

THE ROLE OF STANDARDS IN
BIOMEDICAL DEVICE
TESTING: A SURGEON'S
PERSPECTIVE

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Perspectives

- **Standards Committee Chairman (ASTM F04)**
- **Biomedical Researcher**
- **Orthopaedic Surgeon**

Medical Technological Advancements

- **Rapidly accelerating**
- **Sources of improved understanding of disease**
- **Sources of improved treatment modalities**

Medical Technological Advancements

- **Novel materials**
- **Computer-assisted surgery**
- **Growth factors (BMP, TGF- β)**
- **Tissue Engineering**
- **Minimally invasive surgery**
- **Molecular-based diagnostics**
- **Implantable sensors/nanotechnology**

Medical Technological Advancements

- **Many have unproven clinical outcomes**
- **Financial stress on health care systems**
 - ◆ **Clinical Research**
 - ◆ **Reimbursement**
- **Challenge for regulators**
- **Adverse impact on patient safety?**

PATIENT SAFETY

■ IOM Reports

- *To Err is Human, 1999*
- *Crossing the Quality Chasm, 2001*

■ Nationwide Movement

- **Public - National Patient Safety Foundation**
- **Private - Leapfrog Group**
- **Governmental - President: “Top Priority”**

To Err is Human

Institute of Medicine Report

Patient Deaths Due to Medical Errors

➤ “at least 44,000”

➤ “possibly as high as 98,000”

Figures Imply Medical Errors

➤ 8th leading cause of death (1977 figures)

➤ Aids 16,516

➤ Breast Cancer 42,297

➤ MVA's 43,458

How Does the Public Perceive Health Care in the US

- **Satisfied with health care: 8% (1 in 12)**
- **Confidence in getting care in the future:**
 - **NO: 15% (good health)**
 - **NO: 24% (Fair or poor health)**

How Does the Public Perceive Health Care in the US

- Individual or family member experienced error: 22%
 - 23 million people
- Wrong medication or dose: 16%
 - Serious: 22% (8 million people)

Commonwealth Fund, April 2002

**More recent research indicates
that 40% of Patients Have
Experienced a Medical Error
(directly or through a family
member or friend)**

New England Journal of Medicine, 12/12/02

SIX SIGMA GOAL

**To set tolerance levels for
defective products/
services at fewer than
3.4 defects per million unit
opportunities.**

Where Does Medicine Fall in This Analysis?

- **Medicine, Generally: 4 SIGMA**
 - **6,210 errors/million events**
- **Medications: 2 SIGMA**
 - **308,000 errors/million events**

Health Care Error Rate = 1%

Ten Times the Error Rate of
Industry

Patient Safety: Medical Devices

- **83.7 Adverse Medical Device Events (AMDE) per 1000 admissions using more extensive modes of surveillance than previous studies.**
- **For ICD-9 coding-based flags for hospital admission, orthopaedic devices comprised 25%, vascular devices 19%, and dialysis 15%.**
- **“The high rate of AMDEs suggests that AMDEs are an important patient safety issue...”**

Samore et al JAMA 291:325, 2004.

Benefits of Standards for Biomedical Engineering Materials and Devices

- **Regulatory**
- **Legal**
- **Commerce**
- **Research**
- **Development**
 - ◆ **Technology Transfer**
- **Clinical Practice**
 - ◆ **Patient Safety**

**THE BIOLOGICAL
REVOLUTION MEETS
ADULT RECONSTRUCTIVE
ORTHOPAEDIC SURGERY**

NIH Consensus Conference 1994

“Total hip replacement is an option for nearly all patients with diseases of the hip that cause chronic discomfort and significant functional impairment. Most patients have an excellent prognosis for long-term improvement in symptoms and physical function.”

