crude manufacture
- Crude technique
- 28-year implant survivorship of 74%


Retrieved prosthesis after being implanted for 38 years

Brown et al 2002

Long-term results with first generation implants



Jacobsson et al 1996

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Conclusions in 2000

- Not all patients are the same
- Not all plastic bearings are created equal
- What are clinician's options?
- Hard-on-hard bearing looks attractive…

Background to Technology Review

- MoM marketed in US prior to 1976
- DePuy ASR approved in US in 2005
- Zimmer Durom, Smith and Nephew BHR approved in 2006
- Durom, ASR soon withdrawn

Background to Technology Review

- Feb 2011: FDA issues public communication about metal-on-metal
- May 2011: FDA orders manufacturers to conduct post-market surveillance
- June 2011: AAOS creates Technology Overview group

AAOS Technology Review

- Clinicians and researchers
- Relevant questions chosen
- Prepared using systematic review methodology
- Summarizes findings of studies published as of July 15, 2011 on modern metal-on-metal hip implants

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- **Question #1: What are the clinical outcomes in patients with metal-on-metal hip replacements in comparison with other bearing surface combinations?**

- **Question #2: What are the patient, implant, and surgical factors that best predict successful/unsuccessful outcomes of metal-on-metal hip replacement?**

- **Question #3: What is the prevalence of adverse clinical problems from metal-on-metal hip replacement compared to other bearing surface combinations?**

Outcomes considered

- Patient focused: Harris Hip Score, WOMAC, etc
- Revision rates
- Serum ion as potential surrogate marker
- Imaging

Systematic review

- Frame key question(s)
- Rules for inclusion
- Comprehensive literature review
- Evaluation of quality of studies

Systematic review rules

- Criteria established prior to literature search
- Highest possible levels of evidence
- Published, peer-reviewed only
- Contemporary implants only

Literature quality

- Searches identified 3038 hip replacement citations and data from 8 joint registries that were potentially relevant
- 19 articles and 2 joint registry reports met inclusion criteria

1: Clinical outcomes

- Registry data (UK-Wales, Australia)
- Metal-on-metal HRA and THA have higher risk of revision
- No clinical superiority for any particular bearing surface
- Not clear if particular patients benefit

2: Predictive factors

- Larger femoral head components in MoM THA have higher revision rates
- Increased age associated with increased revision risks MoM THA
- HRA patients in all age groups, except males <55 years of age, at increased revision risk

2. Predictive factors

- Head size and risk of revision for HRA inversely related (opposite of THA)
- Analysis difficult
- Conclusions should be made cautiously

3. Prevalence in MoM versus others

- Limited data exists comparing prevalence of adverse clinical problems with MoM versus other bearing surfaces
- High sensitivity to component position
- Clinical significance of elevated serum metal ion concentrations remains unknown

Serum metal ions

- All MoM hip implants wear and cause metal ion release
- Believed to cause soft tissue reactions in periprosthetic space
- Data comparing metal-on-metal THA/HRA to other bearing surfaces are sparse and drawing conclusions is difficult

Registry data valuable, but…

- Pro
  - Large patient numbers
  - Quick identification of problematic implants
- Con
  - "Lumping" versus "splitting"
  - Complexity of needed data makes collection/compliance difficult

Increasing number of positive reports

- Reports of small diameter MOM bearings with survival rates of ≥ 95% at 10 years
  - Grübl et al. JOR 2007 25(7):841-8.
  - Delaunay et al. 2008 CORR 466(2):340-6
  - Girard et al. 2010 JBJS-A 92(14):2419-26
  - Hwang et al. 2011 JOA 26(8):1481-7
  - Nikolaou et al. 2011 Bull NYU Hosp 69:S77-83
  - Migaud et al. 2011 JBJS-A 93(Suppl 2):137-42
  - Randelli et al. 2012 JOA 27(2):186-92

MoM vs CoP in patients < 50 yrs

- Comparison between:
  - 39 MoM hips w. ø28 mm head
    AlloClassic system; patients <50 yrs
  - 39 ZrO2 - UHMWPE hips
    ABG stem / Harris-Galante cup; patients <50 yrs
- Matched group for age, diagnosis, activity and pre-operative Harris hip score

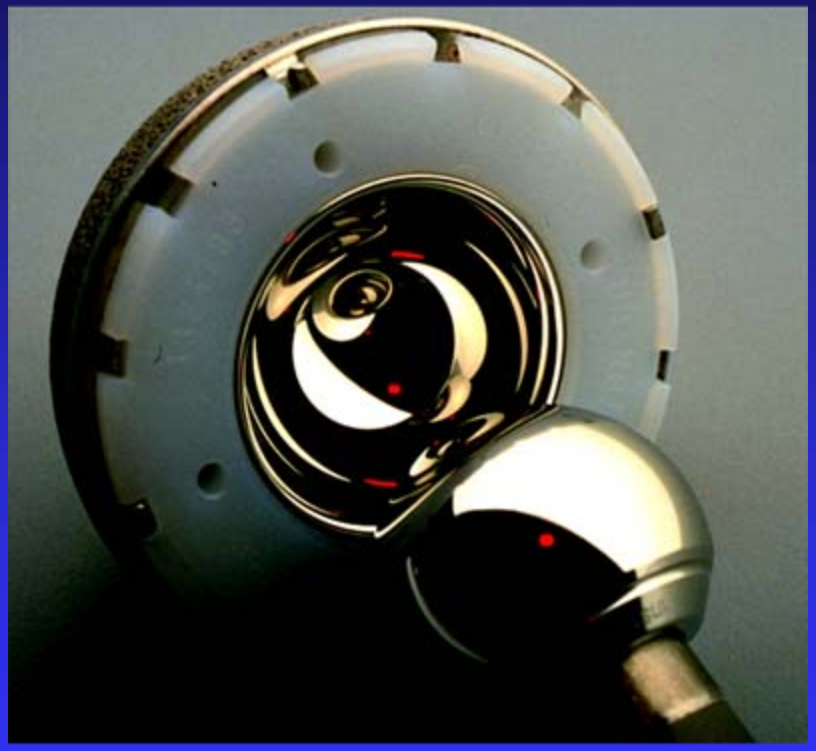
H. Migaud et al, JBJS, 93A, Suppl 2, 2011, p. 137

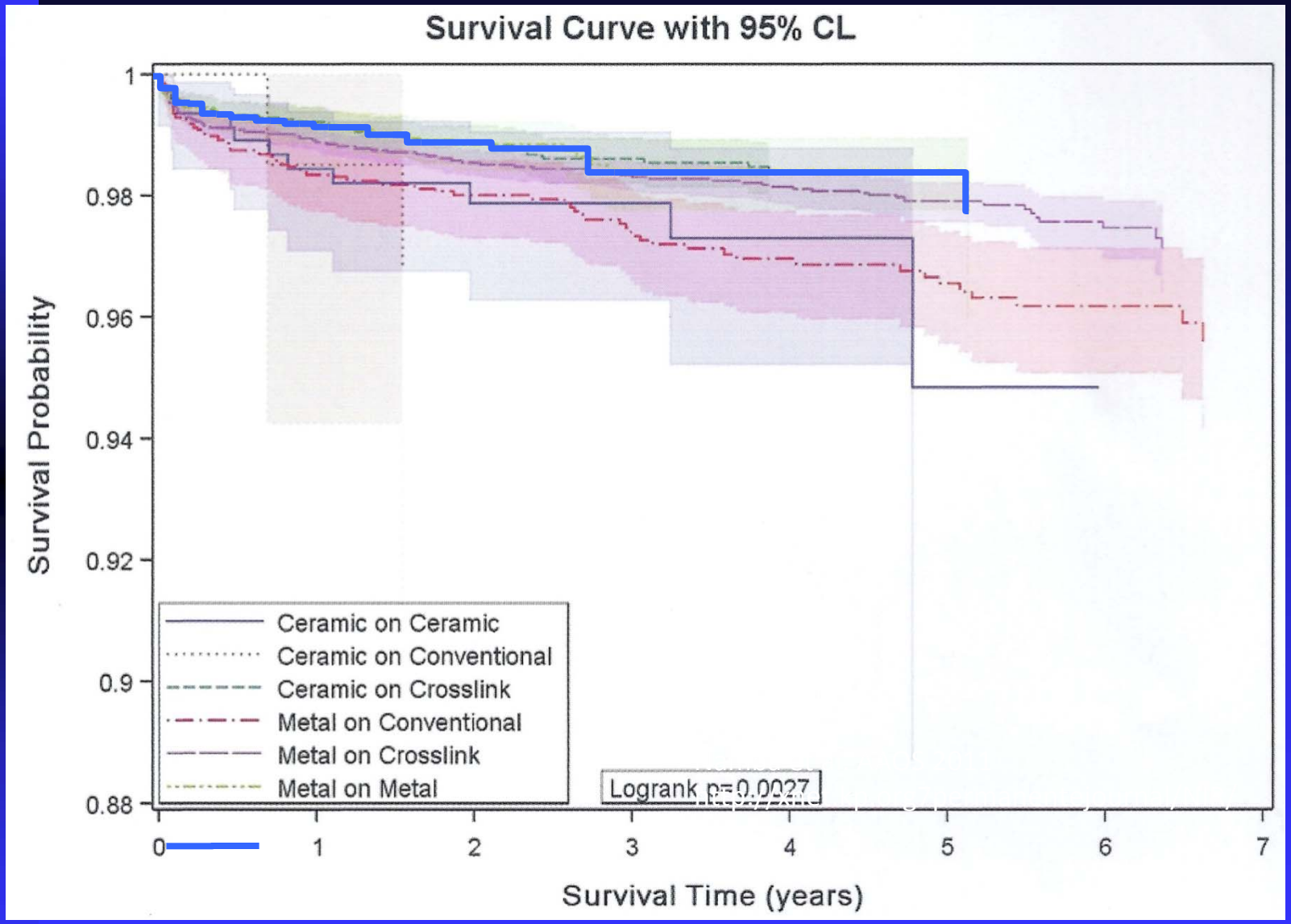
MoM vs CoP in patients < 50 yrs

	MoM small head	ZrO_2 - UHMWPE
Min follow-up	144 months	110 months
Harris hip score	92.8	91.2
Osteolysis	1 (3%)	18 (46%)
Revision	0 (0%)	13 (33%)
Survival rate	100%	70%

H. Migaud et al, JBJS, 93A, Suppl 2, 2011, p. 137

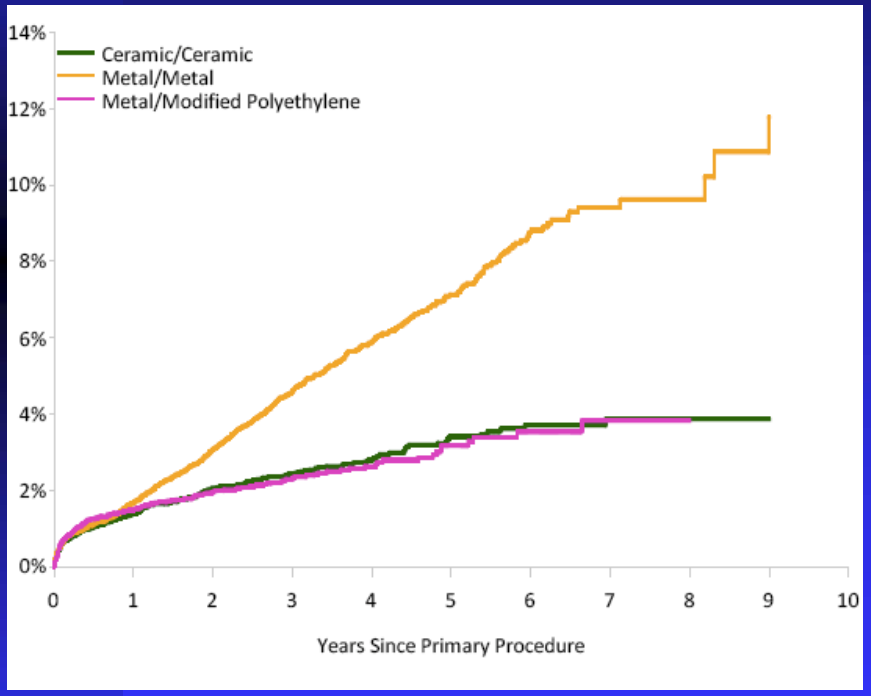
Are these the same?

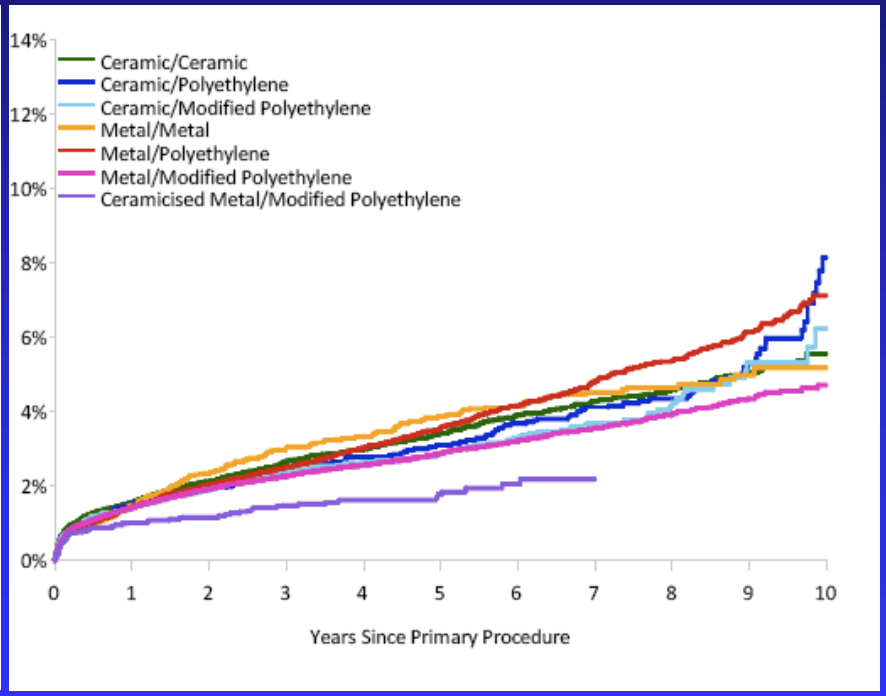




2011 Australian Registry

- >32mm heads
- ≤32mm heads





2012 AAHKS Survey

- 1363 active members
- 598 responses (44%)

BEARING OF CHOICE FOR MAJORITY OF PATIENTS

Metal-on-poly	84.5%
Ceramic-on-poly	14.1%
Metal-on-metal	1.4%

2012 AAHKS Survey

- 1363 active members
- 598 responses (44%)

USE OF METAL-METAL BEARINGS (CHANGE 2009-2012)

Discontinued / never used	69.2%
Decreased	23.9%
Unchanged	4.6%

Conclusions in 2012

- As with polyethylene, some implants may be heroes, and some may be goats
- Adverse local tissue reaction (ALTR) is response in a given patient to a given material used in a given design
- Blanket approval/condemnation not an adequate answer

Conclusions in 2012

- Can't determine whether one particular type of patient fares better than others
- Need to account for effects of all patient and device characteristics of interest
- Analyze interactions between relevant variables
- To date, such analyses have not been conducted

Thank you

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TRIBOLOGY AND PRE-CLINICAL TESTING IN MOM HIP JOINTS

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American Association of Orthopaedic Surgeons

Disclosure

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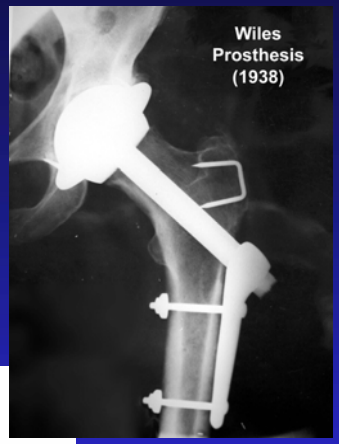
- Unpaid consultant for Endolab in Germany.

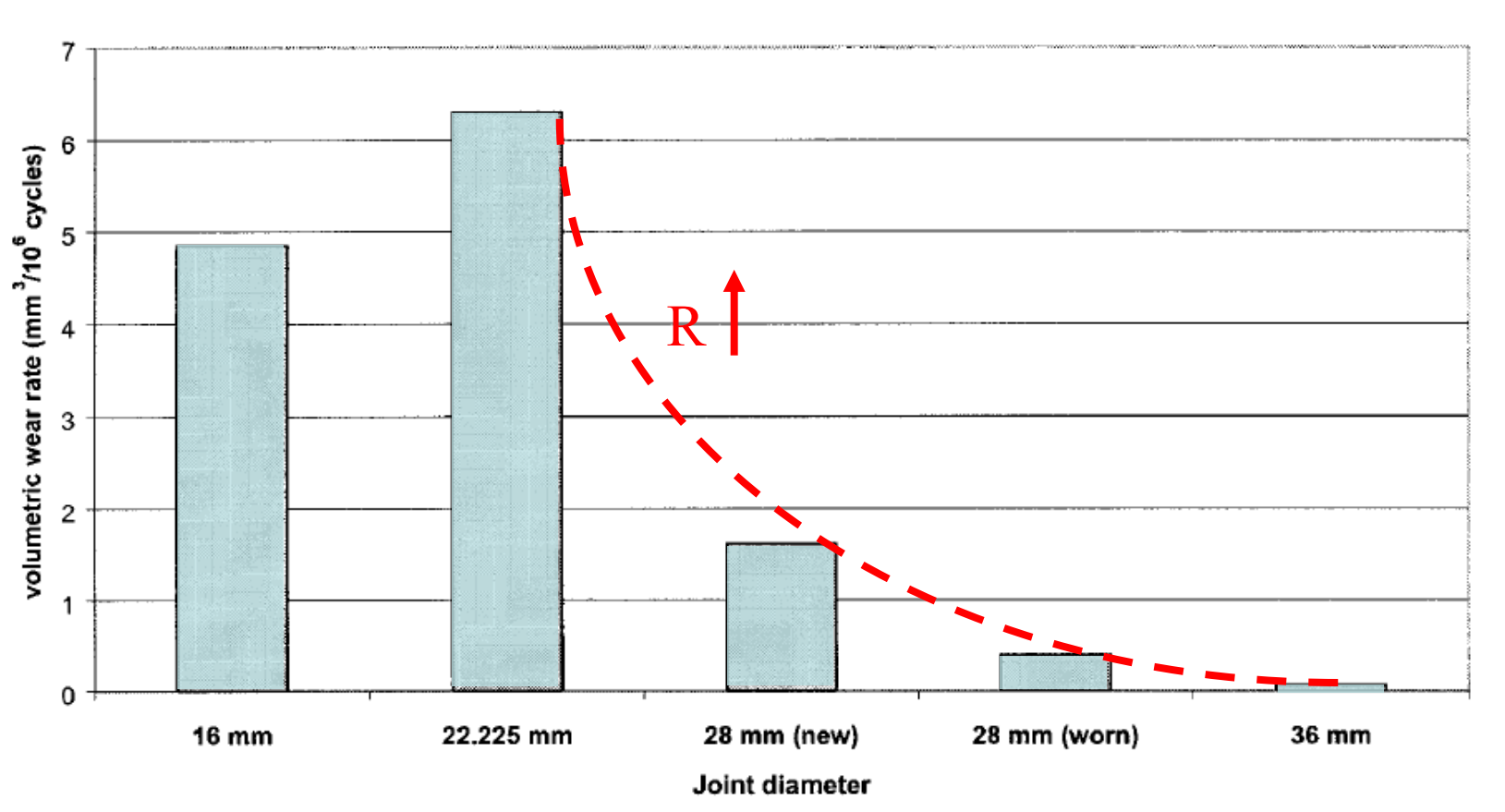
History of Metal-on-Metal

- 1930's: Wiles tries 304L steel for hip prosthesis MGH dentists use Co-base alloys w. success
- 1950's Co-base alloys introduced to THR
- 1960's: McKee-Farrar choose CoCrMo alloy based on Stanmore hip
- 1980's: New generation of MoM bearings with 28 mm head size (which function well till today)
- Late 1990's: McMinn popularizes hip resurfacing
- 2000's: Large head sizes (>36 mm) for THR to (1) avoid dislocation and (2) improve tribology



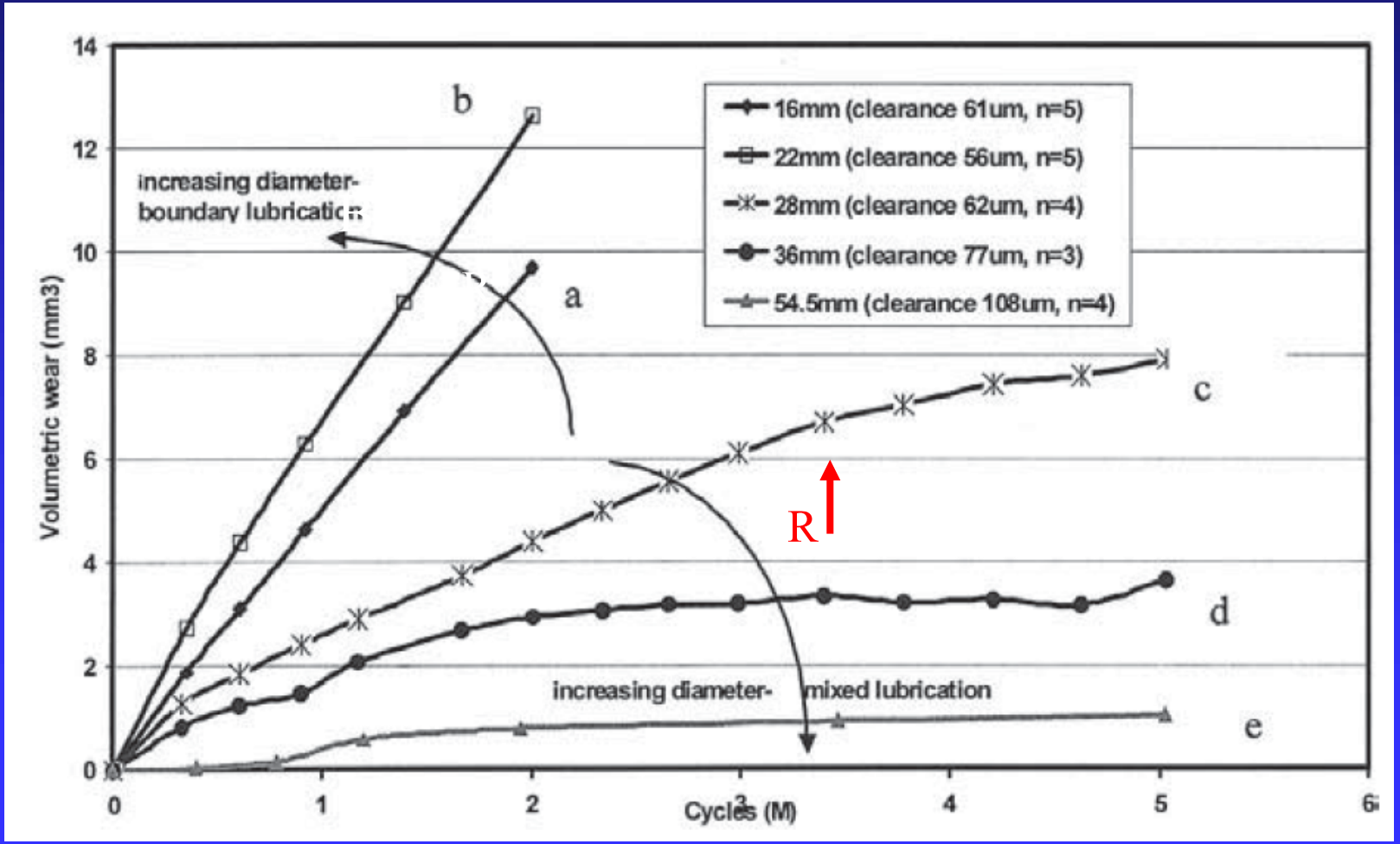
Influence of Head Radii on Wear

Smith, Dowson et al. Proc Instn Mech Engrs Vol 215 Part H, 2001

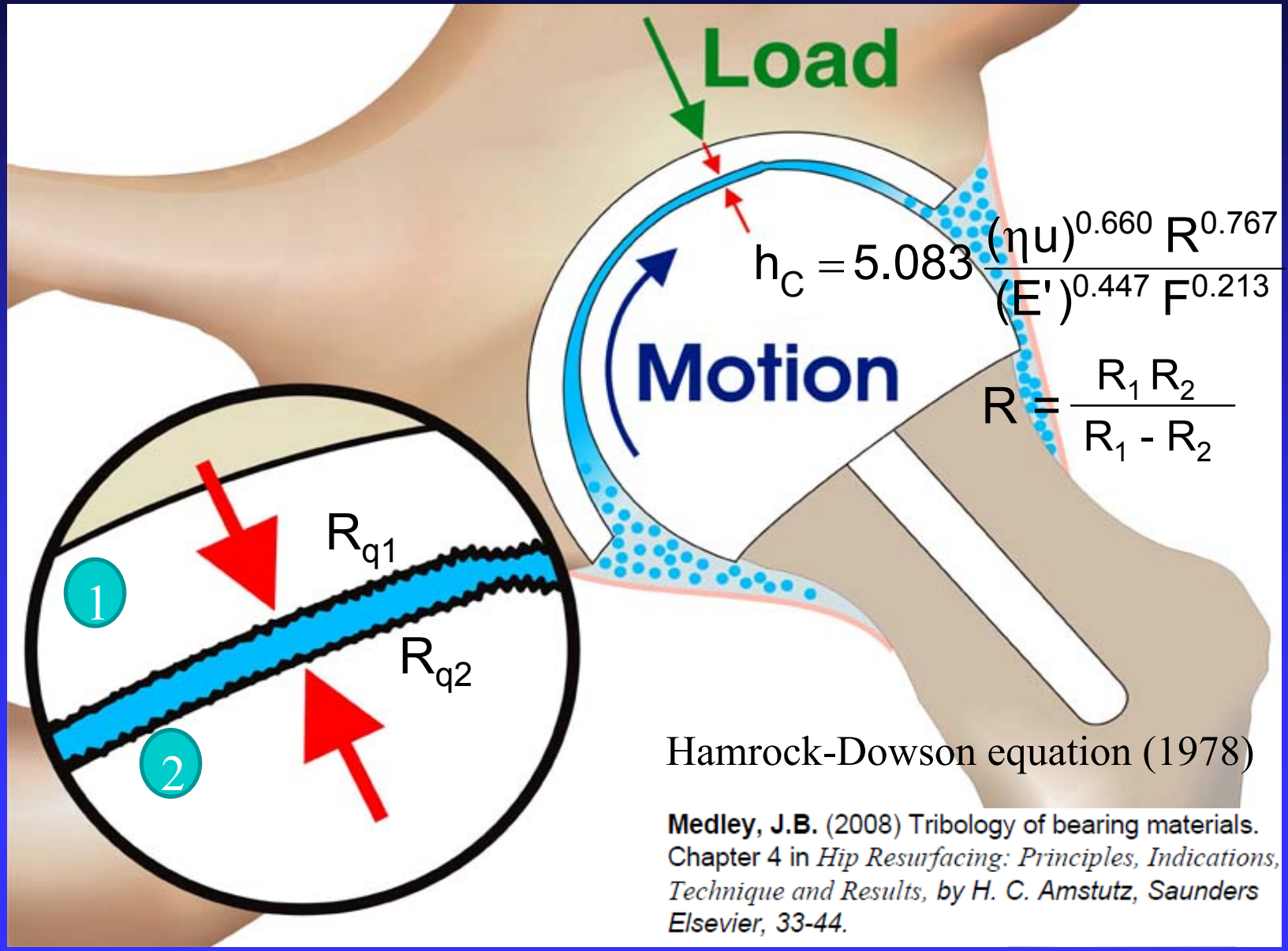


Influence of Head Radii on Wear

Dowson et al. J Arthrop 19(8), Suppl.3:124-130, 2004



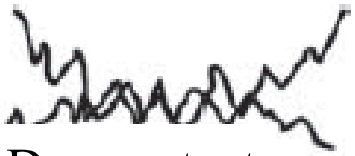
Lubrication Theory



Hamrock-Dowson equation (1978)

Medley, J.B. (2008) Tribology of bearing materials. Chapter 4 in *Hip Resurfacing: Principles, Indications, Technique and Results*, by H. C. Amstutz, Saunders Elsevier, 33-44.

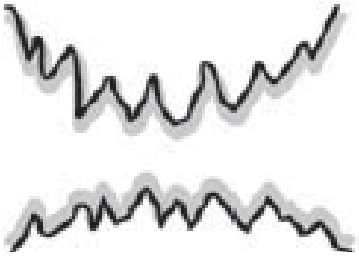
Lubrication Theory



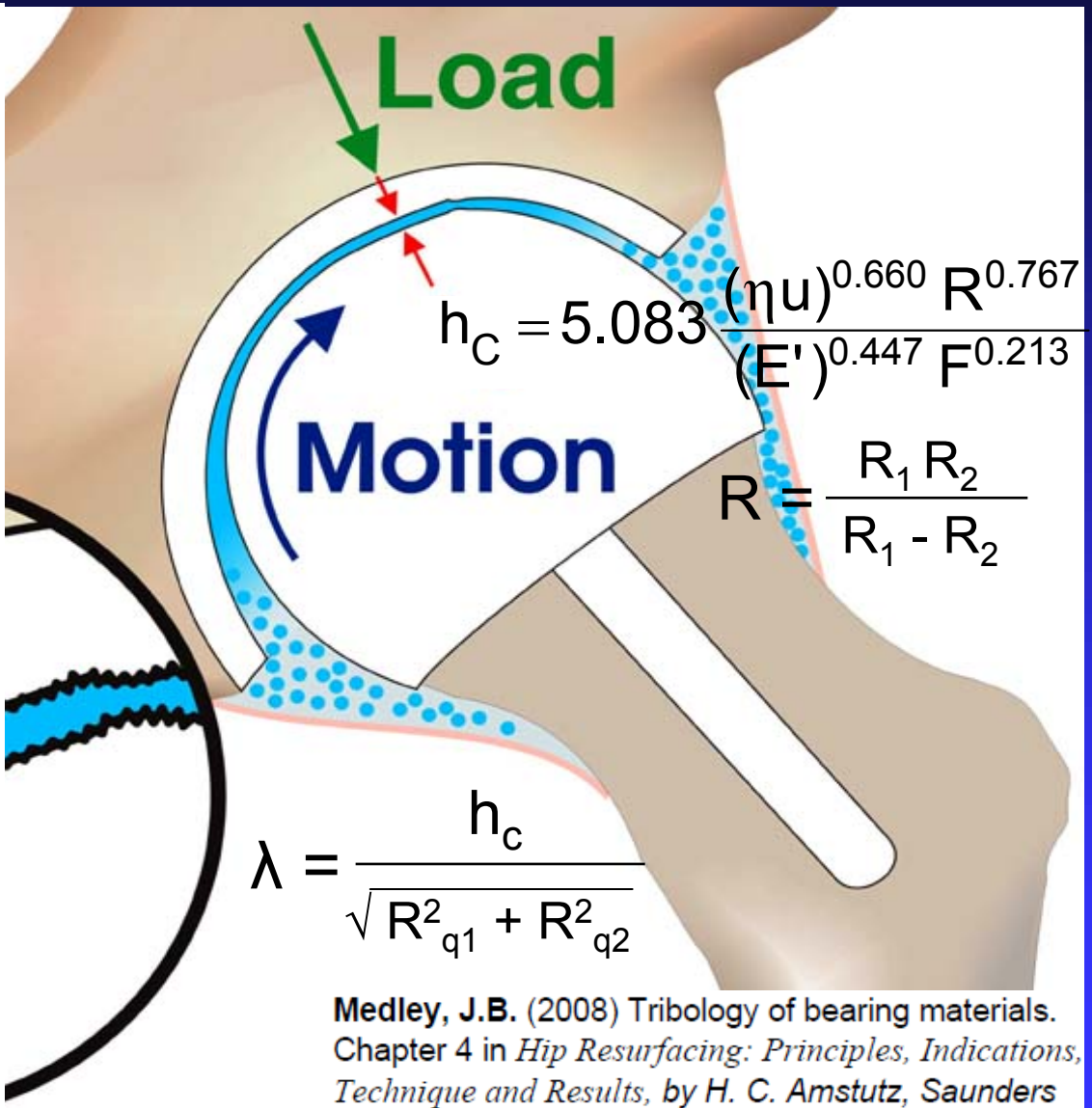
Dry contact

Boundary Lubrication

Mixed lubrication



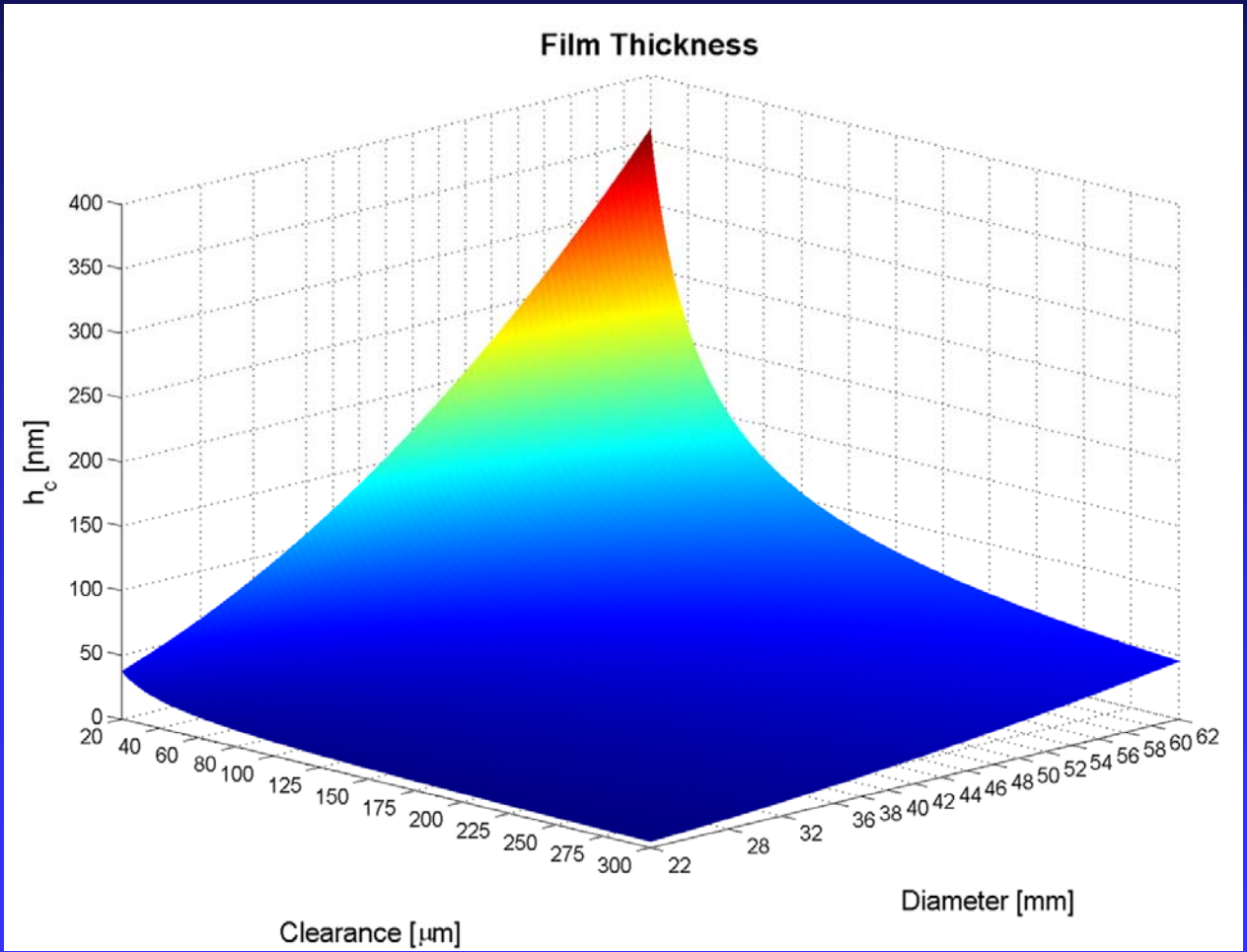
Fluid film lubrication



Medley, J.B. (2008) Tribology of bearing materials. Chapter 4 in *Hip Resurfacing: Principles, Indications, Technique and Results,* by H. C. Amstutz, Saunders Elsevier, 33-44.

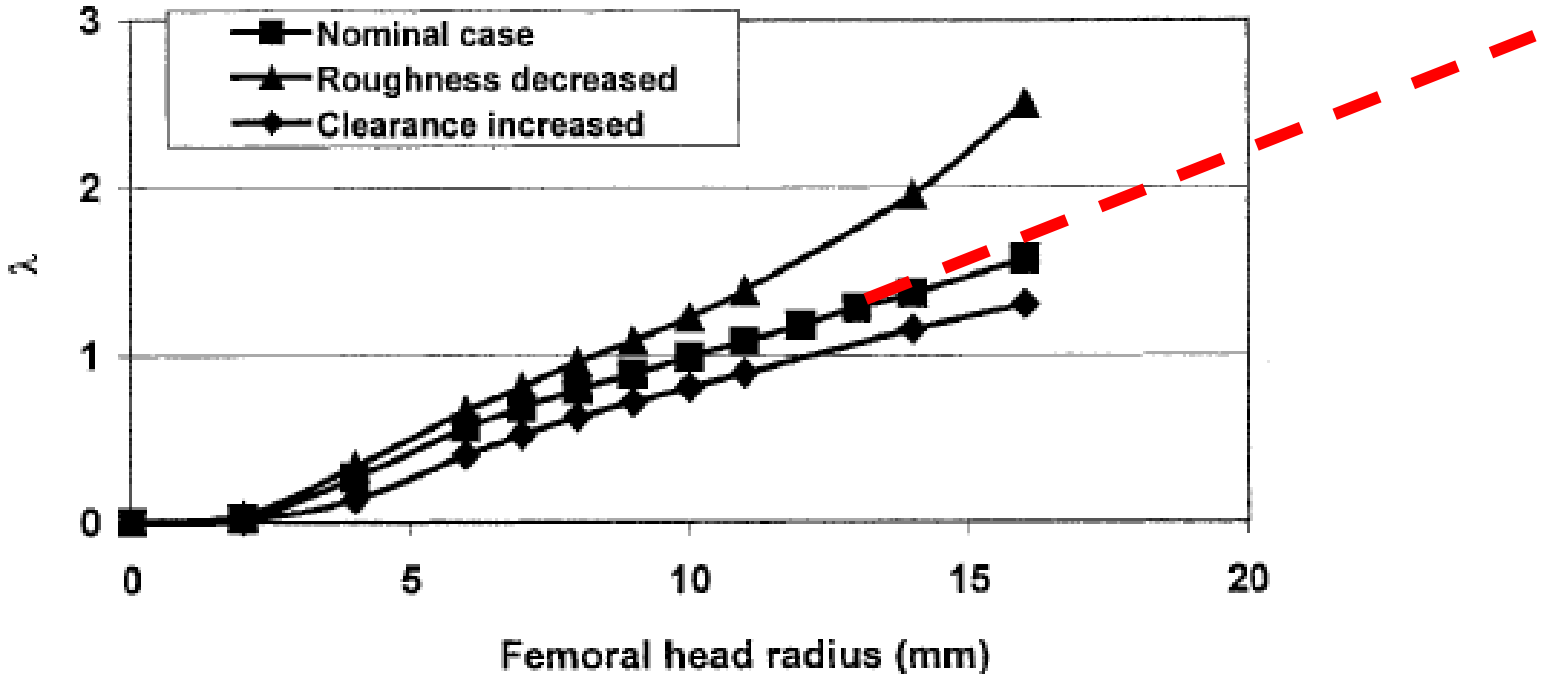
Film thickness (Hamrock-Dowson)

- Input: Load F=3.000 N; fluid viscosity η= 0.005 Pa·s



Influence of Radius on Fluid Film

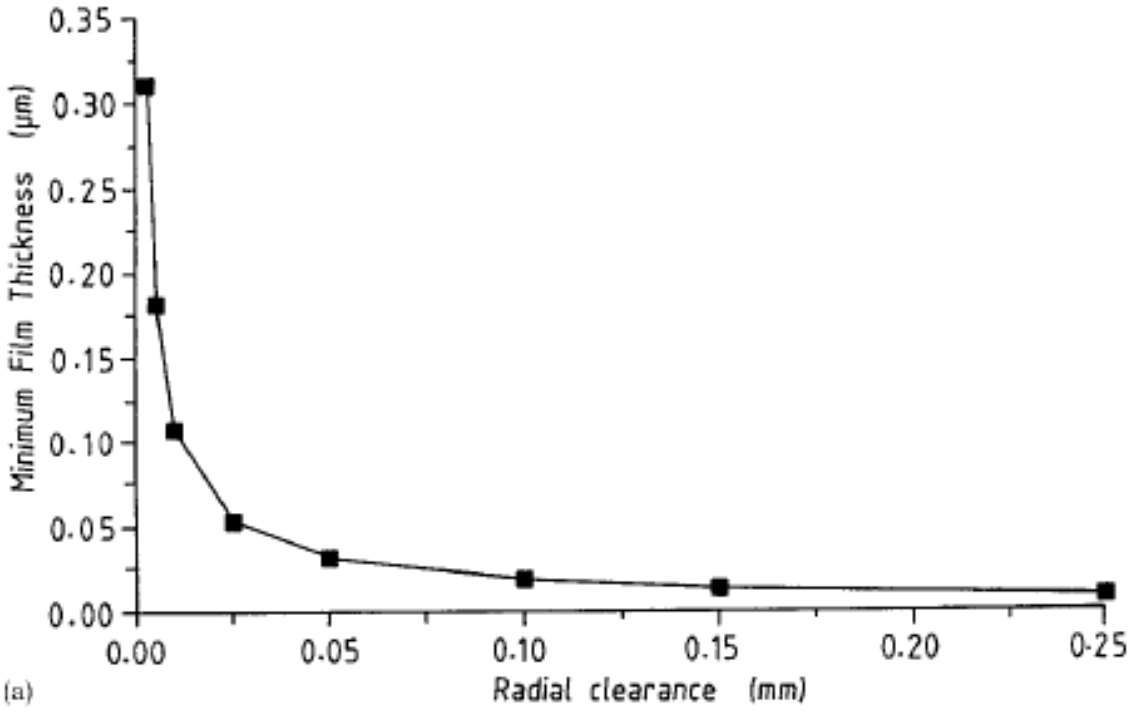
- Jin et al. Analysis of mixed lubrication mechanism in metal-on-metal THR. Proc Inst Mech Eng H. 21685, 2002



Prediction of the λ ratio as a function of the femoral head radius for the nominal conditions (Table 1), a decrease in the surface roughness to 0.01 μm and an increase in the radial clearance to 80 μm

Influence of Clearance on Fluid Film

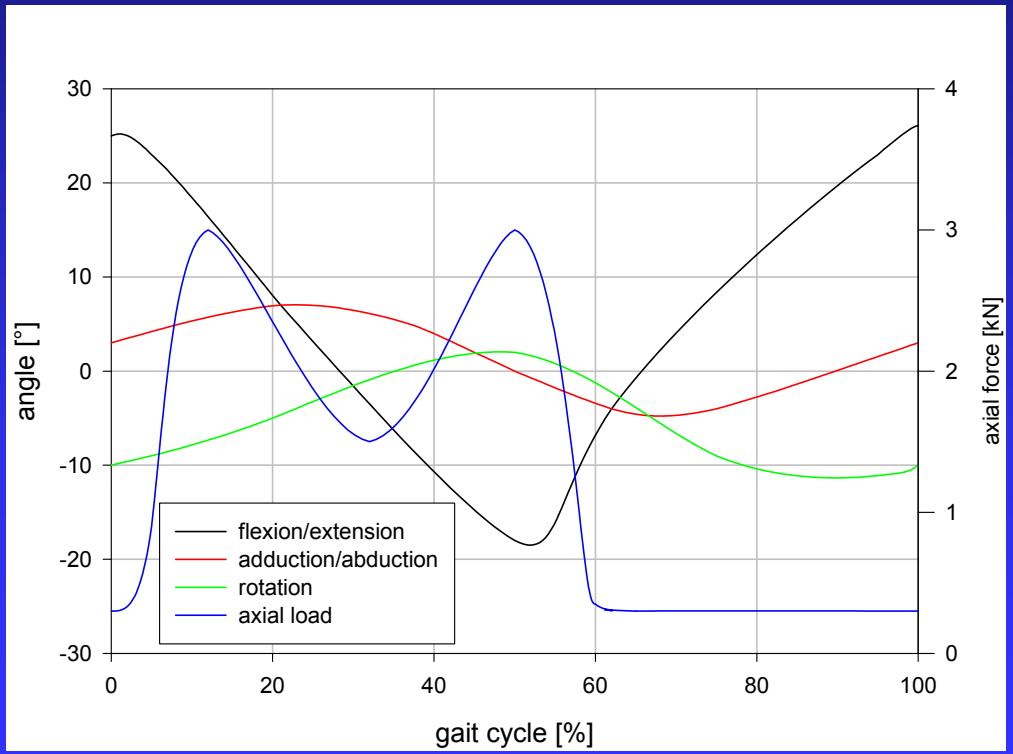
- Jin et al. Analysis of mixed lubrication mechanism in metal-on-metal THR. Proc Inst Mech Eng H. 21685, 2002