Survivorship

THA

- 9 years 94 - 97%
- 17 years 81- 86%

Swedish Registry 1979 - 1996

Total Hip Arthroplasty

- 1996 - 138,000
(81,000 F; 57,000 M)
- 2030 (proj.) - 248,000
(142,000 F; 106,000 M)
- National Center for Health Statistics

Osteolysis and Aseptic Loosening: Etiology

- **Mechanical Factors**
 - Design
 - Fixation
 - Surgical Technique
- **Biological Factors**
 - Particulate Load
 - Host Response
 - Anatomic Variability
- **Mechanical/Biological Synergy**

Osteolysis and Aseptic Loosening: Proposed Solution

REDUCE VOLUMETRIC WEAR

- “Conventional UHMWPE”: 30 - 120 mm³/yr
- Ceramic-on-ceramic bearings: 0.04 mm³/yr
- Metal-on-metal bearings: 6 mm³/yr
- X-linked UHMWPE: 55 mm³/yr

Osteolysis and Aseptic Loosening: Proposed Solution

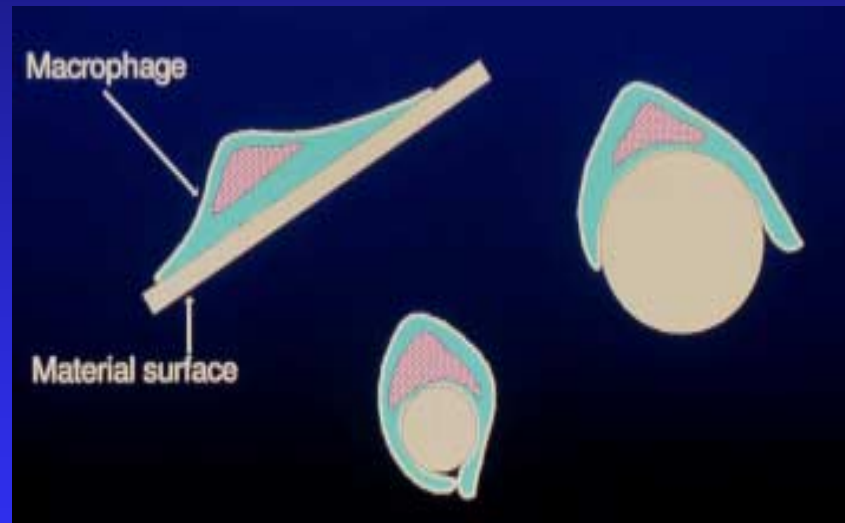
REDUCE VOLUMETRIC WEAR

Is this sufficient?