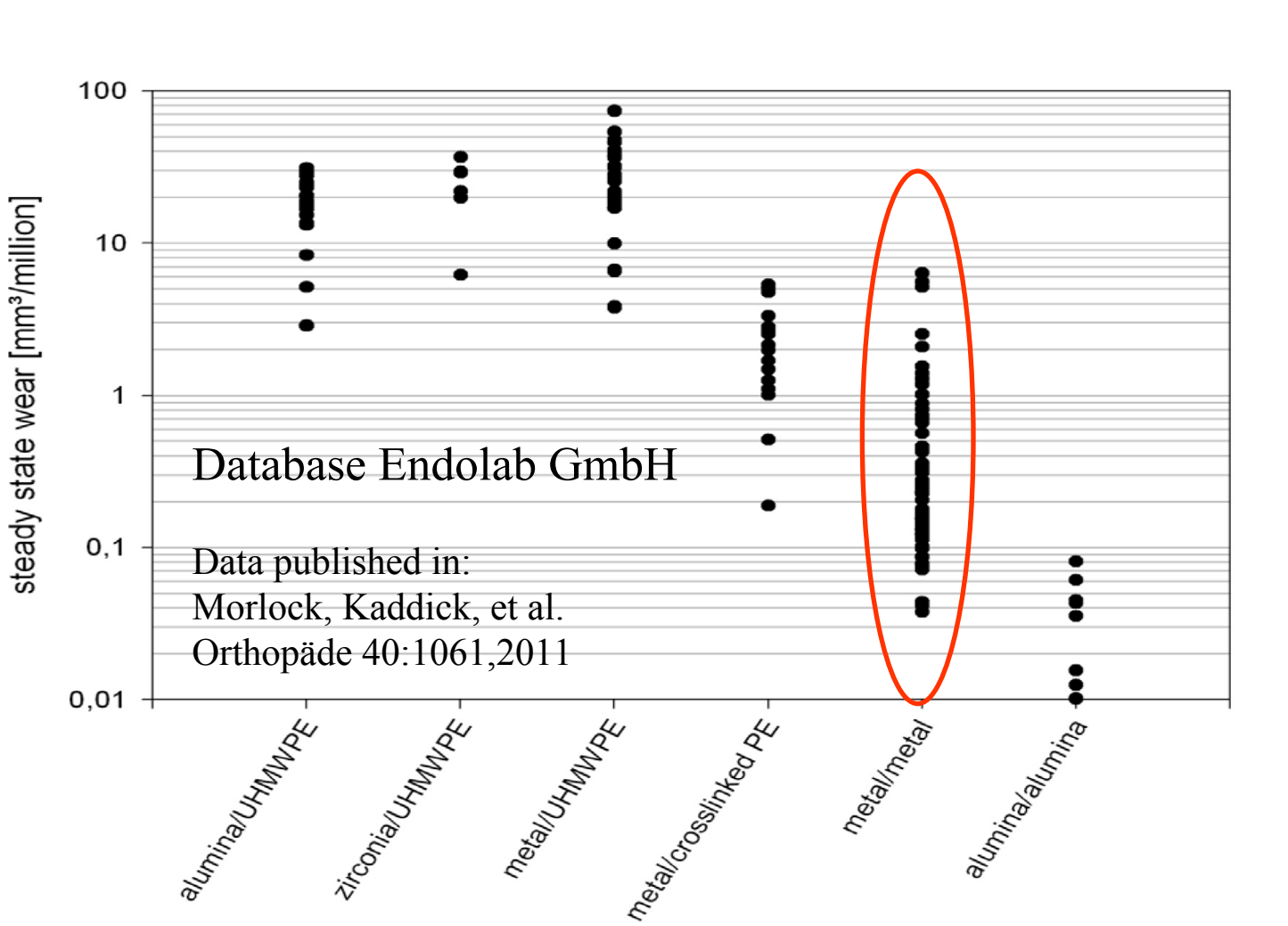
Prediction of minimum film thickness for metal-on-metal hip joint replacements for different radial clearances ($w = 2.5$ kN, $R_1 = 14$ mm, $E_1 = 230$ GPa, $E_2 = 230$ GPa, $\nu_1 = 0.3$, $\nu_2 = 0.3$, $u = 0.015$ m/s, $\eta = 0.005$ Pa s)

Current wear testing procedures

- Input defined in ISO 14242-1 and ISO 14242-3
  - 5 million cycles at ~1Hz
  - Lubricant: bovine serum (30g/L protein)



ISO Hip Simulator Wear Rates



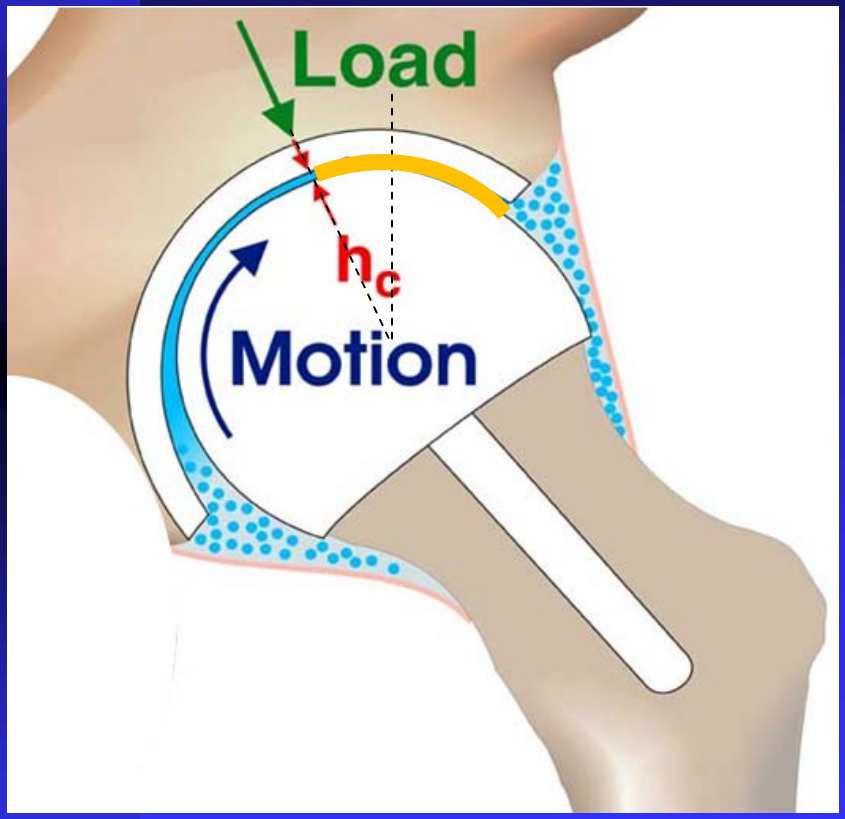
Over 100-fold (!) difference in wear of MoM bearings

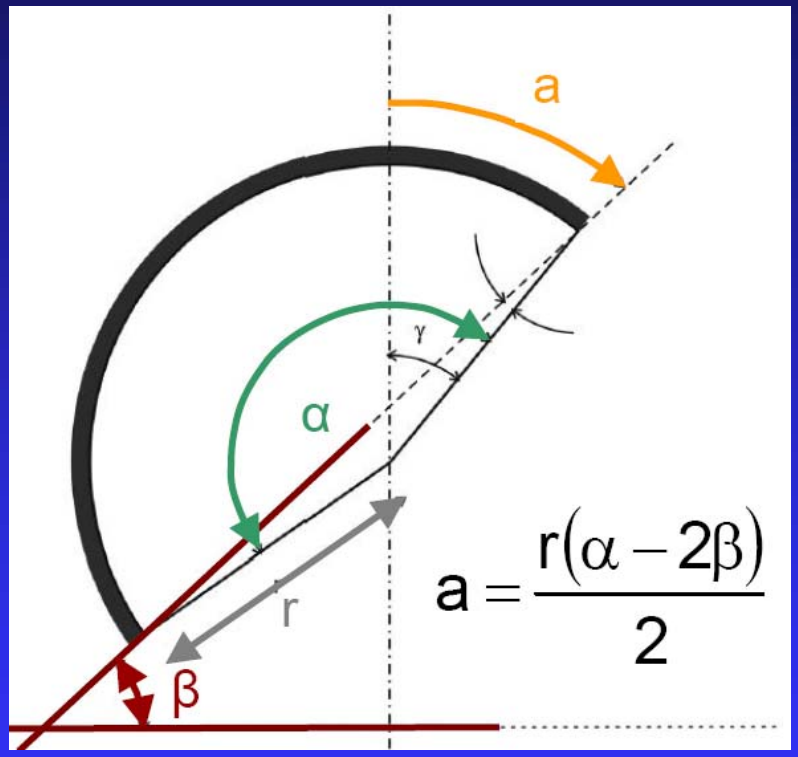
How can we make pre-clinical testing more predictive ?

=> Include adverse conditions observed in clinical service

1) Malpositioning

Steep inclination=> small ‘coverage angle’[1]





[1] De Haan et al., JBJS-Br 90B:1291, 2008

Wear and inclination (retrieval study)

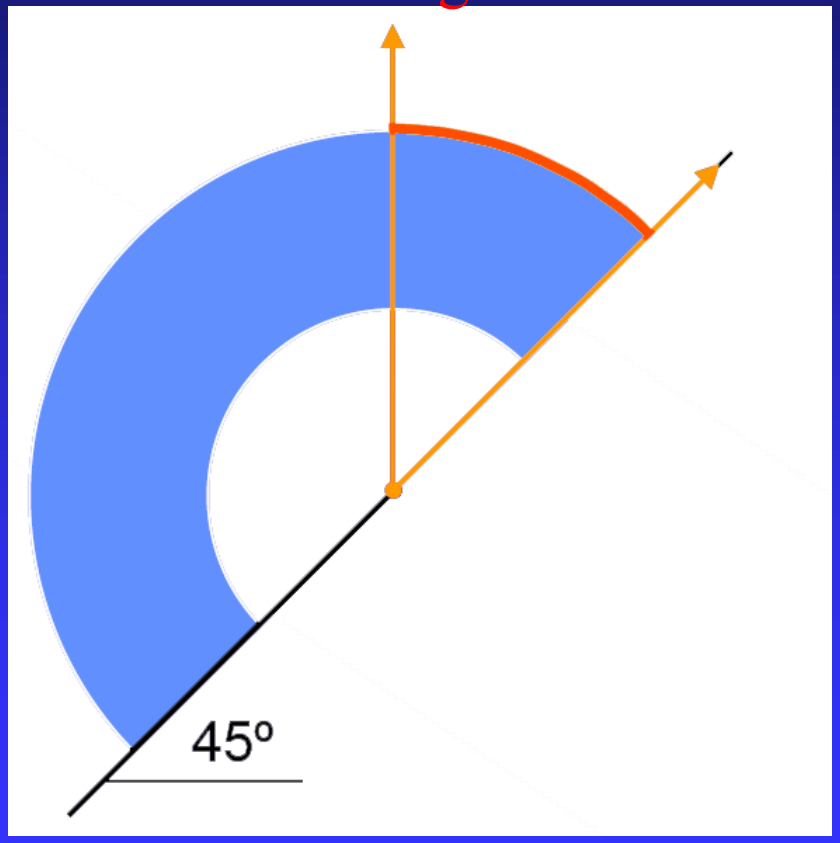
	Wear Volume [mm³/ year]		Inclination [°]	
	Head	Cup	Head	Cup
No Rimloading				
n	129	10	108	8
mean	0.24	0.66	47.7	49.0
StD	0.53	1.54	6.9	4.0
Min	0.00	0.00	30.0	42.0
Max	3.04	4.89	65.3	54.0
Rimloading				
n	23	15	22	10
mean	7.14	14.41	55.5	58.0
StD	5.20	16.33	10.3	10.9
Min	1.06	0.17	40.0	45.0
Max	22.38	59.83	75.0	75.0
p=	<0.001	0.015	<0.001	0.043

Morlock et al; JBJS 2008;90:89

Influence of design on malpositioning

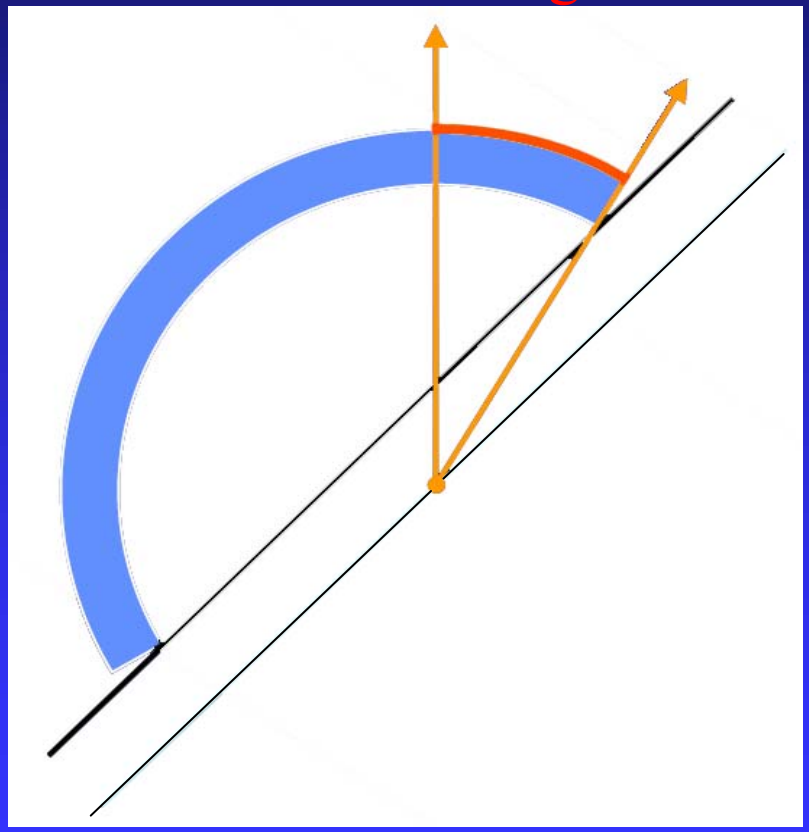
Fully hemispherical bearing surface

Articulation angle: 180°



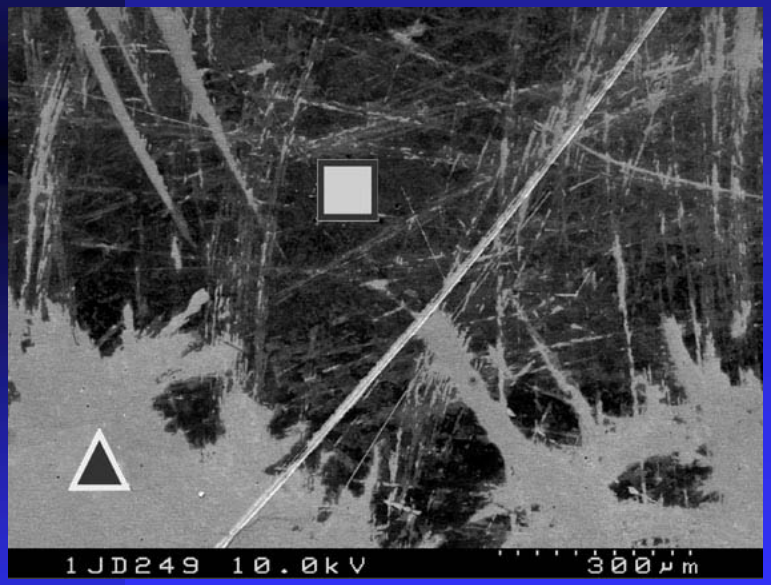
Truncated bearing surface

Articulation angle: 165°

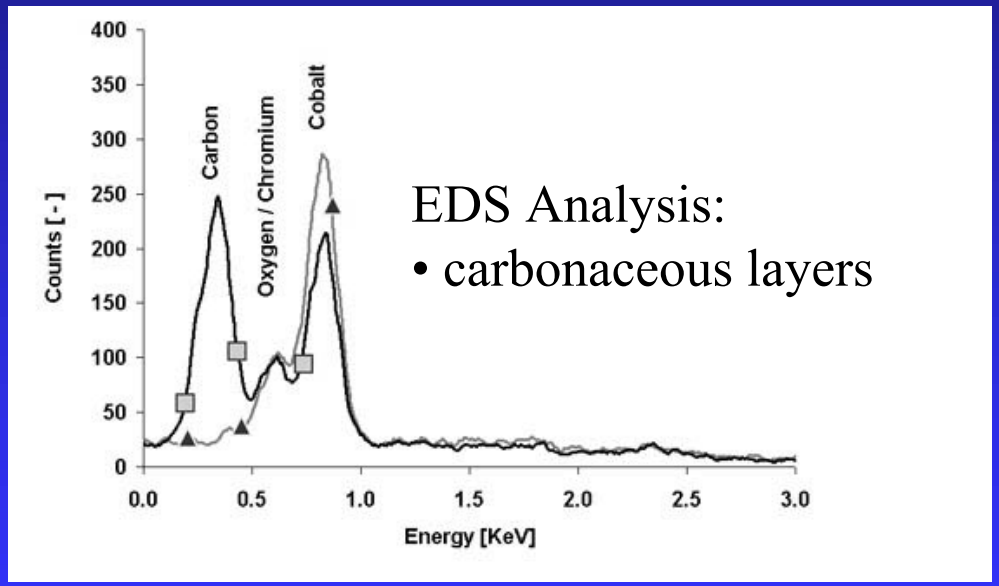


2) Lack of fluid film

- Predominantly mixed lubrication during many occasions of daily living
  => requires tribofilm at the surface to avoid metal/metal contact



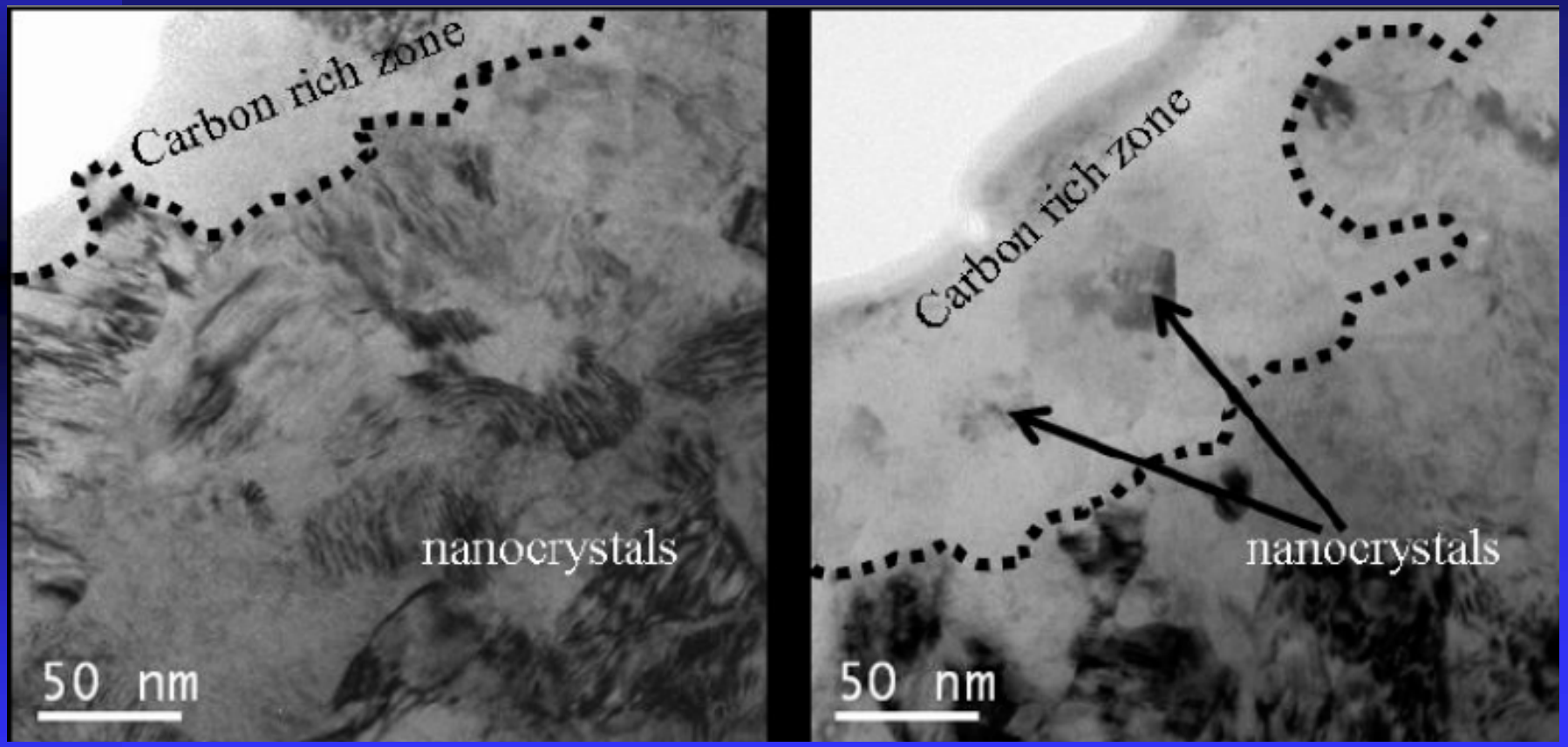
Wimmer, Fischer at al., Wear 2003



Tribofilm cross-section

carbonaceous composite with metallic, ceramic nano-crystals

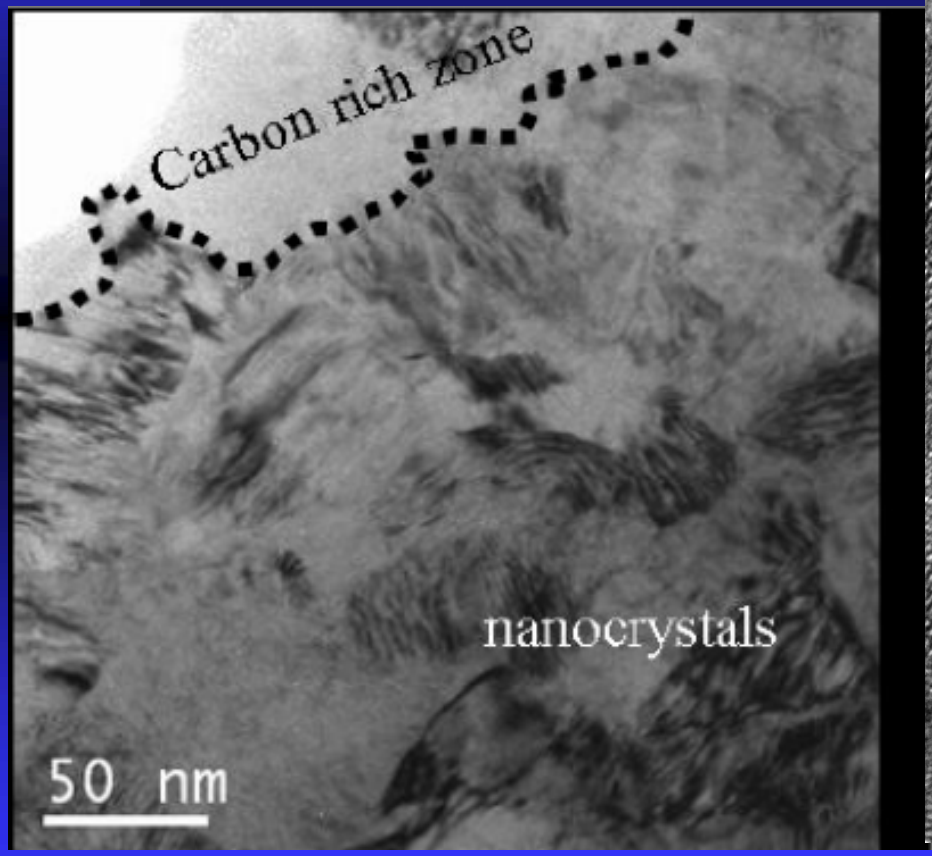
Pourzal et al. J Mech Behavior Biomed Mat 2009

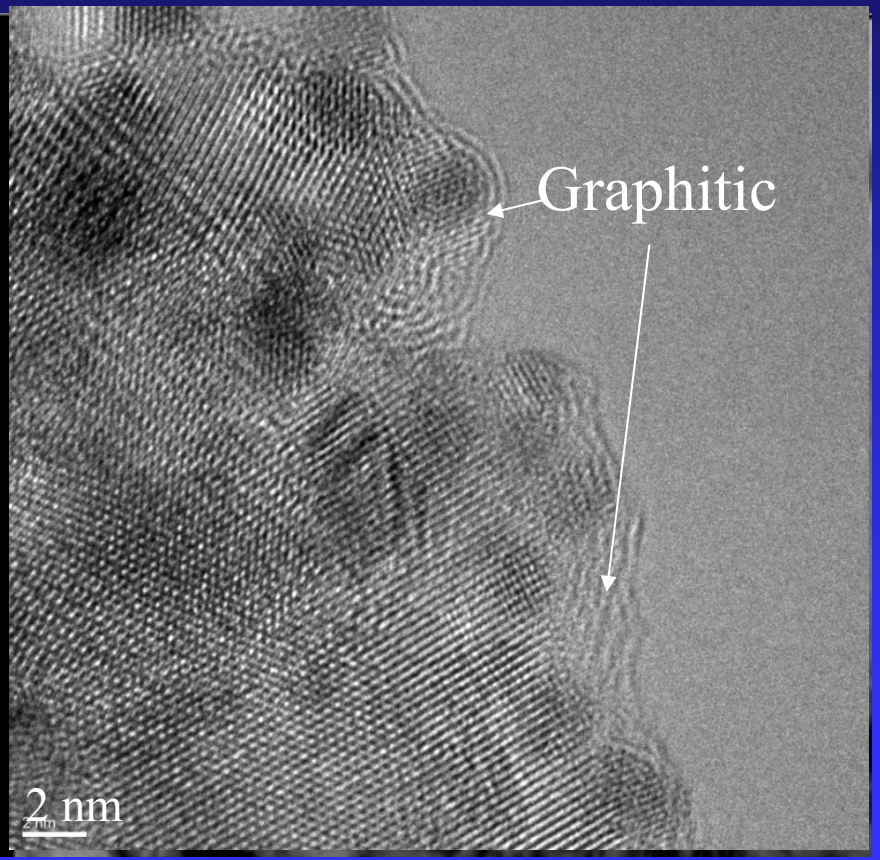


Tribofilm cross-section

carbonaceous composite with metallic, ceramic nano-crystals and graphitic material

Liao et al. Science 334:1687, 2011



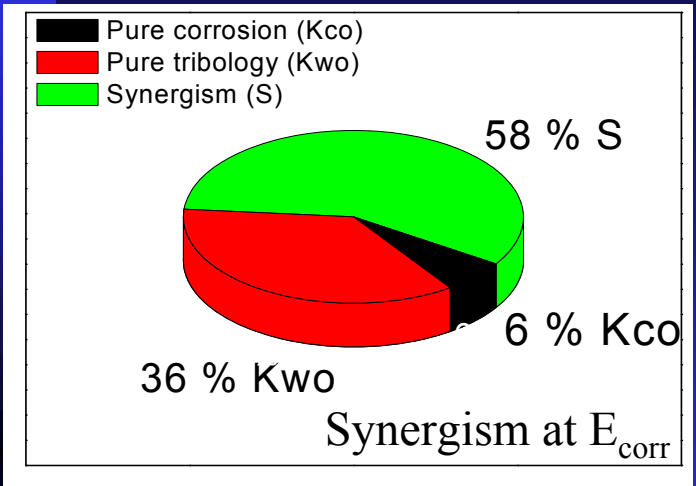


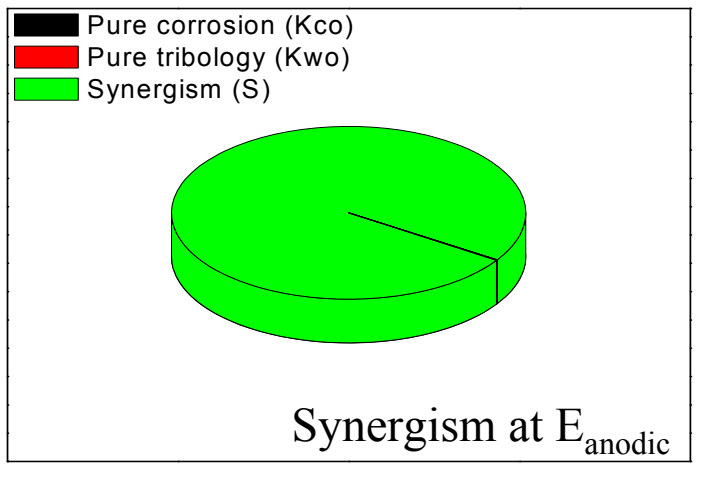
Beneficial role of tribofilm

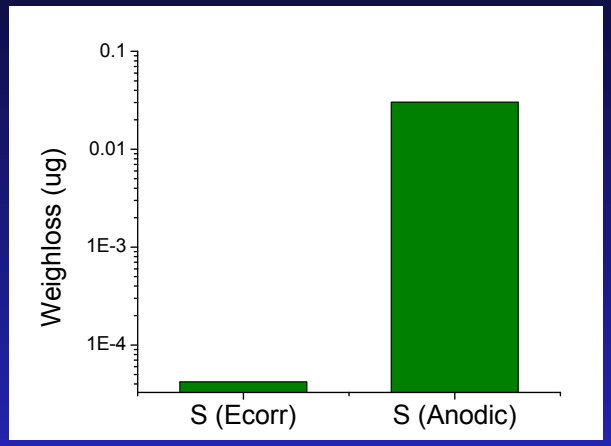
- Mechanical protection of the underlying metal surface, similar to low-friction, anti-wear additives of high performance lubricants
- Graphitic sliding CoF < 0.05
- Reduced friction => reduced wear
- Also: improves (tribo-)corrosion behavior

Mathew et al, ORS 36:384, 2011

3) Synergistic interaction of wear and corrosion







Comparison between synergistic component at E corr and E anodic

Synergistic interaction at E_{anodic} is so high that pure tribology and corrosion components are negligible.

At E_{corr} interplay of the wear and corrosion mechanisms become the driving mechanisms.

Runa, Mathew et al, ORS 36:1128, 2011

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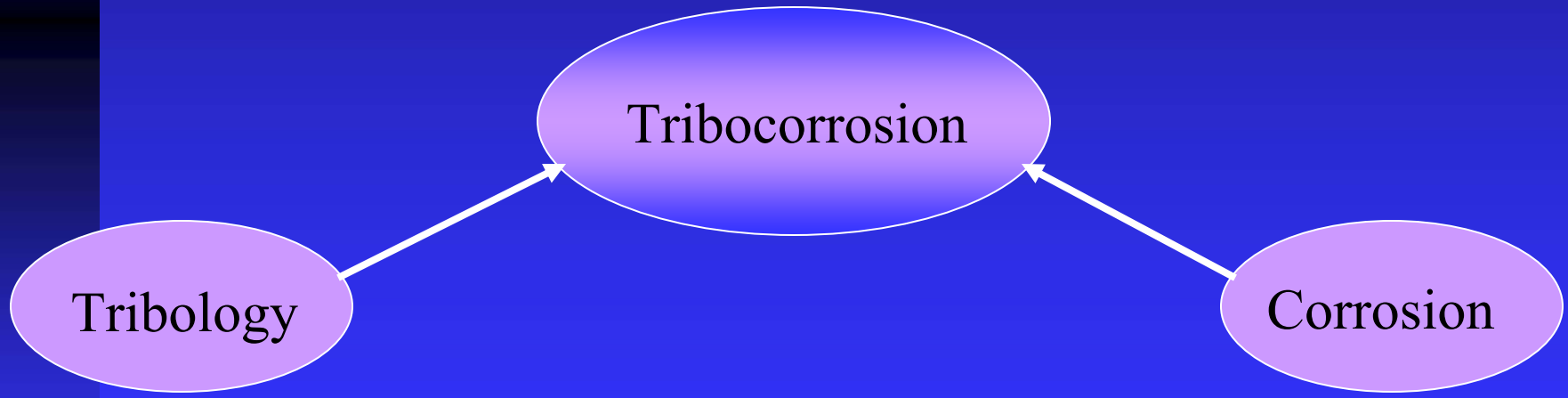
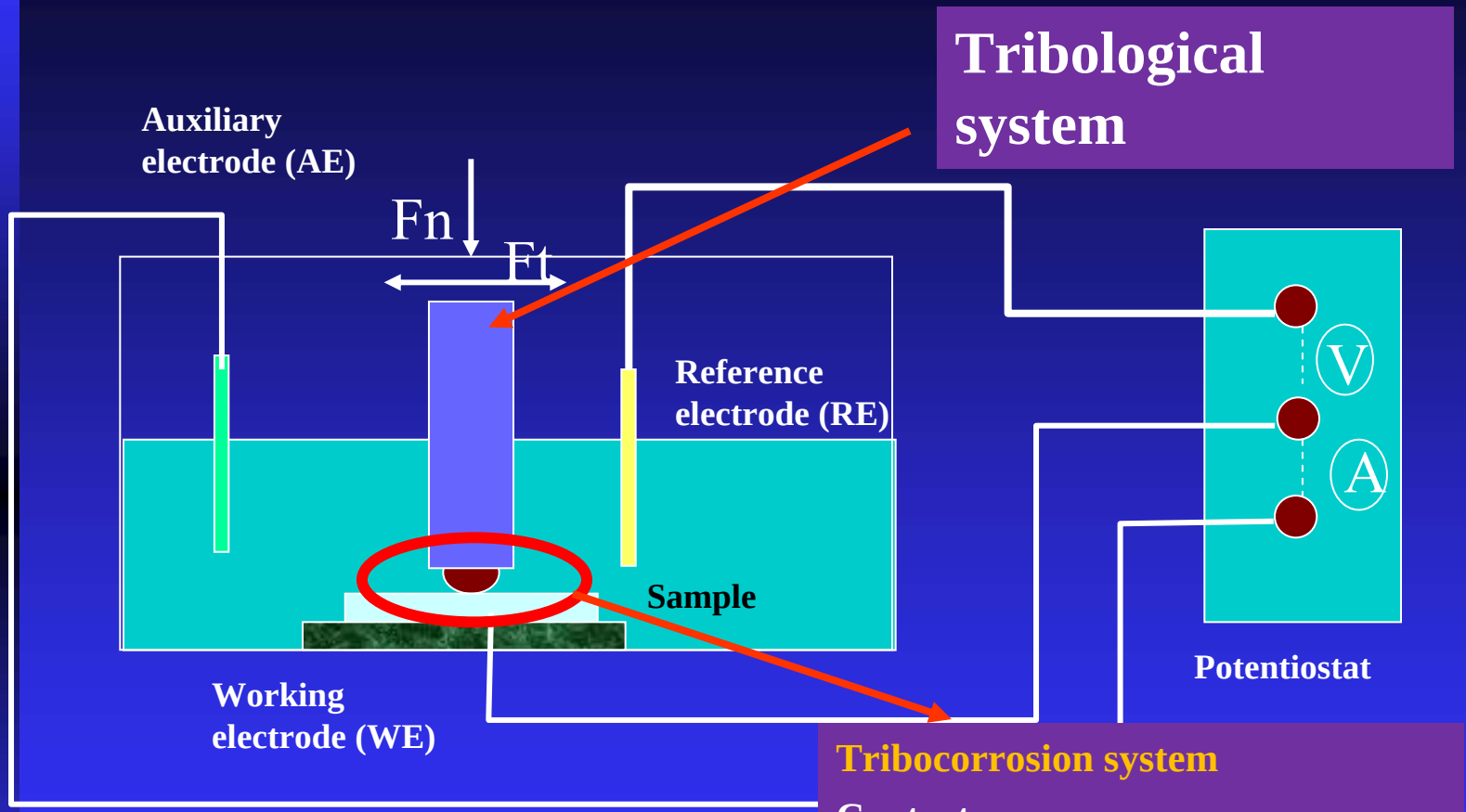
Tribocorrosion

- is an irreversible transformation of material in tribological contact caused by simultaneous physico-chemical and mechanical surface interactions.



Tribocorrosion system (principle)



Tribocorrosion system

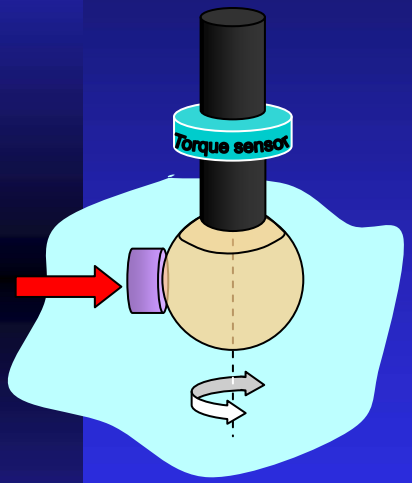
Contact zone

Tribology: Friction coefficients

Corrosion: Current or potential changes

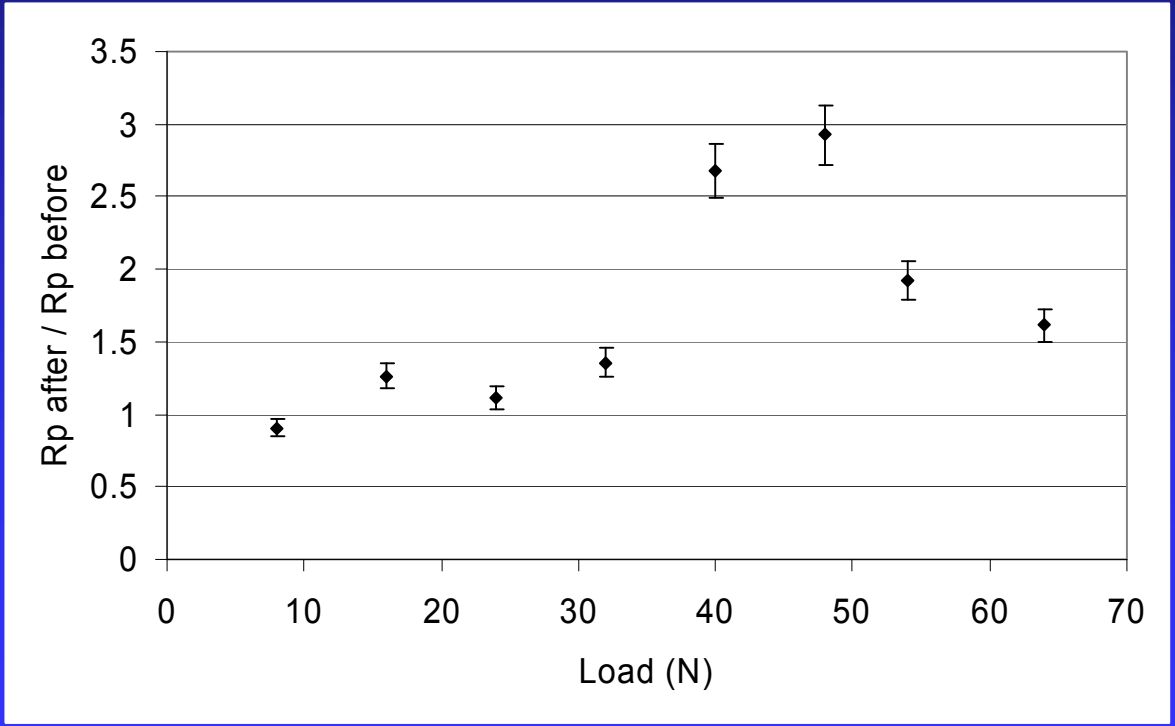
Formation and retention of tribofilm

- Tribofim only generated and retained in a certain range of loads (~50-80 MPa)



- LC-CoCrMo
- Bovine serum
- Frequency: 1 Hz
- Cycles: 1,800

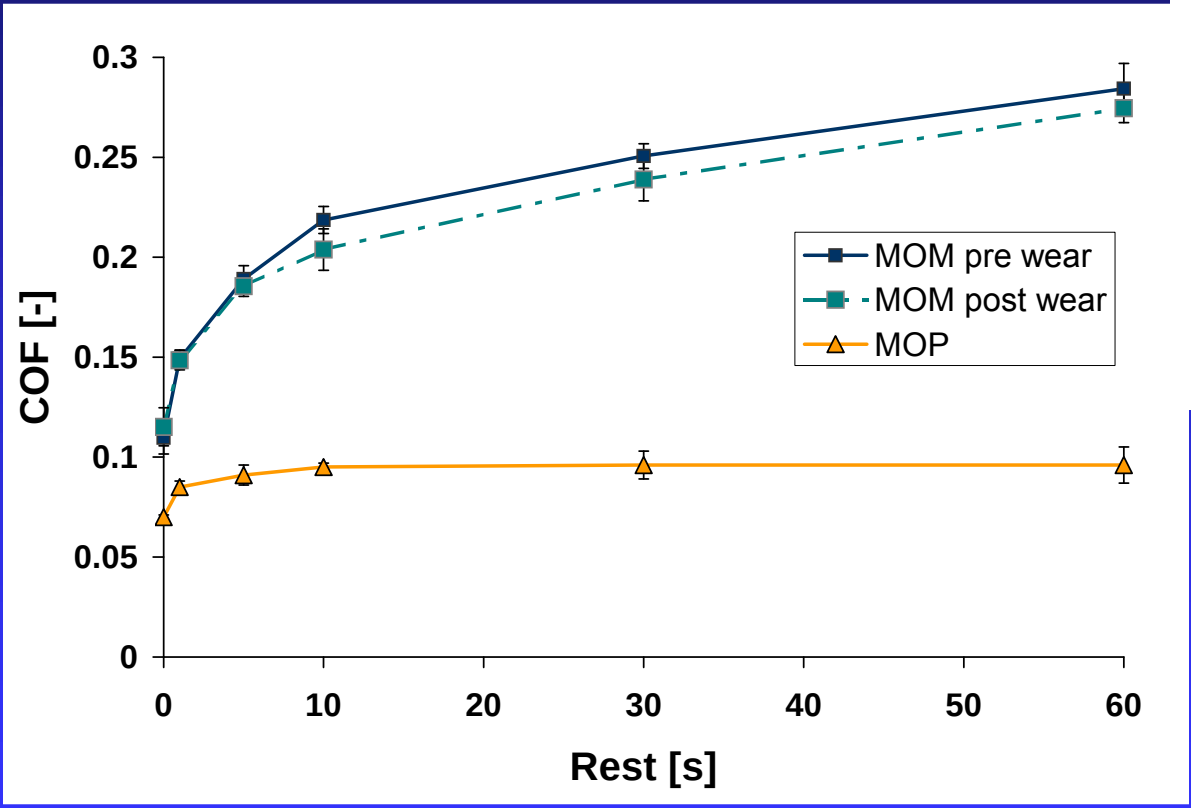
Normalized electrical film resistance after sliding

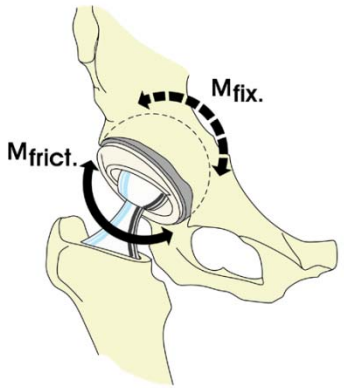


Wimmer et al, ORS 37:1036, 2012

4) High MoM friction

- Increased friction (particularly, after periods of rest)
- Increased lever-arm in large head MoM