PATHOGENESIS

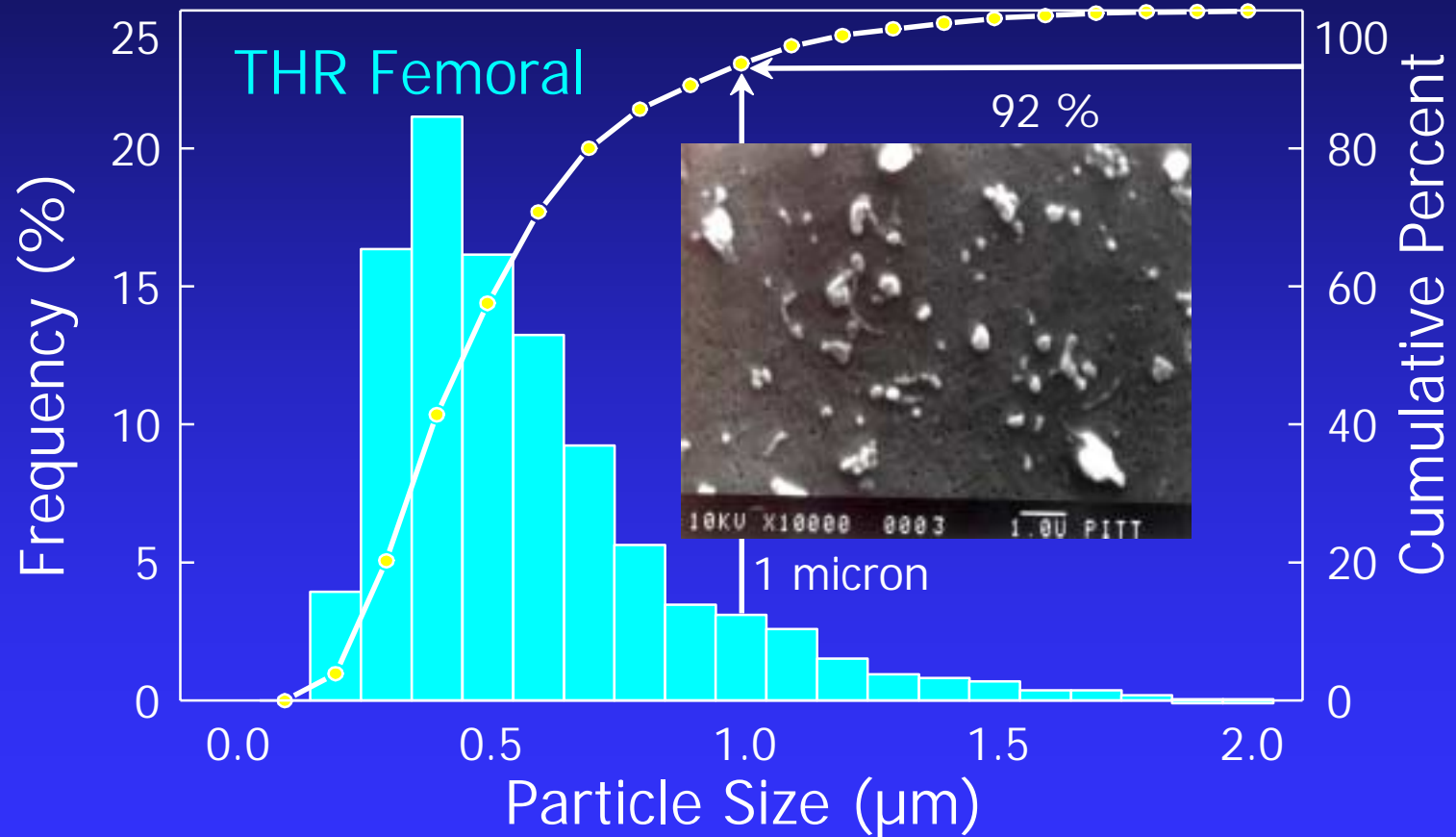
Question:

What are the variables that determine the bioreactivity of a particle?