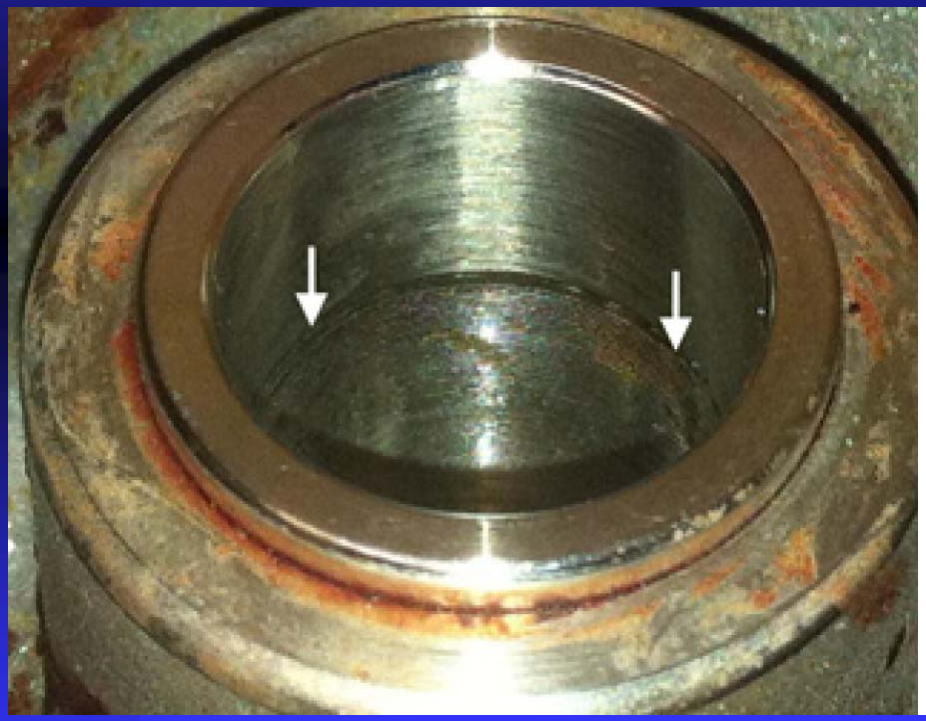


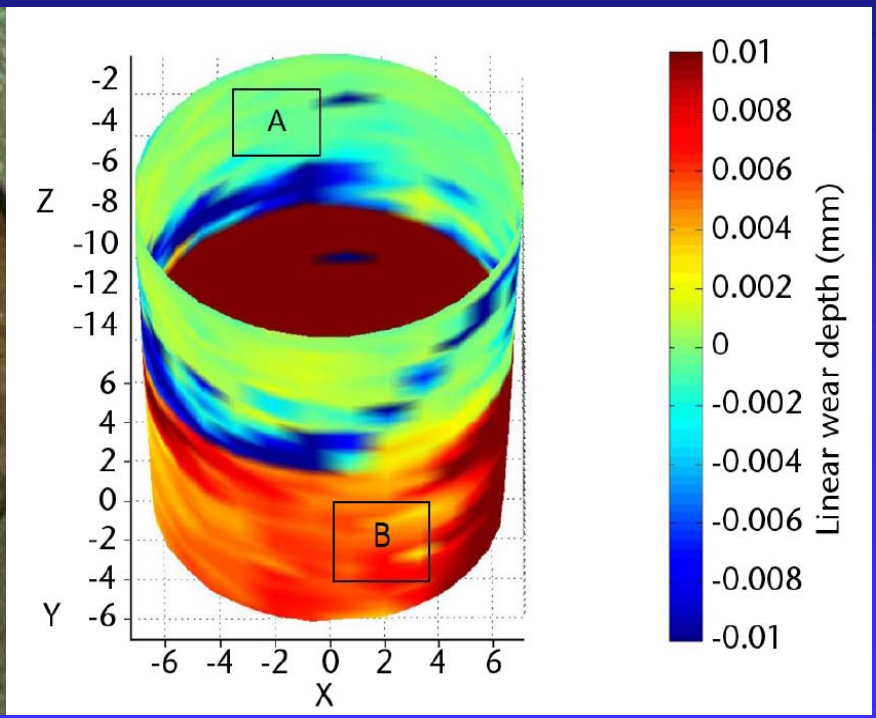


Nassutt et al. CORR 407:127, 2003

Taper junction as another wear source

- Not just an MoM problem (Kop et al, J Arthrop 24:1019, 2009)
- High torque due to large friction and head size

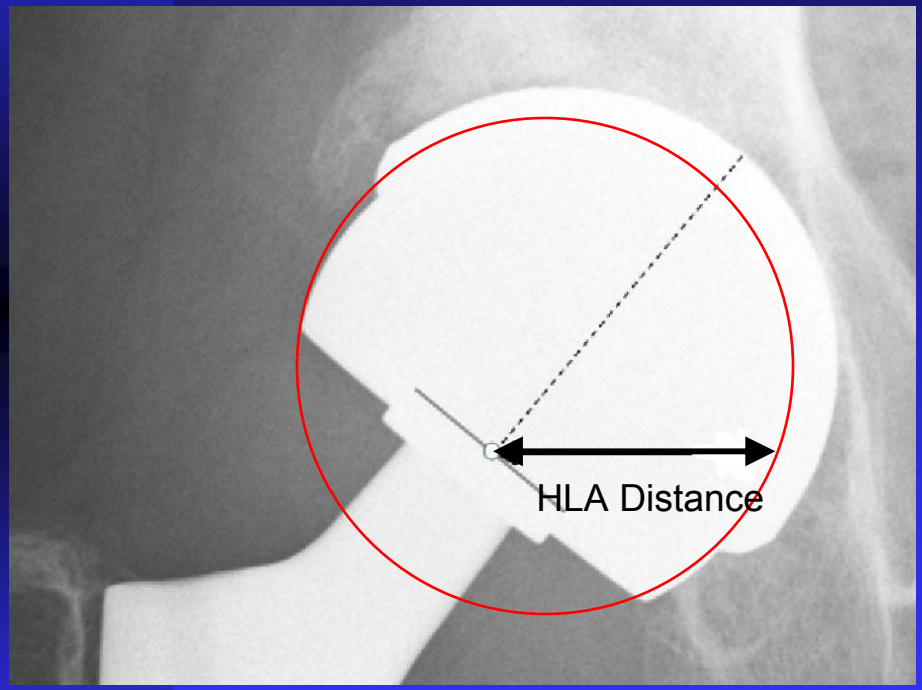


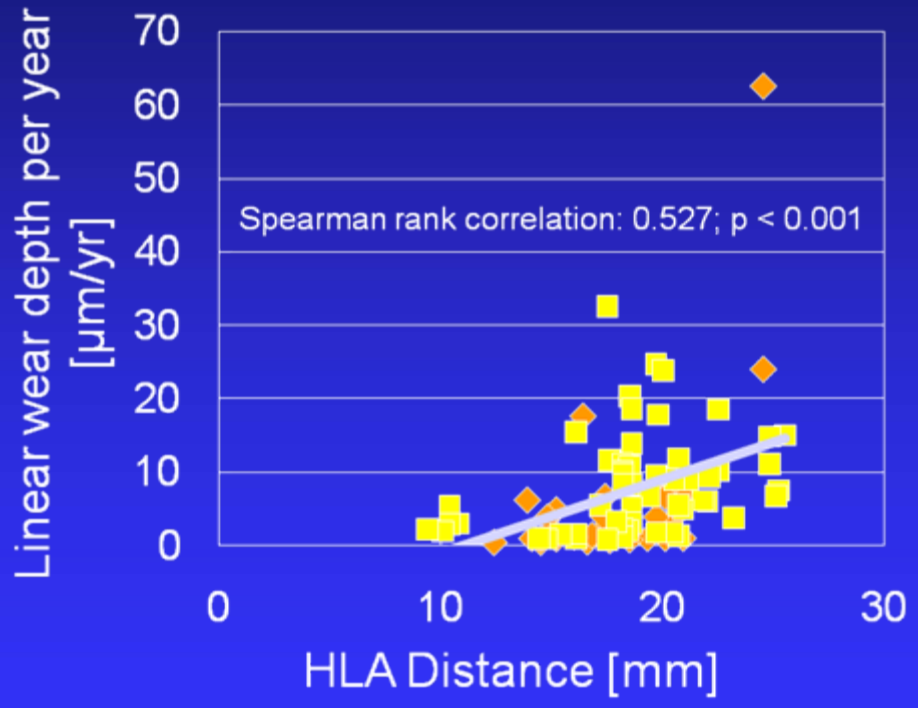


Langton et al,
BJR, 1:56, 2012

Taper junction as another wear source

- Taper wear increases with head size

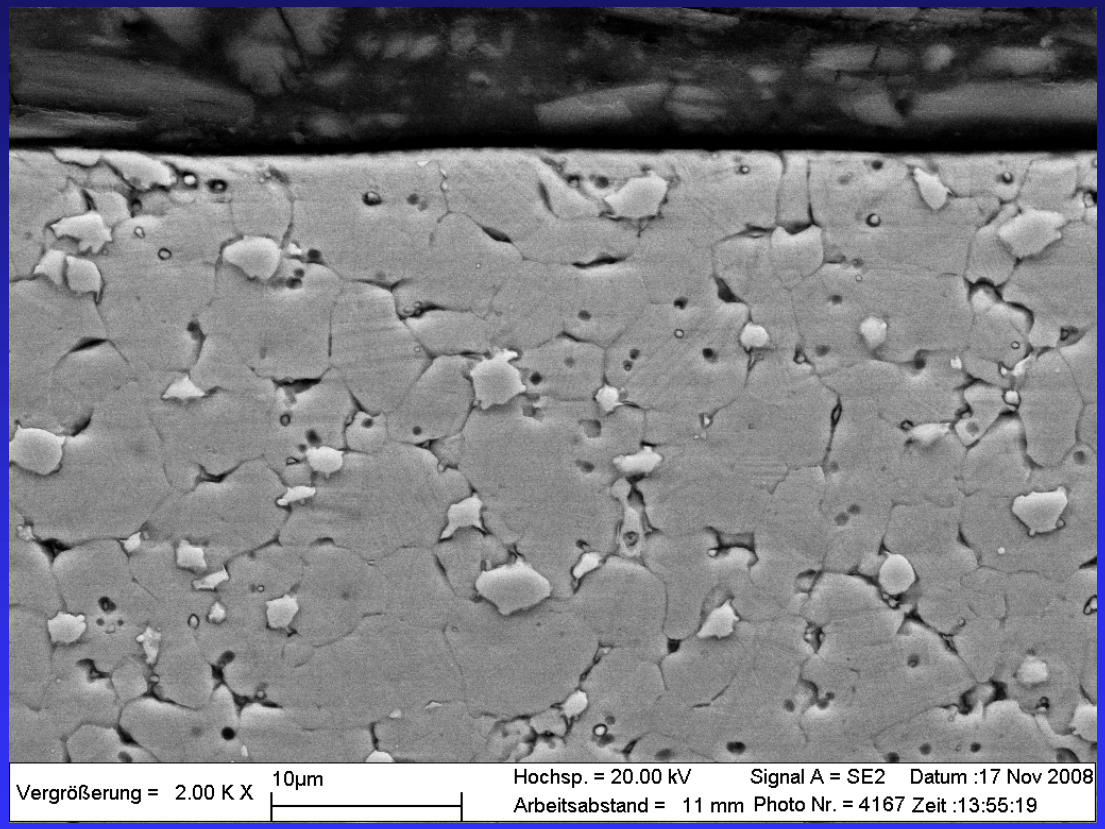




Langton et al,
BJR, 1:56, 2012

5) Variable Metallurgy

- Role of hard phases on wear?



Fischer et al.,
MoM Symp 2012
ASTM STP 1560

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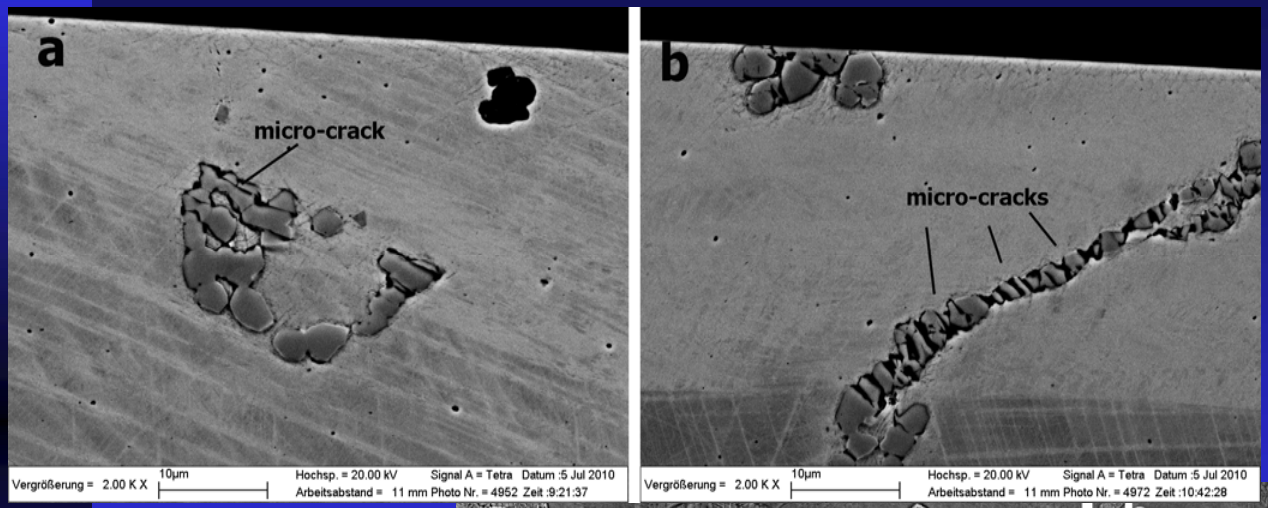
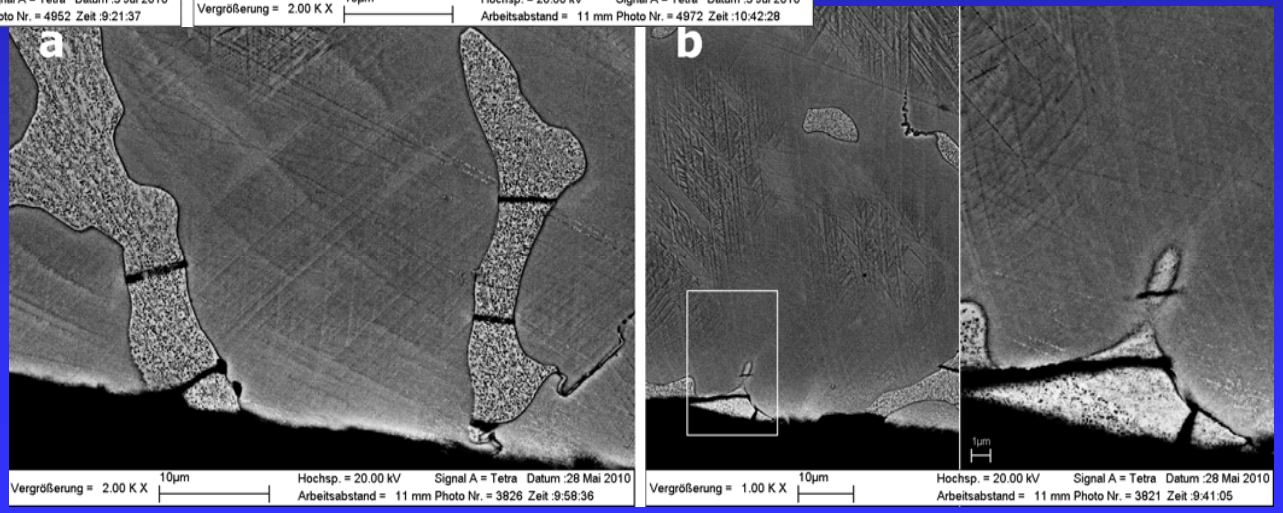
5) Variable Metallurgy

- Role of hard phases on wear?





Fischer et al.,
MoM Symp 2012
ASTM STP 1560

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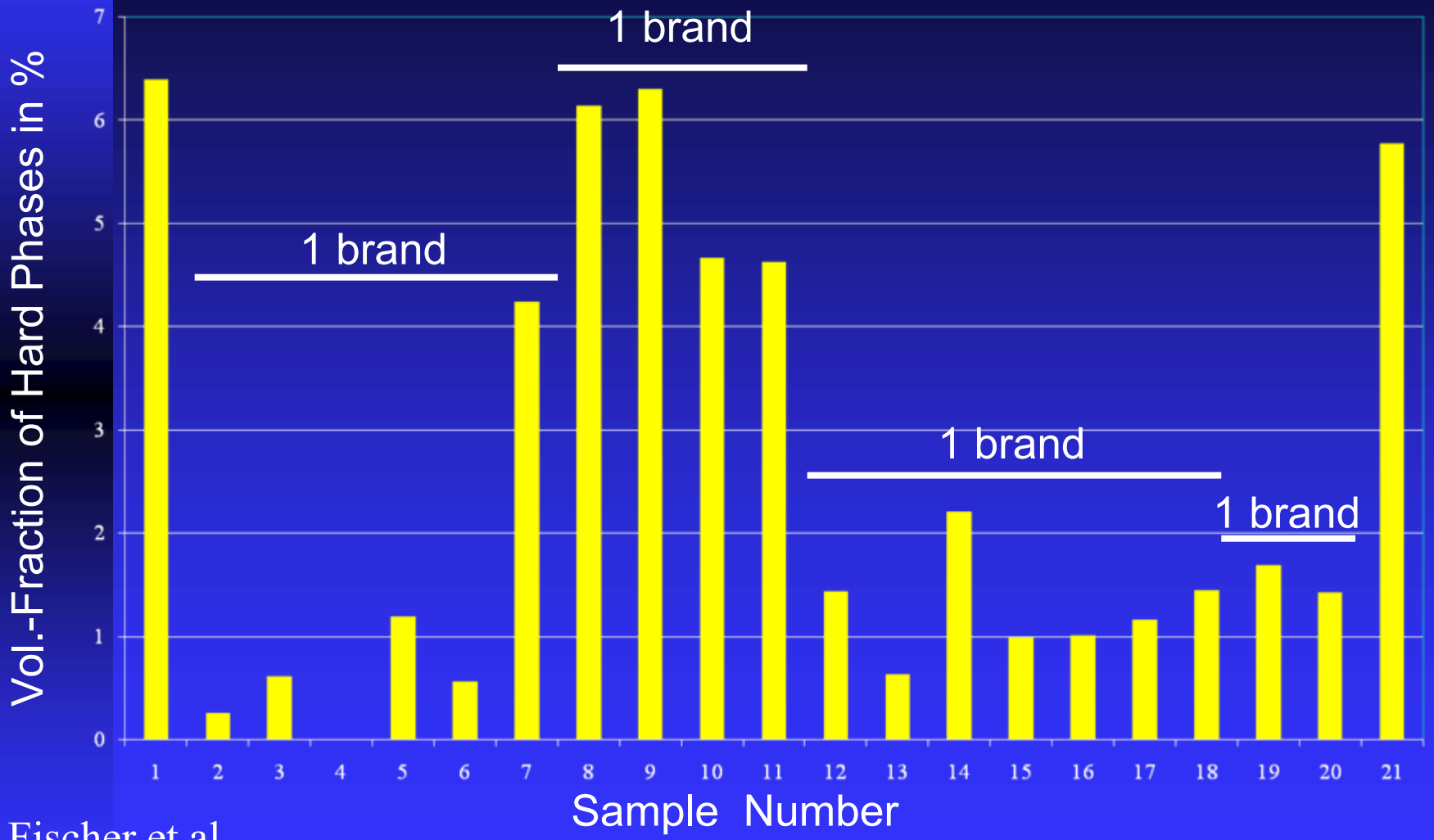
5) Variable Metallurgy



Fischer et al.,
MoM Symp 2012
ASTM STP 1560

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6) Other adverse conditions

- **Mechanical**
  - Micro-separation
  - Third bodies (intrinsic / extrinsic)
- **Chemical**
  - Creation of local cell (potential shift)
  - pH shift away from neutral
  - Bacterial infection (LPS presence)
- **Combined mechanical /chemical attack**
  - Tribo-corrosion
  - Stress corrosion

Current activities & research needs identified by ASTM

- Standard in development for bearing surface wear in MOM bearings
- Differentiate between types of ALTRs (e.g., hypersensitivity, ALVALs, metal toxicity, pseudotumors)
- Standardize particle characterization for MOM bearings

Current activities & research needs identified by ASTM

- Standard for taper wear and measurement
- Standard for orthopedic tapers
- Algorithmic approach for synthesis of clinical data (x-rays, MRI), wear measurement (CMM, OOR), surface analysis techniques (SEM), histological analysis and fluid characterization

Current activities & research needs identified by ASTM

- Standardize hypersensivity testing
- Standardize metal ion testing in body fluids
- Adverse preclinical testing
- Synovial fluid characterization
- Preserve history of retrieval analysis

Thank you

FDA Orthopaedic Rehabilitation Devices Panel
Medical Devices Advisory Committee Meeting
Wednesday June 27th 2012

BIOLOGICAL REACTIONS TO METAL-ON-METAL HIP IMPLANTS

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AAOS American Academy of Orthopaedic Surgeons
American Association of Orthopaedic Surgeons

Disclosure

- No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this testimony.

Biological Reactions to MoM

- Systemic
  - Chromosomal/ Carcinogenesis
  - Teratogenecity
  - ‘Cobaltism’
- Local
  - Osteolysis
  - Hypersensitivity
  - Pseudotumours

Systemic Adverse MoM Reactions

- Metal ions lead to the generation of free radicals
- Free radicals induce DNA cross-links
- Chromosome translocations and aneuploidy in peripheral blood lymphocytes at 6, 12 and 24 months post surgery (Ladon *et al*. JOA 2004)
- Permanent modification of genetic material may represent the first step involved in carcinogenesis.

Carcinogenesis

- The carcinogenic potential of cobalt and chromium wear particles have been demonstrated in animal models (Heath *et al.* Lancet 1971)
- Currently available data on risk of cancer does ***not*** support a causal link (Smith *et al.* BMJ 2012; Silva *et al.* CORR 2005; Tharani *et al.* JBJS A 2001)
- These studies limited by a small number of patients and short follow up period.

Teratogenicity

- MoM performed in young patients, including females of child bearing age, concern that mutagenic or teratogenic effects
- Cord blood levels of cobalt and chromium were 60% of the mean maternal blood levels in patients with hip resurfacing (Ziaee *et al*. JBJS B 2007)
- Placenta may exert a modulatory effect on the rate of metal

‘Cobaltism’

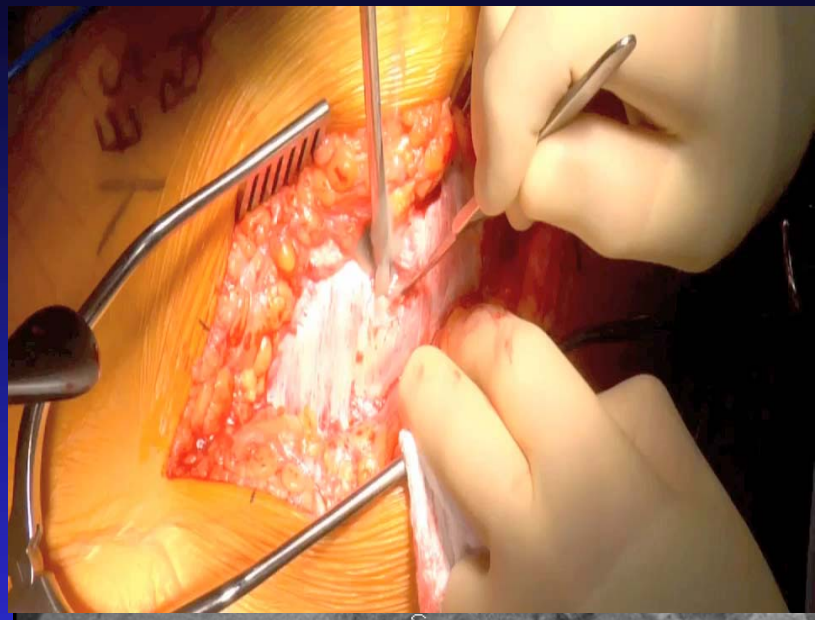
- Series of case reports describing temporal association of metal toxicity **(Tower JBJS A 2010; Mao *et al*. MJA 2011)**
- Neurologic and cardiac dysfunction
- Case reports with ASR MoM THA
- Cobalt serum level 35-112 ug/L
- Optic atrophy and cardiac dysfunction

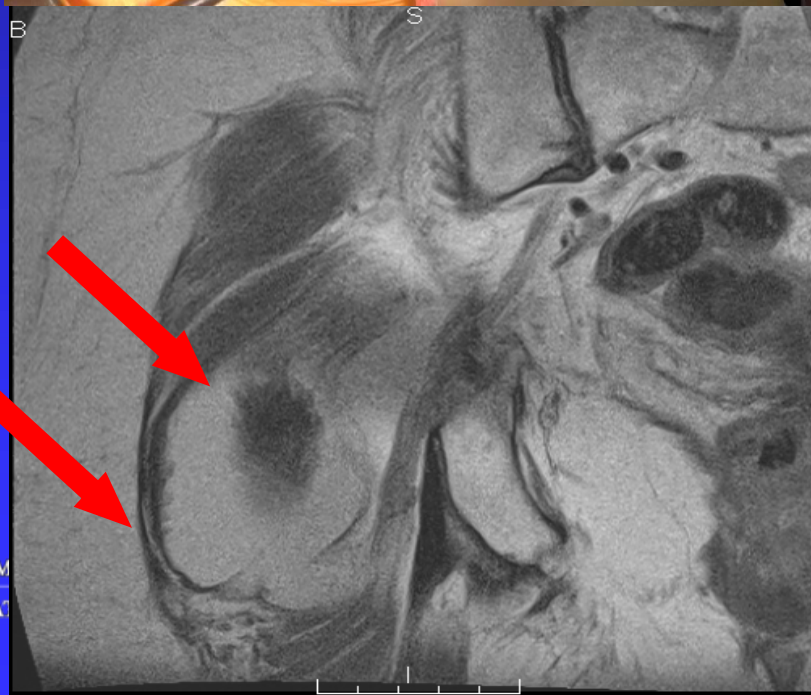
Local Adverse MoM Reactions

- Osteolysis (Park *et al.* JBJS 2005)
- Adverse Soft Tissue Reactions
  - 'Hypersensitivity' (ALVAL)
  - 'Pseudotumours'
- **How Big is the Problem?**
- Is it Metal Hypersensitivity?
- Is there Increased Metal Debris?

Local Abnormal Soft Tissue Reactions

- Observed in Patients following MoM resurfacing & MoM THA
- Described as "Pseudotumour"
- Many other names:
  - Metallosis
  - A.L.V.A.L
  - A.R.M.D
  - A.L.T.R





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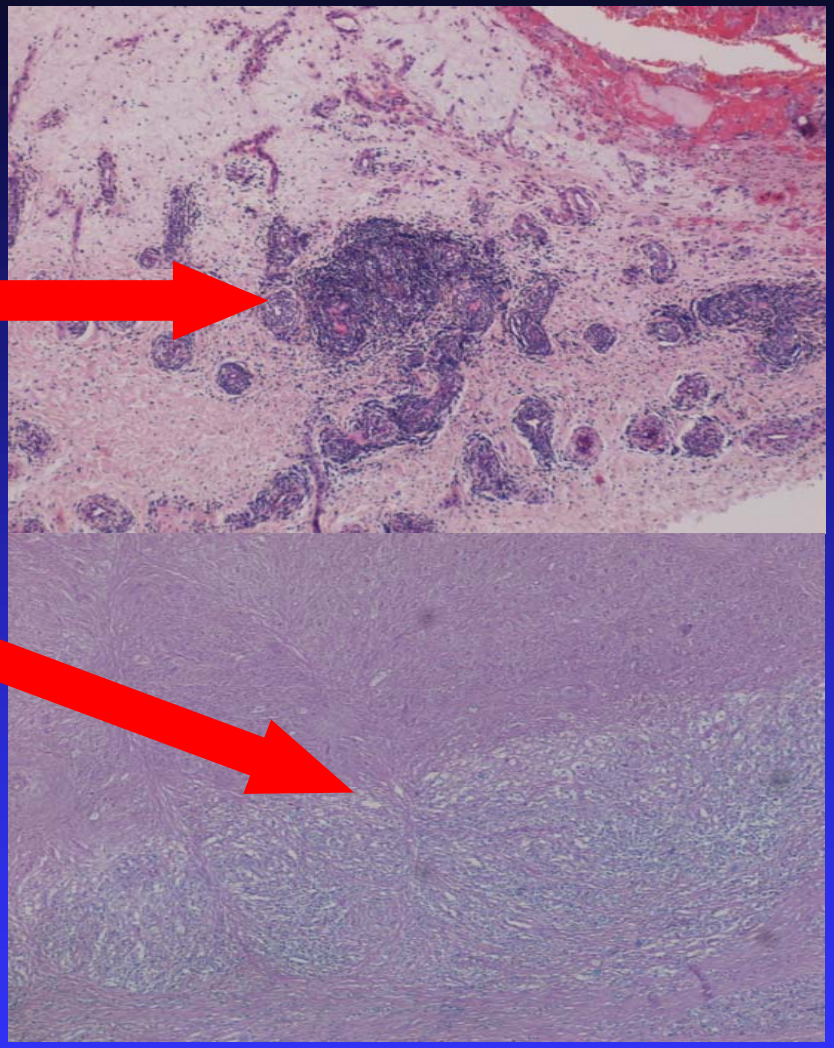
Histology

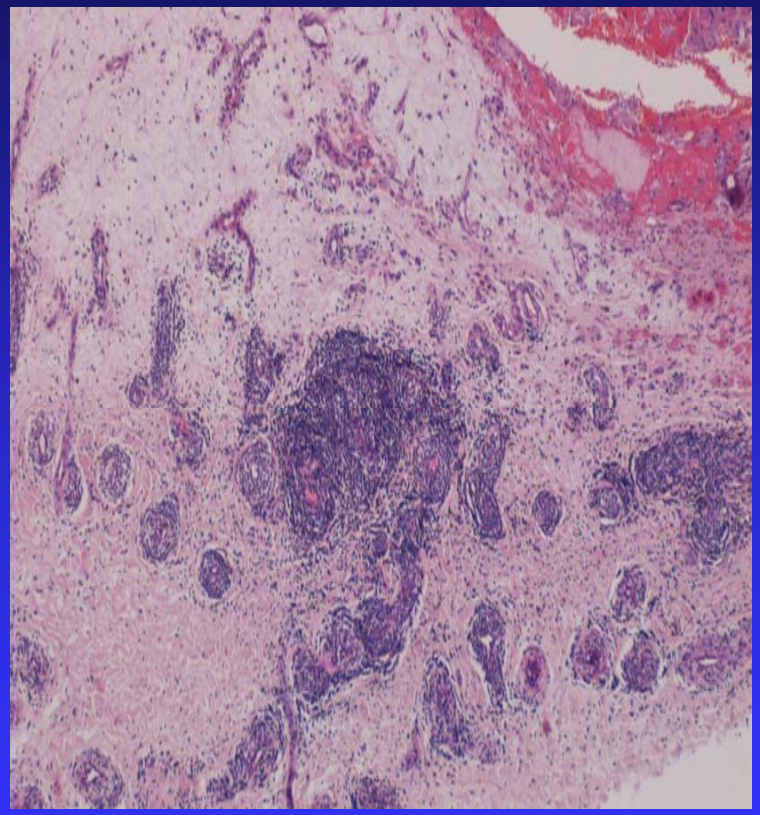
- Lymphocyte infiltration
  - Similar to A.L.V.A.L (Willert JBJS 2005)
- But extensive necrosis with collection of dead macrophages with metal wear debris (essential feature)



Mabilleau, Kwon *et al.* Acta Orthop 2008

Histology

- Spectrum of histological features (Campbell *et al.* CORR 2010)
  - Scoring system
  - Synovial lining; cell types; tissue organization
  - Metal allergy *vs.* necrosis



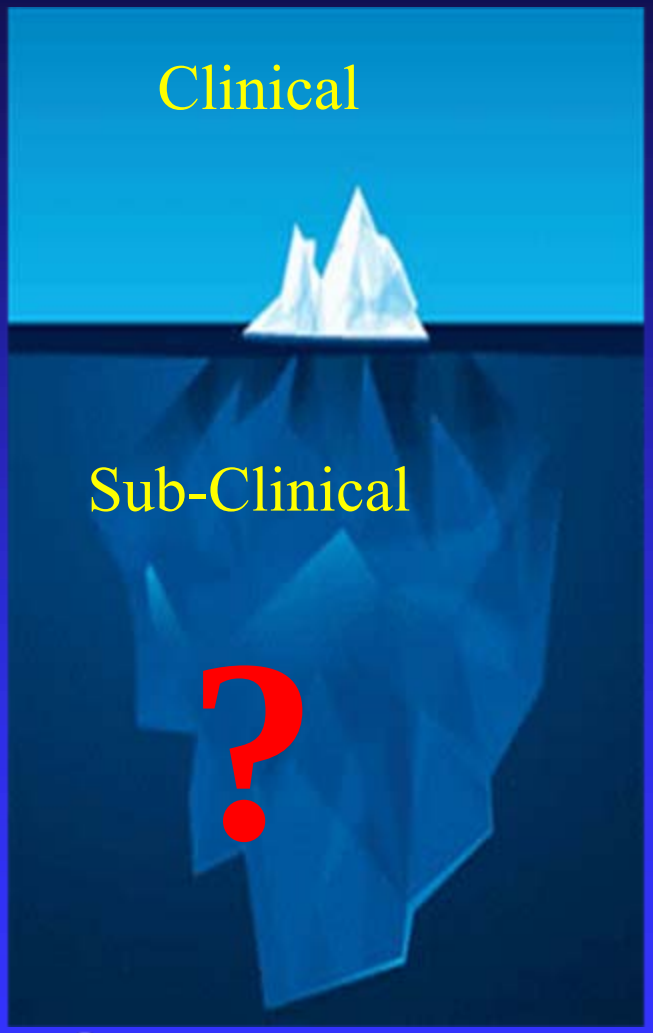
How Big Is The Problem?

- Incidence varies between centers and different end-points
- Hard-Endpoint (Revision for Pseudotumour)
- Overall incidence 0.1-3%
- Some centers higher
- Designer surgeon centers lower

‘Asymptomatic’ Pseudotumours

- Some patients with bilateral MoMHRA presented with symptom in one hip only
- However, pseudotumours found in both **symptomatic** and **asymptomatic** resurfaced hips

‘Asymptomatic’ Pseudotumours



‘Asymptomatic’ Pseudotumours

Kwon *et al*. JoA 2011

- N=201 consecutive MoMHRA
- Asymptomatic
- ‘Screened’ using US/MRI
- 4% Prevalence
- Size ranges 2×1×2 cm to 8×7×8 cm

‘Asymptomatic’ Pseudotumours

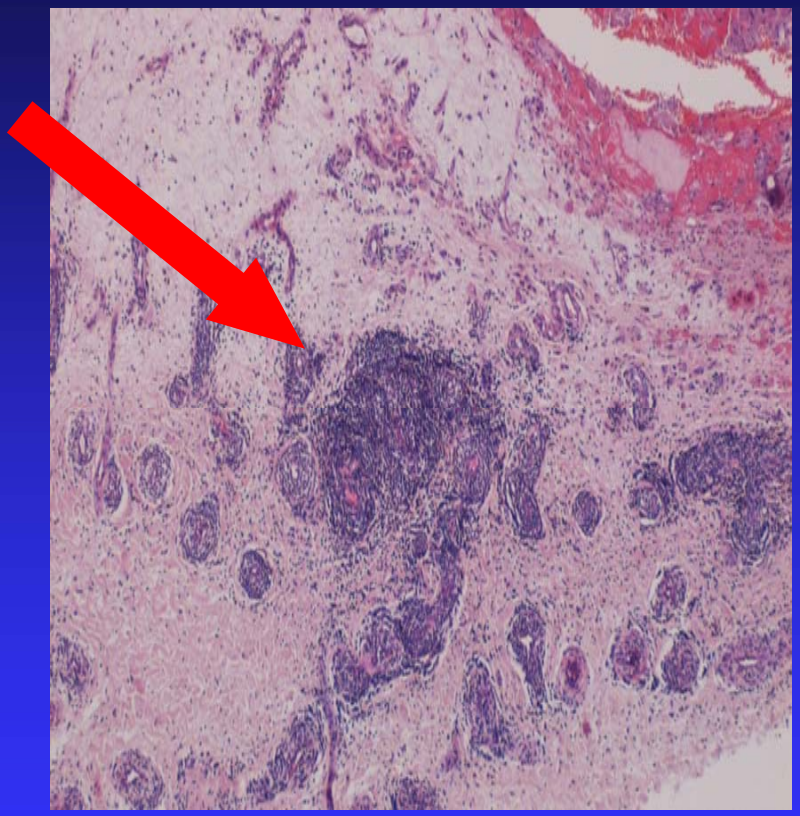
- Williams *et al*. JBJS Am 2011
  - N=73 Asymptomatic ‘Screened’ using US
  - Prevalence 27% MoM THA; 14% MoMHRA
- Wynn-Jones *et al*. Acta Orthop 2011
  - N=77 Asymptomatic ASR ‘Screened’ using MRI
  - Prevalence 31%
- Bosker *et al*. Paper #303, AAOS 2012
  - Prevalence 31% following CT screening
  - No difference in clinical outcome scores

How Big Is The Problem?

- The precise prevalence is unknown
- Appreciable number of ‘asymptomatic’ or sub-clinical pseudotumors
- US/MRI scans required to detect or ‘screen’ for pseudotumors
- Concern that ‘asymptomatic’ pseudotumors increase the incidence of symptomatic pseudotumors

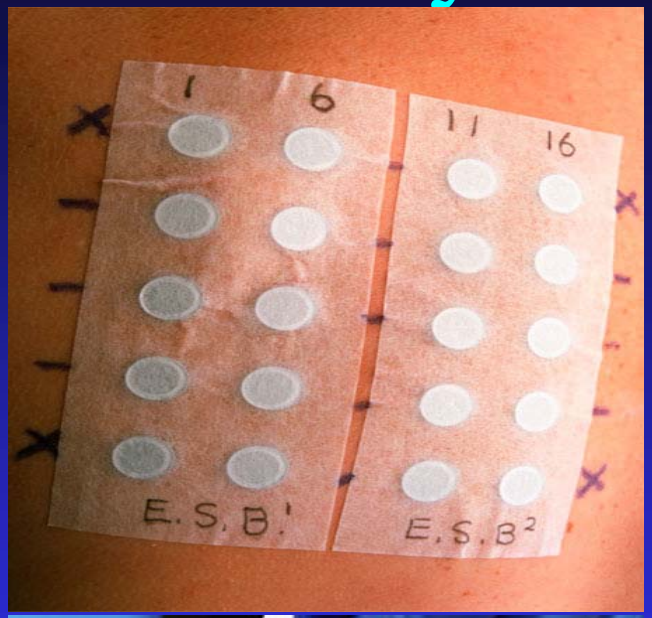
Is It Hypersensitivity Reaction?

- Lymphocyte infiltration
  - Similar to A.L.V.A.L (Willert *et al.* JBJS A 2005)
- ALVAL:
  - Type IV delayed hypersensitivity reaction
  - Driven by T-lymphocytes
  - Sensitized due to continuous exposure to metal ions



Testing for Hypersensitivity

- Traditional *in vivo* Skin Patch Testing
- Limitations
  - Dermal vs. deep tissue
  - Duration of exposure
  - Falsely negative in immunosuppressed, tolerance
  - Sensitisation



Jacobs *et al.* JBJS A 2006

Lymphocyte Transformation Tests

- Lymphocyte proliferation response to a challenging agent
- T lymphocyte responsible for activation and memory in type IV hypersensitivity (ALVAL)
- Measures sensitisation
  - Previous exposure
  - Immune memory and response

Lymphocyte Transformation Tests

- Lymphocyte proliferation response to a challenging agent
- T lymphocyte responsible for activation and memory in type IV hypersensitivity **(ALVAL)**
- Measures sensitisation
  - Previous exposure
  - Immune memory and response
- **? Pre-operative screening test**

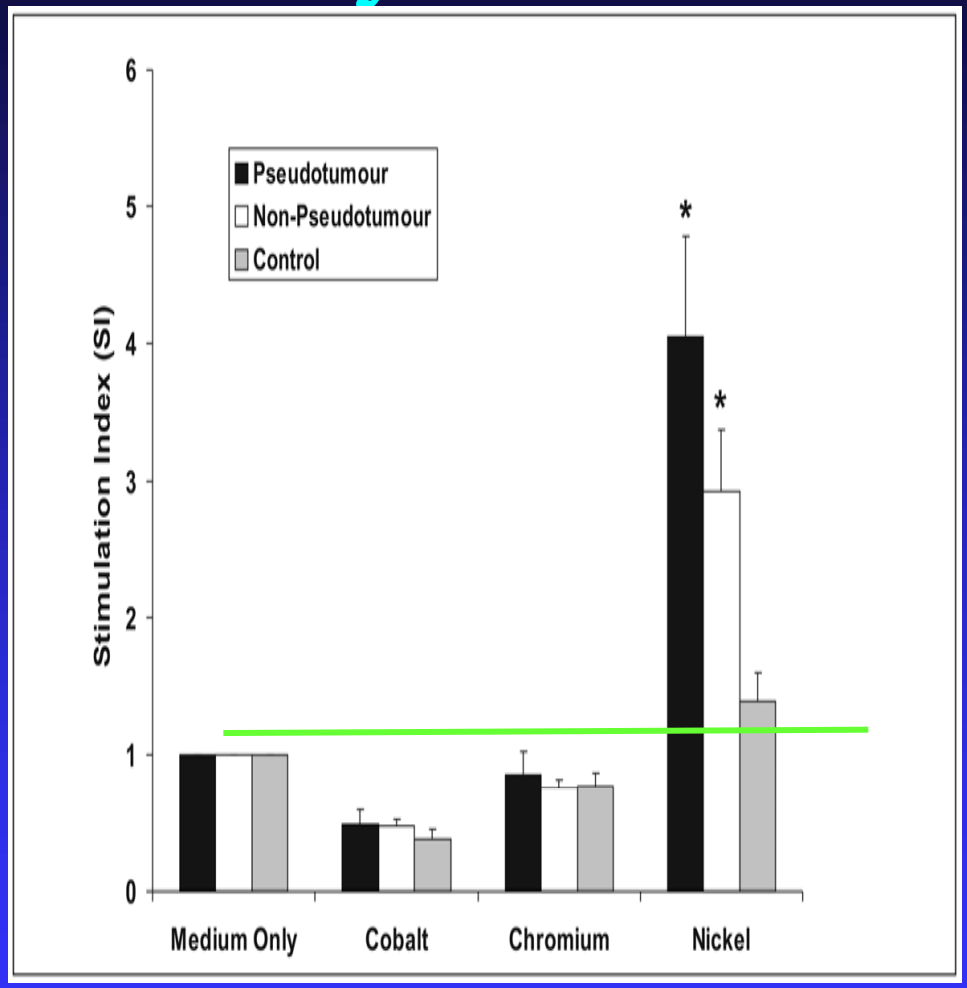
Lymphocyte Transformation Tests

Patient Group	Number	Mean Age (years)	Mean Follow-up (months)
Pseudotumour	10 (1M:9F)	56 (45-62)	65 (19-79)
Non-Pseudotumour	60 (30M:30F)	55 (40-69)	61 (13-88)
Control	22 (13M:9F)	55 (50-58)	Pre-operative

Kwon *et al.* JOR 2010

Lymphocyte Reactivity

- NO difference in lymphocyte reactivity to Co or Cr between pseudotumour and non-pseudotumour groups



Kwon *et al.* JOR 2010

Lymphocyte Reactivity

Langton *et al.* JBJS Br 2010

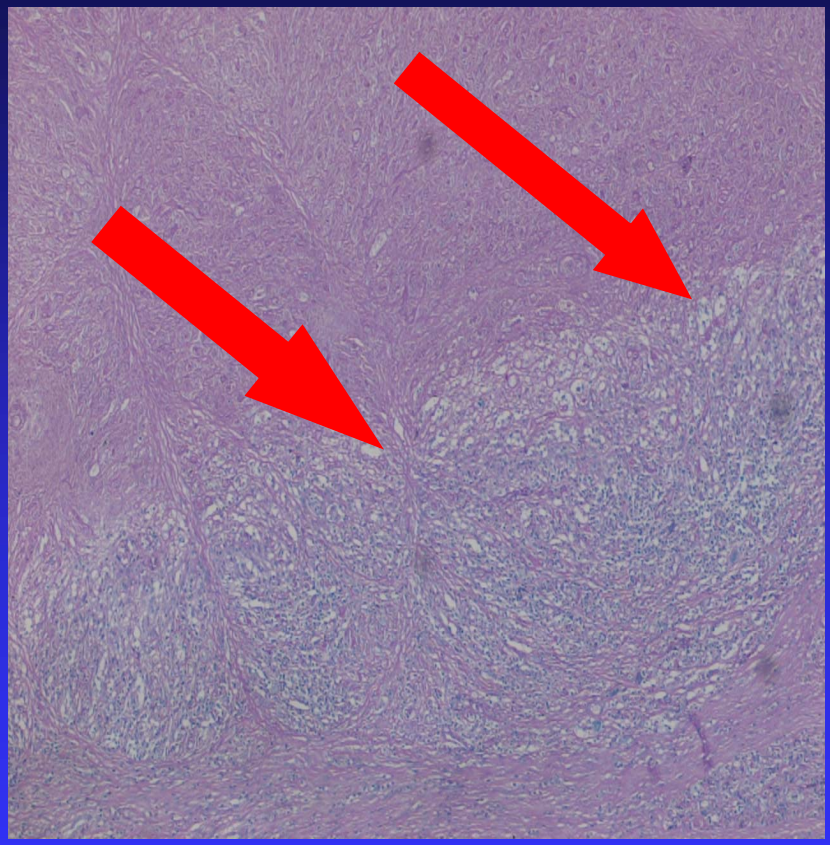
- Patients with ASR with adverse soft tissue reactions undergoing revision
- NO patient with ARMD showed increased lymphocytic reactivity (LTT) to Co or Cr
- One showed a mild reactivity to Ni

Is It Hypersensitivity Reaction?