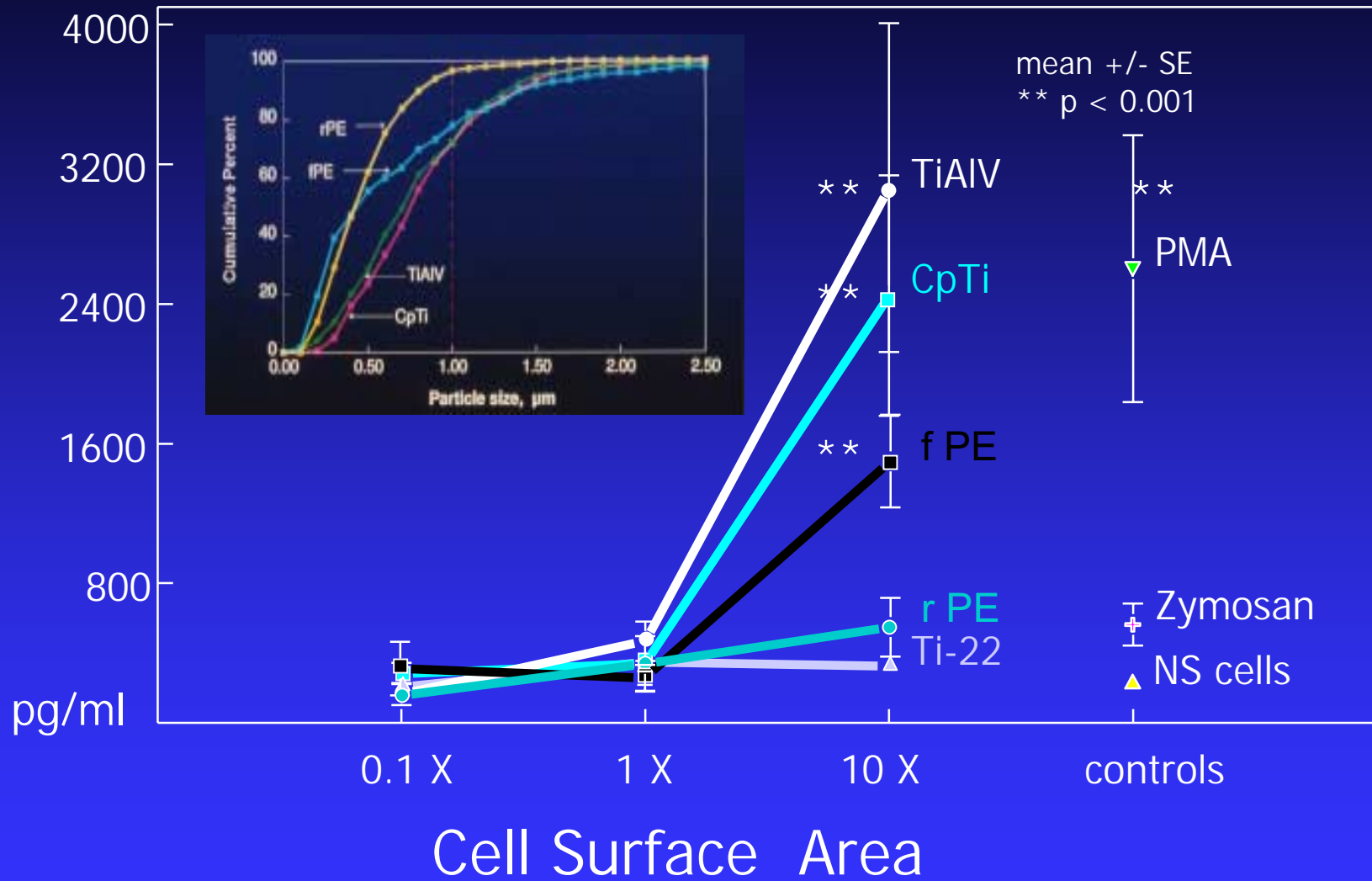
Macrophage / Particle Interactions: Effect of Size, Composition and Surface Area. Shanbhag, A.S., Jacobs, J.J., Black, J. Galante, J.O., and Glant, T.T. *J Biomed Mater. Res.* 28:81-90, 1994

Retrieved UHMWPE Debris



Ref: Shanbhag, Jacobs, Glant, et al., *J Bone Joint Surg* (1994)

Interleukin-1 β Release



Ref: Shanbhag, Jacobs, Black, et al., *J Orthop Res* (1995)

Fundamental Principle of Cell/Particle Biology

- **The cellular response to particle challenge is size, composition and dose-dependent**

Highly Crosslinked UHMWPE Debris

- Ilgen et al (ORS 2003)
 - ◆ Particle size
 - ◆ Highly crosslinked 0.11 μm
 - ◆ Conventional 0.20 μm
 - ◆ Cell response
 - ◆ TNF- α , VEGF
 - ◆ No difference between highly crosslinked and conventional

Highly Crosslinked UHMWPE Debris

- Ingham et al (ORS 2003)
 - ◆ Increased cellular response to highly crosslinked UHMWPE vs. conventional
 - ◆ TNF- α

UHMWPE Debris: Effect of Morphology

- Sieving et al (ORS 2003)
 - ◆ Particles of similar area
 - ◆ Cell response determined by proliferation assay
 - ◆ Order of reactivity (descending)
 - ◆ Rough fibrillar > rough round, smooth fibrillar > smooth round

Net Biological Activity

The product of the normalized biological activity (“specific biological activity” of Fisher) per particle and the number of particles of that size, integrated over all size ranges.