- Hypersensitivity type IV reactions (ALVAL), mediated by lymphocyte reactivity to these metals may play an important role in pathogenesis
- However, ***not*** the only mechanism
- Further research required before recommending routine use of LTT as screening test

Is It Metal Cytotoxicity?

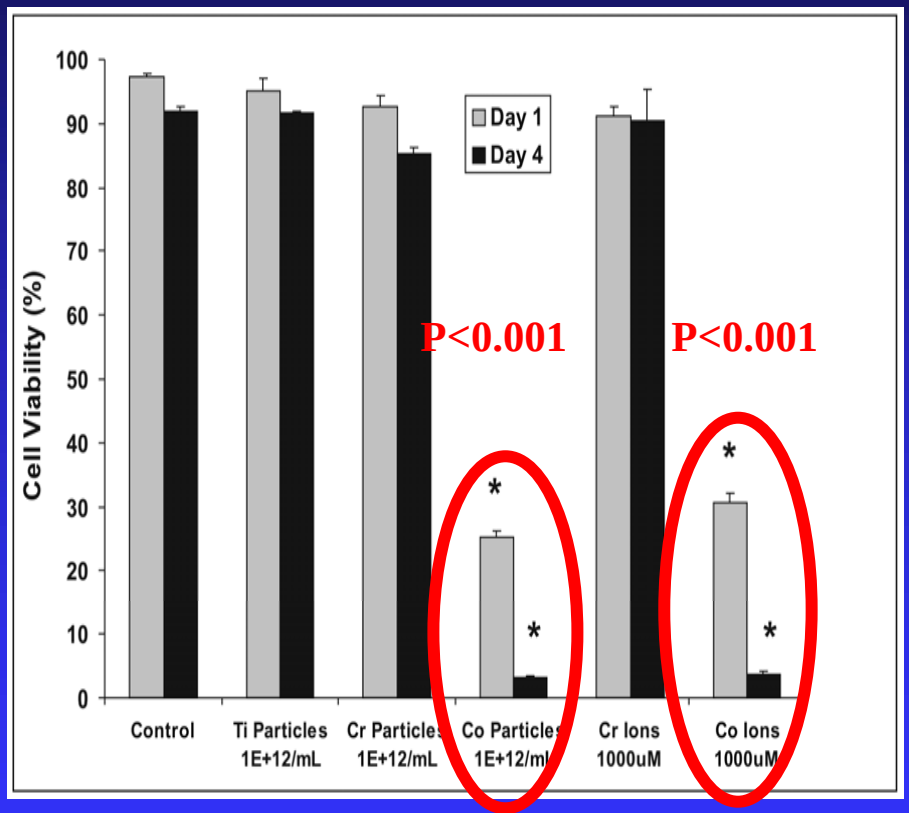
- Histology:
  - Essential feature of extensive necrosis with collection of macrophages
  - Metal particle aggregates



Mabilleau, Kwon *et al*. Acta Orthop 2008

Metal Cytotoxicity

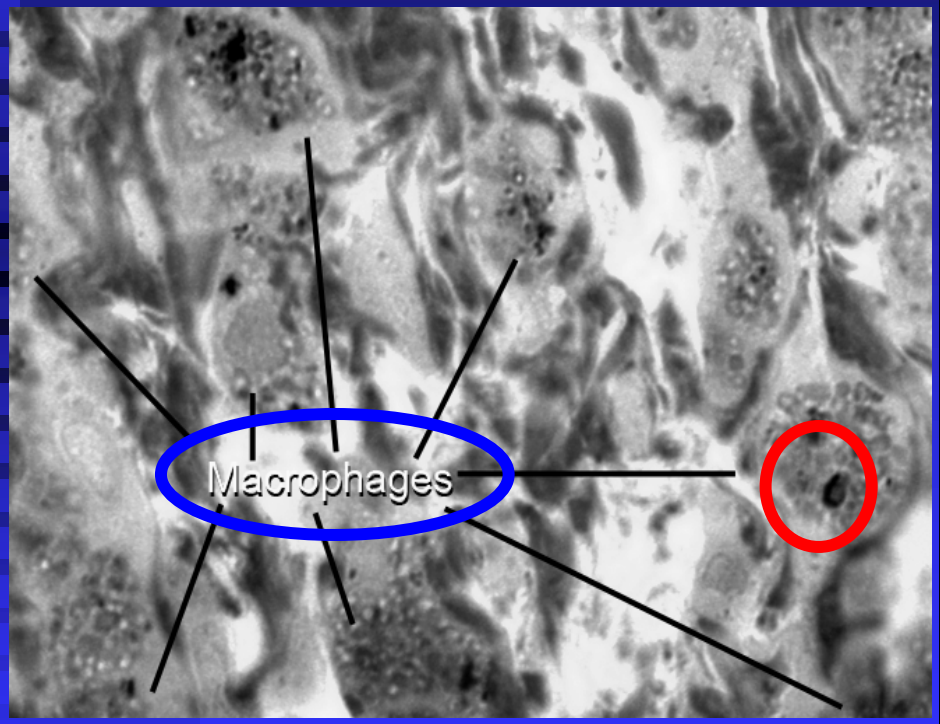
- Cobalt nanoparticles and ions have dose-dependent cytotoxic effects on macrophages *in vitro*
- **In the presence of a high level of metal wear debris** and prolonged exposure *in vivo*, cytotoxicity of macrophages lead to tissue necrosis

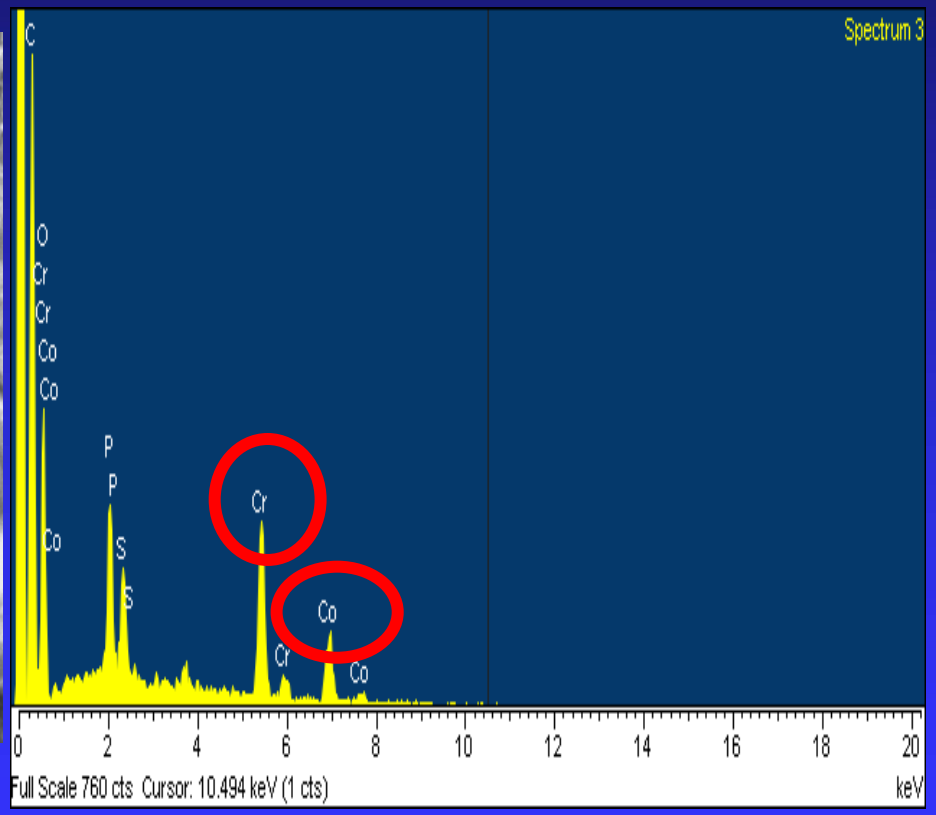


Kwon *et al.* Biomed Materials 2009

SEM/EDX

- Metal particle aggregates within macrophages
- Co and Cr particles



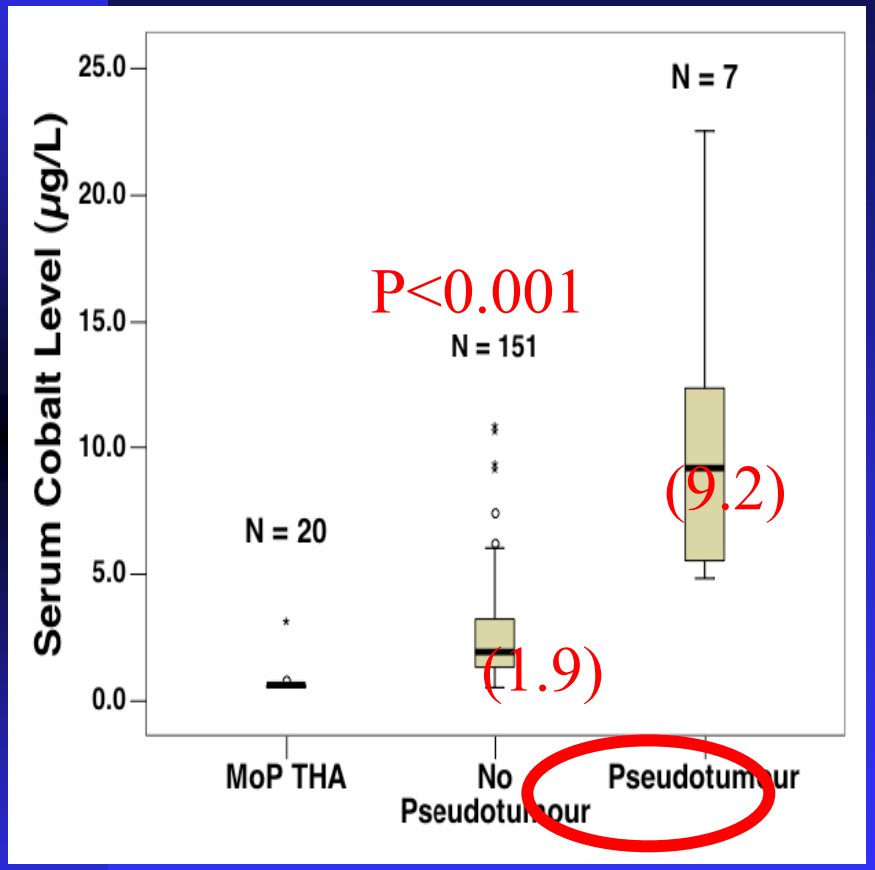


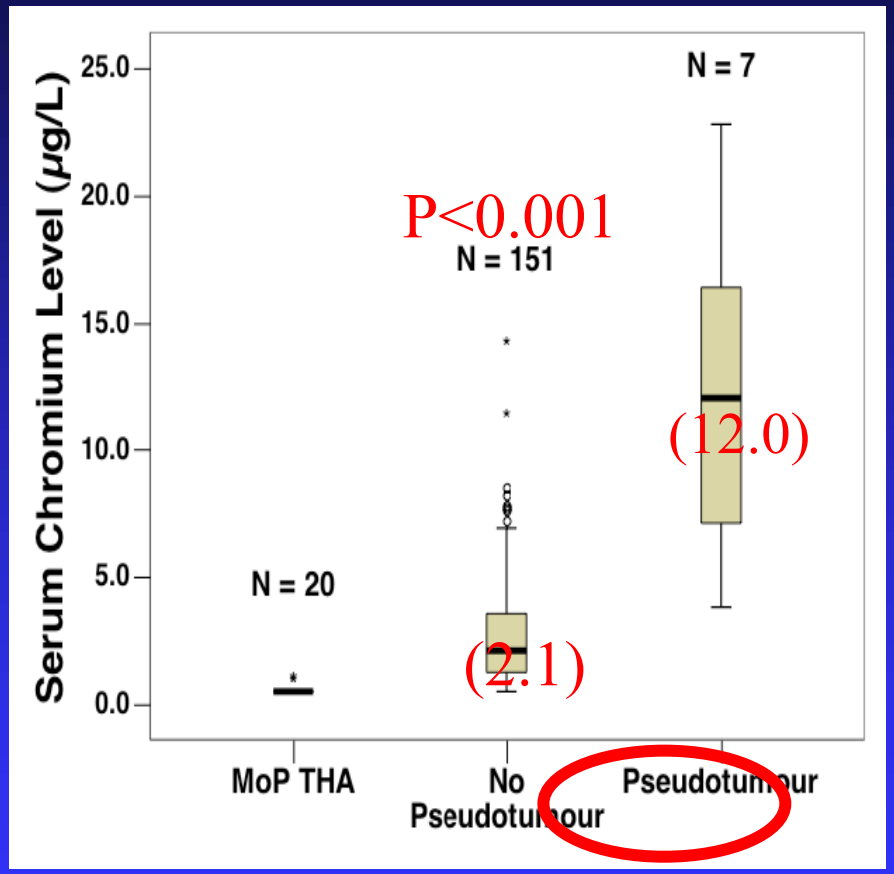
Kwon *et al*. JoA 2010

Is There Increased Metal Wear Debris?

- Elevated Metal ion levels
- Increased implant wear occurring at MoM articulation

Elevated Serum Metal Ion Levels





Kwon *et al.* JoA 2011

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Metal Ion Levels

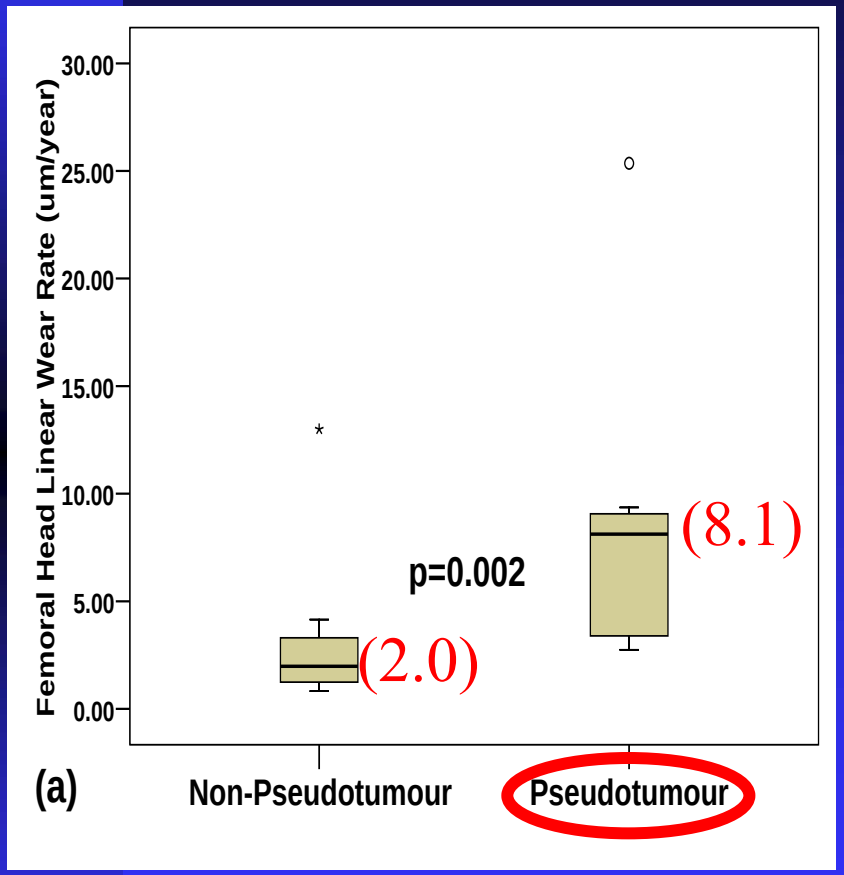
- Cobalt and Chromium ion levels
  - Most pseudotumours detected with the levels higher than reported from well-functioning MoMHRA
- Elevated serum metal ion correlated with MoMHRA wear (De Smet *et al*. JBJS A 2008)
- ? Pseudotumours due to increased wear

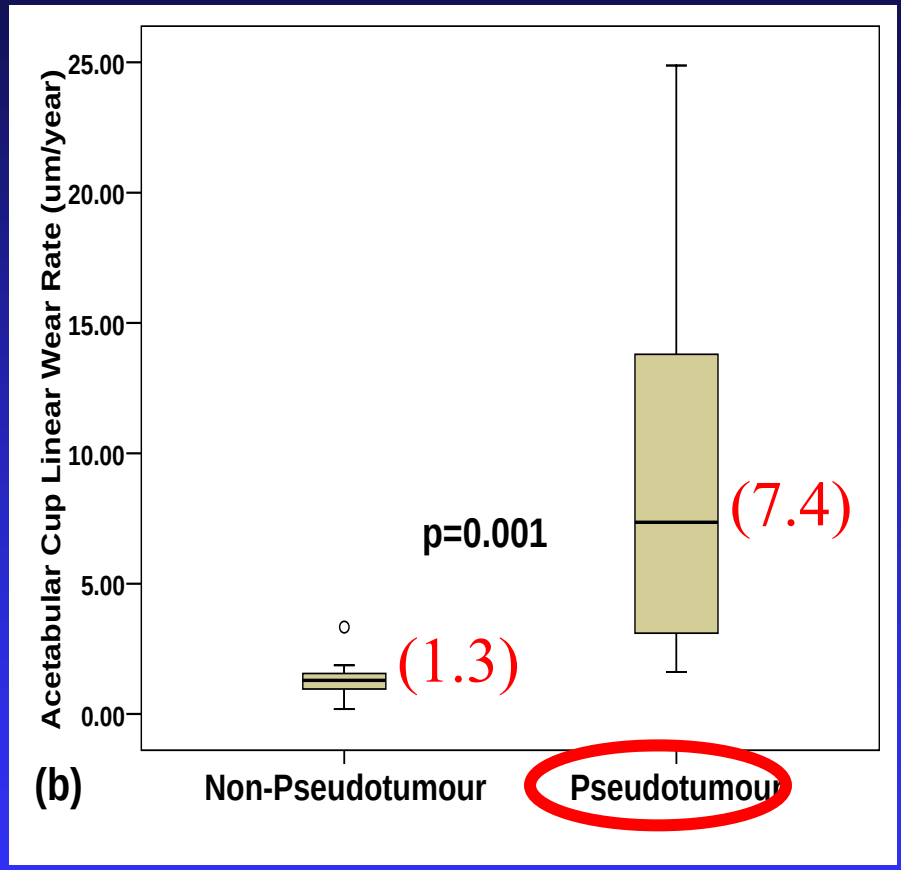
Wear Analysis of Retrieved Implants

	Pseudotumour Group	Non-Pseudotumour Group
Number of implants	8	22
Gender (female: male)	8:0	13:9
Mean Age (years)	52 (range 39 - 65)	54 (range 45 - 70)
Mean Time *in vivo* (years)	3.6 (range 1.1 – 6.6)	2.3 (range 1.0 – 5.8)
Mean Femoral component size (mm)	47 (range 42 - 50)	49 (range 44 - 54)
Implant Type	BHR (5) Conserve Plus (2) Cormet (1)	BHR (18) Conserve Plus (4)

Kwon *et al.* JBJS Br 2010

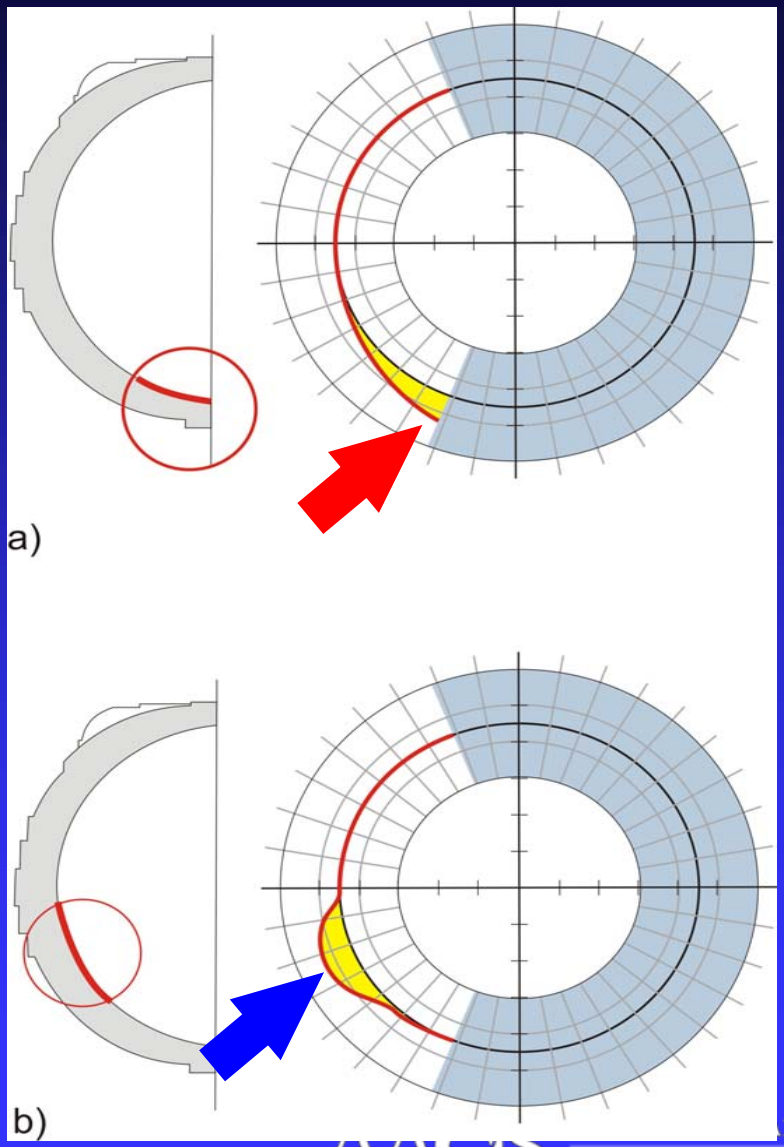
Linear Wear Rate





Kwon *et al.* JBJS Br 2010

Wear Pattern: Edge Loading

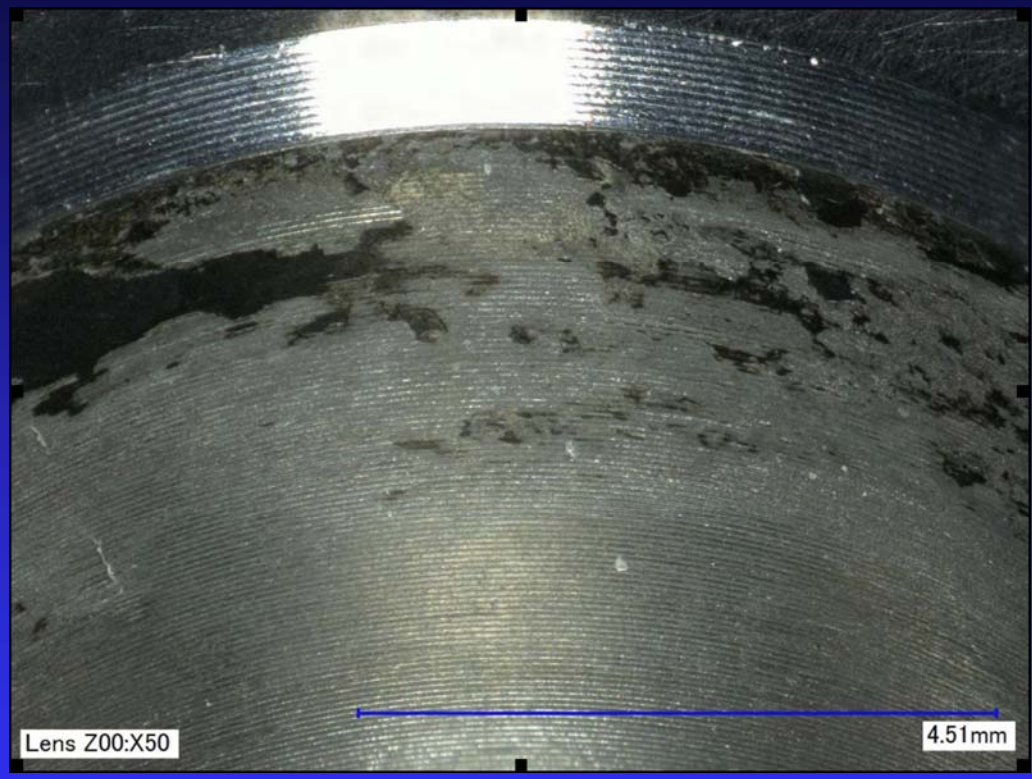


- EL observed in all acetabular implants in the pseudotumour group
- EL observed in one implant in the non-pseudotumour group (p=0.03)

Kwon *et al.* JBJS Br 2010

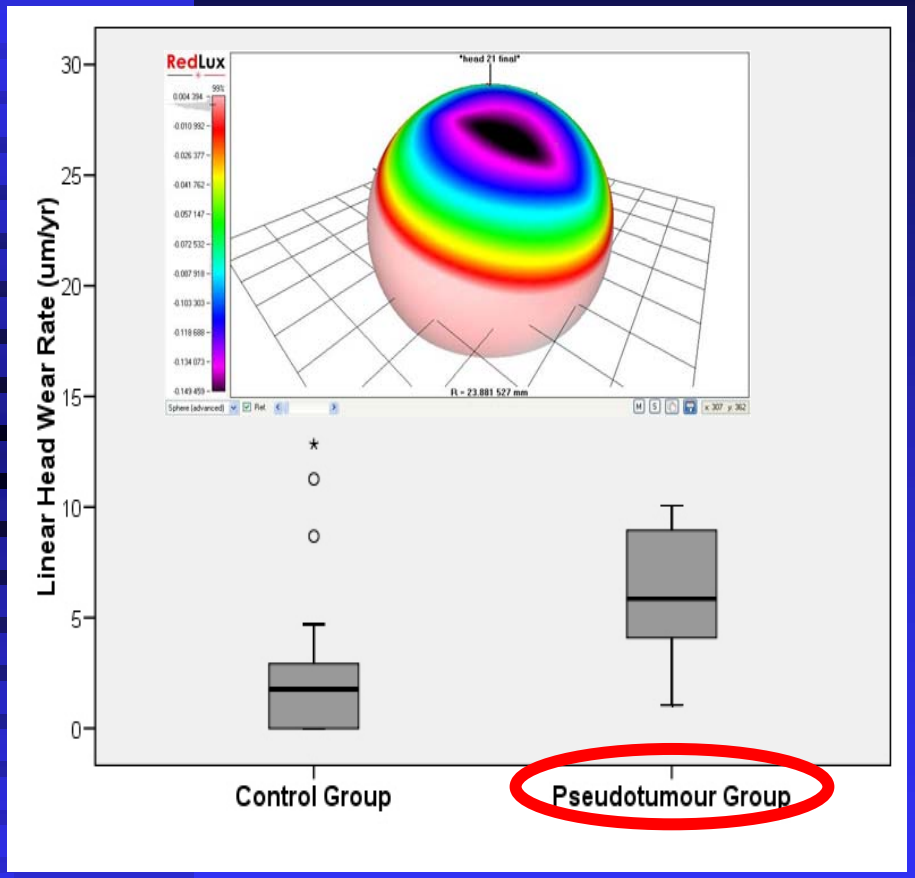
Tribocorrosion in MoM THA

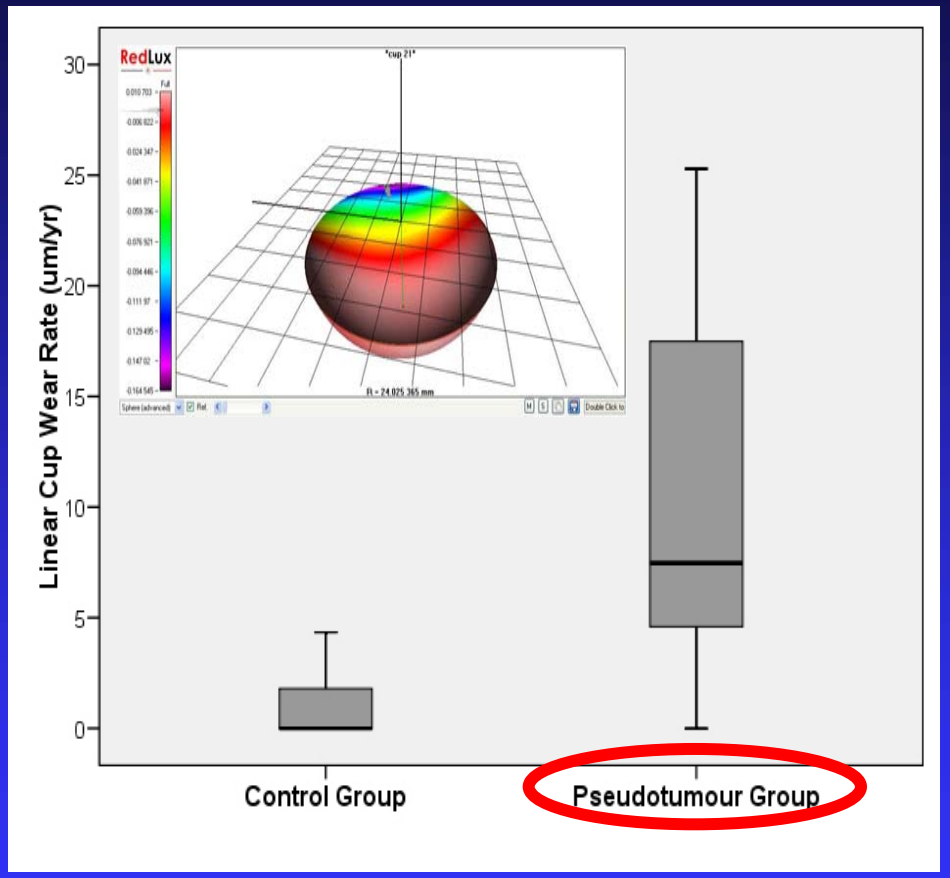
Matthies *et al.*
Paper #357, AAOS 2012
Takamura *et al.*
Paper #562, AAOS 2012
Urban *et al.*
Poster #P012, AAOS 2012
Engh *et al.*
Poster #P068, AAOS 2012



- 48% - 100% extreme taper corrosion association with ridges on female taper surface
- Common with ASTR

‘Low’ Wear Pseudotumours





Glyn-Jones, Roques, Kwon *et al.* JBJS Am 2011

‘Low’ Wear Pseudotumours

- Matthies *et al*. CORR 2012
- Matthies *et al*. Paper #304, AAOS 2012
  - Retrieval study of 105 MoM hips
  - No significant association between many pseudotumours and component wear rates
  - Suggesting important patient susceptibility factors

How to Evaluate Painful MoM

- Systematic Approach
  - Clinical Hx and Physical Exam
  - Radiographs
  - Lab Tests: ESR/CRP/Joint Aspiration
  - Cobalt and Chromium ion levels
  - Cross Sectional Imaging
    - Ultrasound, MRI

Table. Differential Diagnosis for the Painful MoM Hip Arthroplasty

Extrinsic to the Hip
Spine disease: stenosis, disc herniation, spondylolysis, or spondylolisthesis
Peripheral vascular disease
Complex regional pain syndrome
Psychologic disorder
Hernia (femoral, inguinal)
Peripheral nerve injury (eg, sciatic, femoral, meralgia paresthetica)
Malignancy or metastases
Metabolic bone disease (eg, Paget disease, osteomalacia)
Intrinsic to the Hip
Intracapsular/implant related
Infection
Loosening
Instability/subluxation
Periprosthetic fracture
Adverse soft tissue reaction/hypersensitivity
Extracapsular
Trochanteric bursitis
Iliopsoas tendonitis

Kwon, Jacobs *et al*. JoA 2012

Systematic Evaluation Guidelines

Parameters/Categories

- Implant type (Hip resurfacing, Stemmed MoM femoral head <36mm and ≥36mm, Recalled)
- Symptoms symptomatic *vs.* asymptomatic
- Follow up
  - Frequency and duration (? for life of implant)
- Cross-Sectional Imaging
  - MRI *vs.* US
  - Indications
- Metal ions levels
  - Threshold (? >7ppb)
  - Indication for repeat testing
- Indications for revision surgery
  - Imaging abnormal
  - Metal ions rising

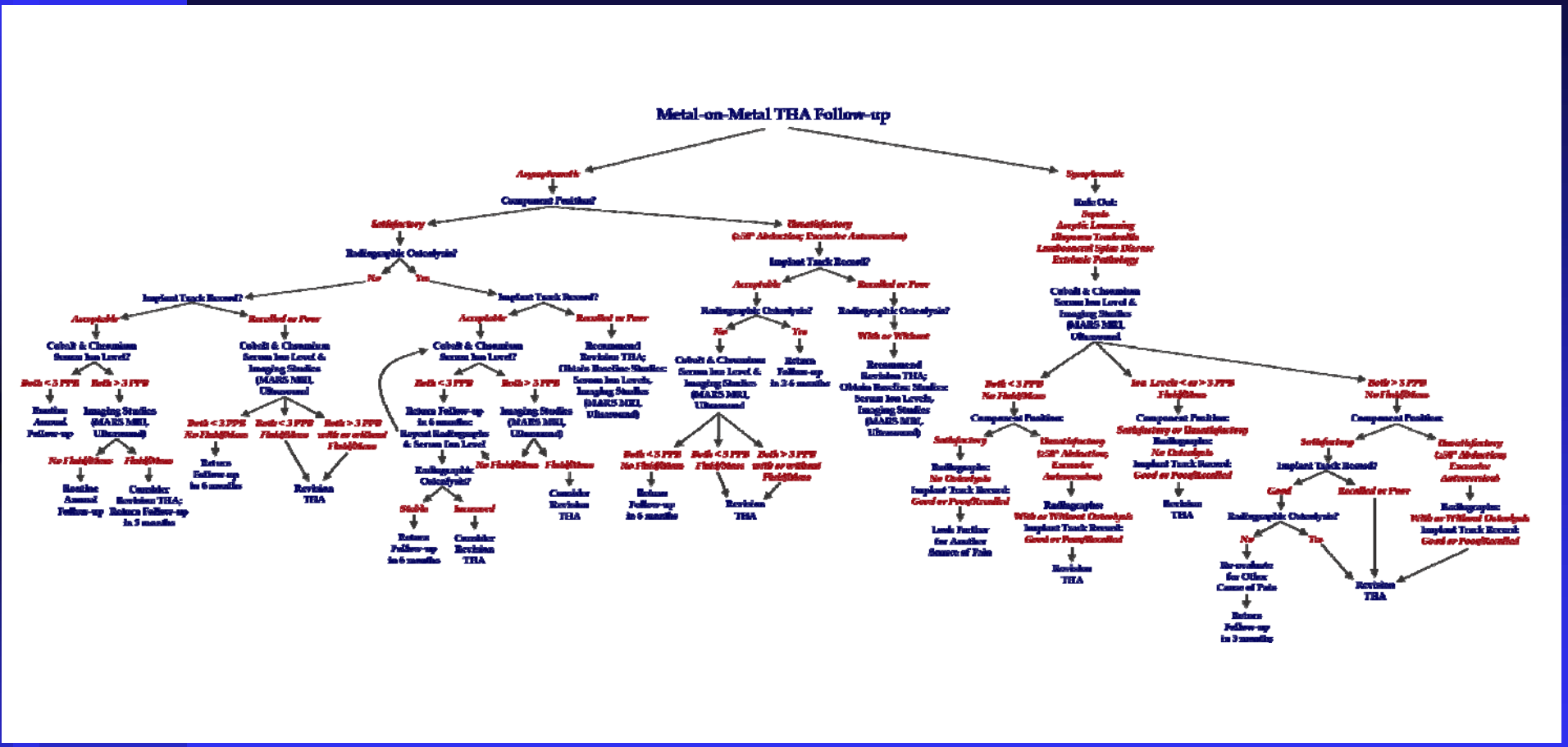
Appendix

Management recommendations for patients with metal-on-metal hip replacement implants

	MoM hip resurfacing (no stem)		Stemmed MoM total hip replacements – femoral head diameter <36mm		Stemmed MoM total hip replacements – femoral head diameter ≥36mm		DePuy ASR™ hip replacements (all types)	
	Symptomatic patients	**Asymptomatic patients**	**Symptomatic patients**	**Asymptomatic patients**	**Symptomatic patients**	**Asymptomatic patients**	**Symptomatic Patients**	**Asymptomatic patients**
Patient follow-up	Annually for not less than five years	According to local protocols	Annually for not less than five years	According to local protocols	Annually for life of implant	Annually for life of implant	Annually for life of implant	Annually for life of implant
Imaging: MARS MRI or ultrasound	Recommended in all cases	**No** - unless concern exists for cohort or patient becomes symptomatic	Recommended in all cases	**No** - unless concern exists for cohort or patient becomes symptomatic	Recommended in all cases	Recommended if blood metal ion levels rising	Recommended in all cases	Recommended in all cases
1st blood metal ion level test	**Yes**	**No** - unless concern exists for cohort or patient becomes symptomatic	**Yes**	**No** - unless concern exists for cohort or patient becomes symptomatic	**Yes**	**Yes**	**Yes**	**Yes**
Results of 1st blood metal ion level test	*Blood metal ion level >7ppb indicates potential for soft tissue reaction*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction*	*If blood metal ion level >7ppb then second blood test required 3 months later*	*Blood metal ion level >7ppb indicates potential for soft tissue reaction*	*If blood metal ion level >7ppb then second blood test required 3 months later*
2nd blood metal ion level test	**Yes** - 3 months after 1st blood test if result was >7ppb		**Yes** - 3 months after 1st blood test if result was >7ppb		**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb	**Yes** - 3 months after 1st blood test if result was >7ppb
Results of 2nd blood metal ion level test	*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*		*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*	*If blood metal ion levels rising - further investigation required including imaging*	*Blood metal ion level >7ppb indicates potential for soft tissue reaction especially if greater than previously*	*Blood metal ion level rising indicates potential for soft tissue reaction*
Consider need for revision	If imaging is abnormal and/or blood metal ion levels rising		If imaging is abnormal and/or blood metal ion levels rising		If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising	If imaging is abnormal and/or blood metal ion levels rising

Notes and guidance on next page

MHRA Medical Device Alert/2012/0008



Lombardi *et al.* AAOS Scientific Exhibit 2012

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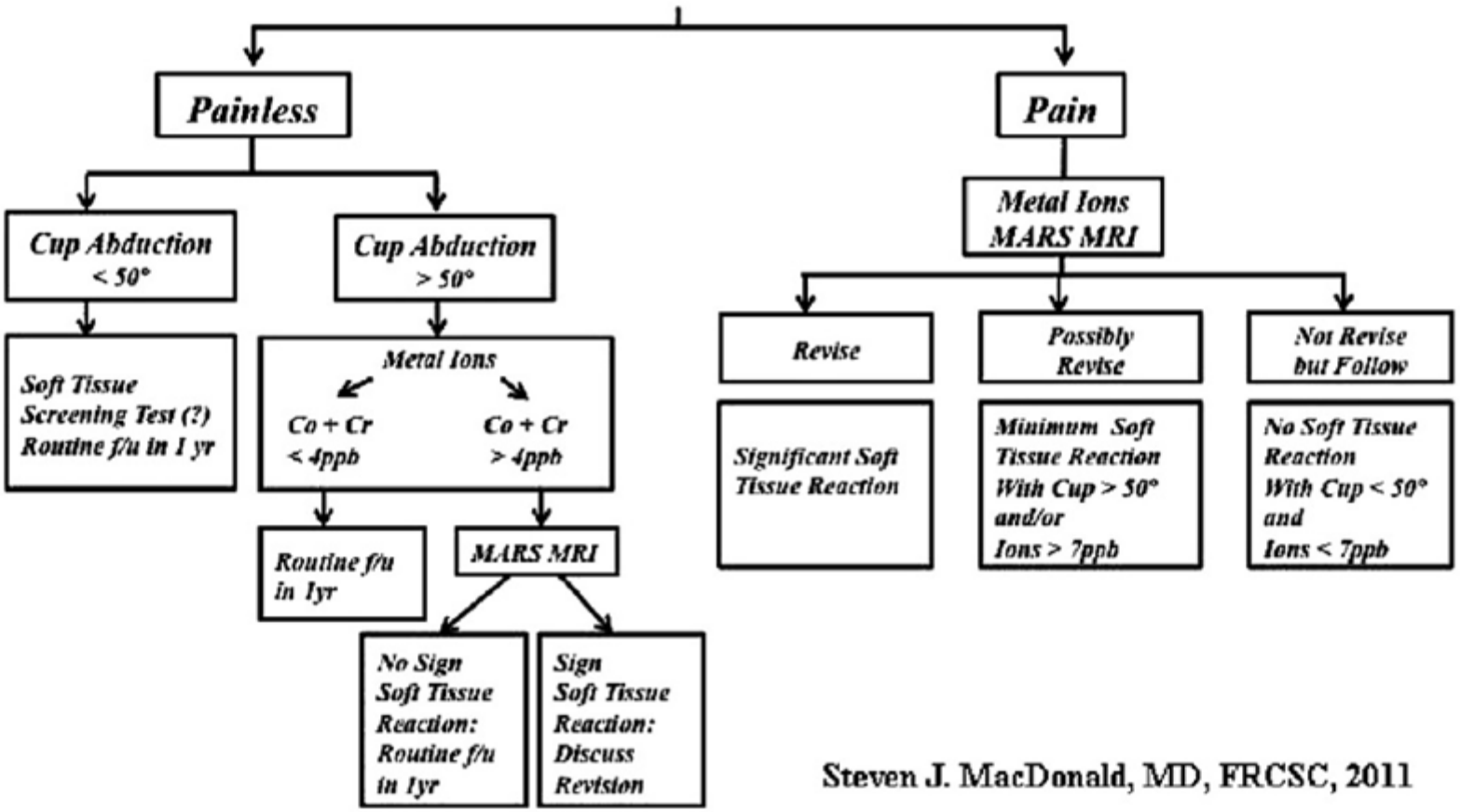

Fig. 1. A diagnostic algorithm for evaluation and treatment for patients with MoM hip arthroplasty.

Kwon, Jacobs *et al.* JoA 2012

Systematic Evaluation Algorithm

- Concerted Initiative
  - AAOS
  - AAHKS
  - Hip Society
- MoM Task Force
  - Currently working on developing algorithm

Summary

- Histological features and MoM implant failure not been fully established
  - ALVAL-like features observed in failures from mechanical causes
- Further standardize histological evaluation of periprosthetic tissues
  - metal allergy *vs.* wear-related necrosis
- Currently, no standardized validated clinical tests to screen or diagnose metal hypersensitivity

Summary

- Spectrum of Clinical Presentations & Etiologies
  - Majority Symptomatic
  - ? Minority 'Asymptomatic'
  - Majority with High-Wearing ± Corrosion (Elevated Metal Ion Levels)
  - ? Minority with Low-Wearing ('Low' Metal Ion Levels)
- Dose-Dependency *vs.* Patient Susceptibility (Hypersensitivity)
- Complex interplay of Implant, Patient and Surgical factors

Summary

- Edge-Loading in MoM
  - Responsible for Localised Excessive Wear
- Low Threshold for Further Evaluation
  - Metal Ion Levels and MARS MRI
- Evidence-based systematic evaluation guidelines
  - Continue to develop with updated evidence
- Further Research required to further identify Multi-Factorial Etiology of Local Adverse Tissue Reactions

Thank You

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Resources from the Societies

- Patient Information at OrthoInfo.org
- Technology Overview
- Participation in ASTM and ISO
- Member education

- ORS.org – Clinical Research symposia and forums
- Patient Information
- Educational programs

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