Debris From Metal-Metal Bearings



In Vivo Degradation Products

- **Particles**
- **Free metallic ions**
- **Colloidal organometallic complexes**
- **Inorganic metal salts/oxides**
- **Organic storage forms (eg. Hemosiderin)**

Doorn et al JBMR 42:103, 1998

- ◆ 13 patients with M/M prostheses
- ◆ *In situ* 7 - 300 months
- ◆ TEM
 - Most particles < 50 nanometers
 - Range: 6 – 834 nanometers

Metal-on-Metal Particles

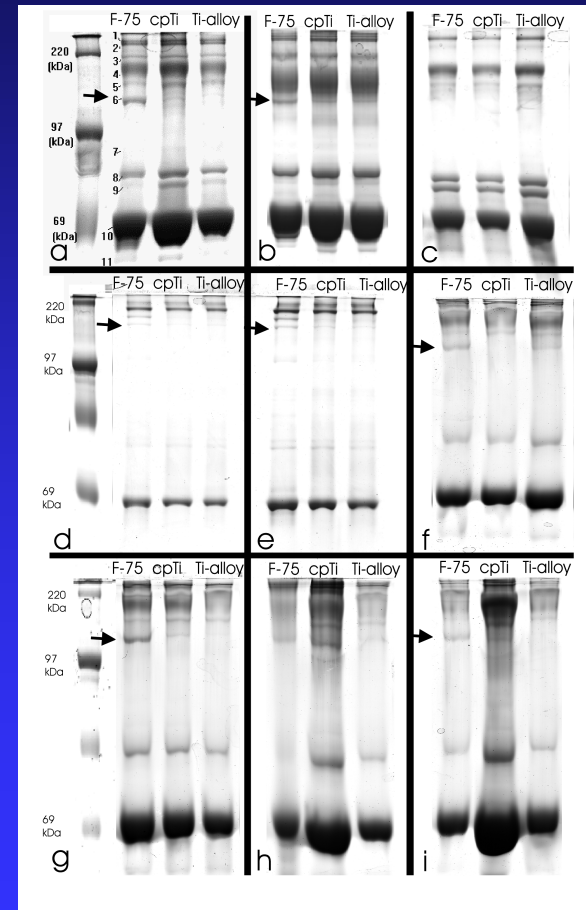
Willert CORR 1996

- Cr/Co ratio in periprosthetic tissue (~1/2 in alloy)
 - ◆ 9:1 (AAS), 5:1 (ICP-MS)
- Suggests a preponderance of corrosion products in the tissue

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Hallab et al JBMR 2003

- Differential protein adsorption for CoCr vs. Ti particles
- ~ 140 kD protein associated with CoCr alloy



Challenges/Opportunities for the 21st Century: Pathogenesis

- Particle characterization
- Composition of adsorbed proteins
- Particle isolation
- Particle fabrication
- “Designer” wear debris

DIAGNOSTICS

Individual Bioreactivity

Paradigm: TNF- α Promoter

- TNF- α gene located within major histocompatibility complex
- Several polymorphisms identified inside TNF- α promoter

***TNF2* allele correlated with
enhanced spontaneous and
stimulated TNF- α production**

Louis et al *Clin Exp Immunol* 1998; 401-406

**-238A allele correlated with
osteolysis and aseptic loosening**

Wilkinson et al *J Bone Min Res* (2003)1995-
2001

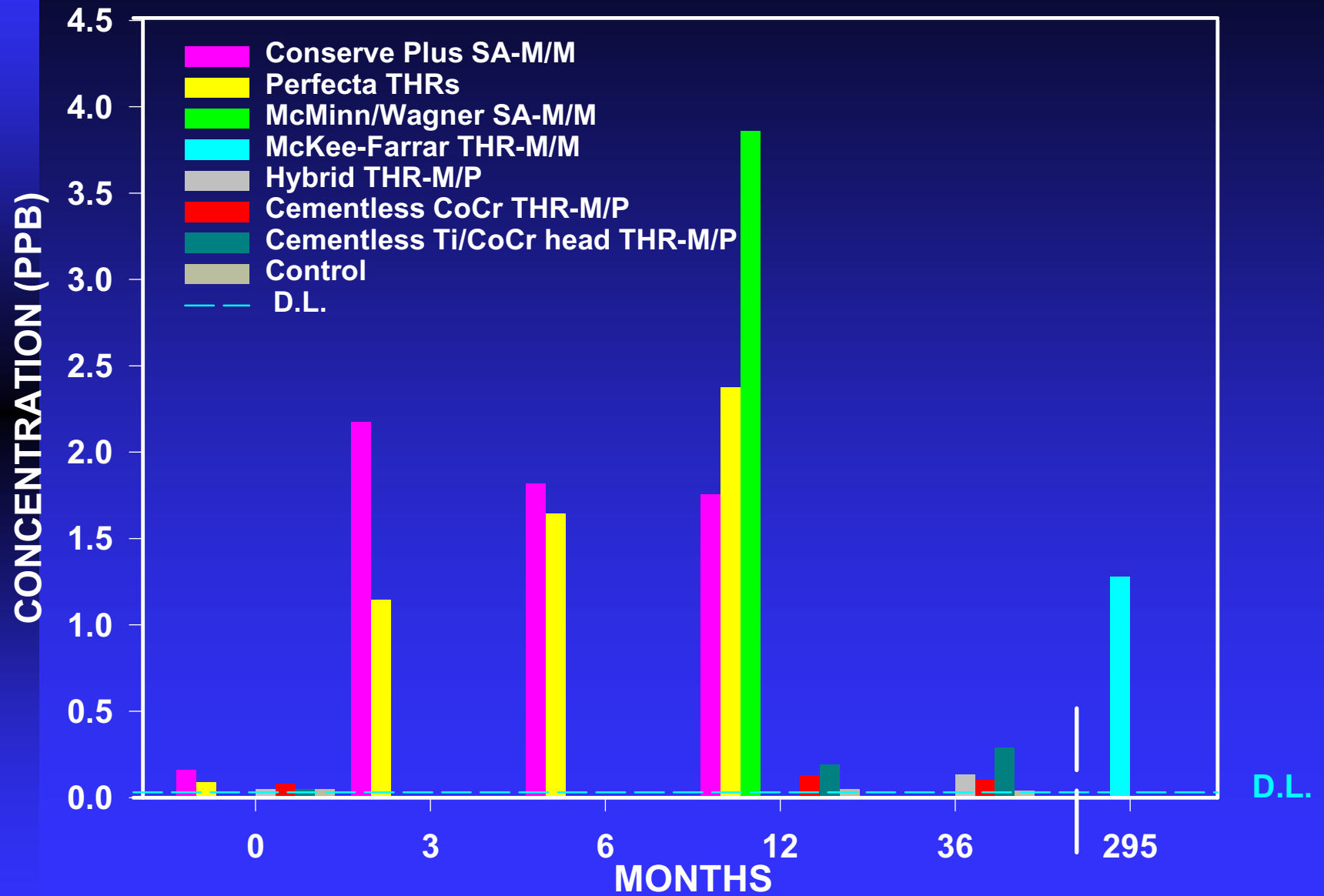
Hypersensitivity Reactions

- 10 – 15% of population have cutaneous metal allergy (Type IV-DTH)
- 25% in patients with TJR
- 50% in patients with failed TJR

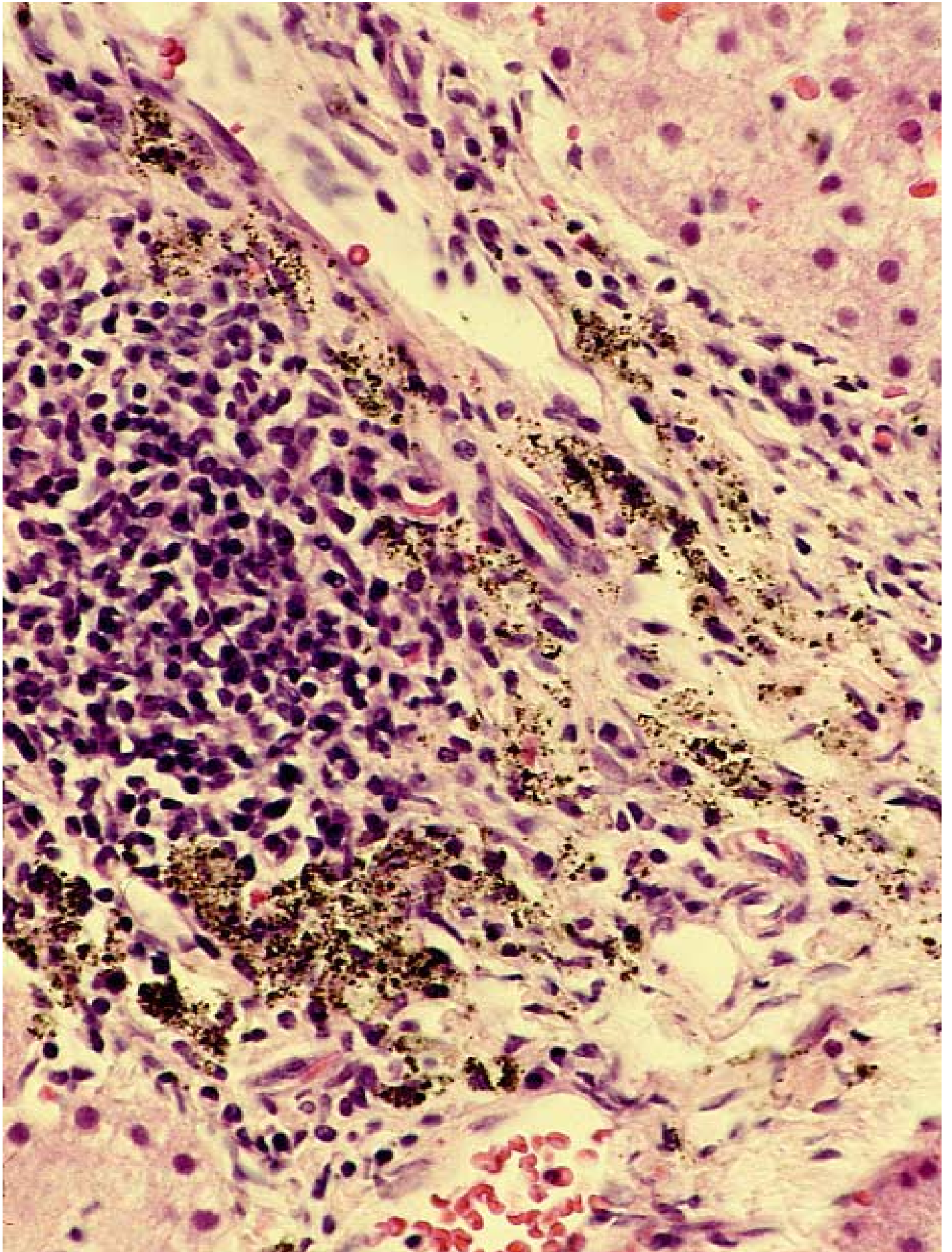
Question:

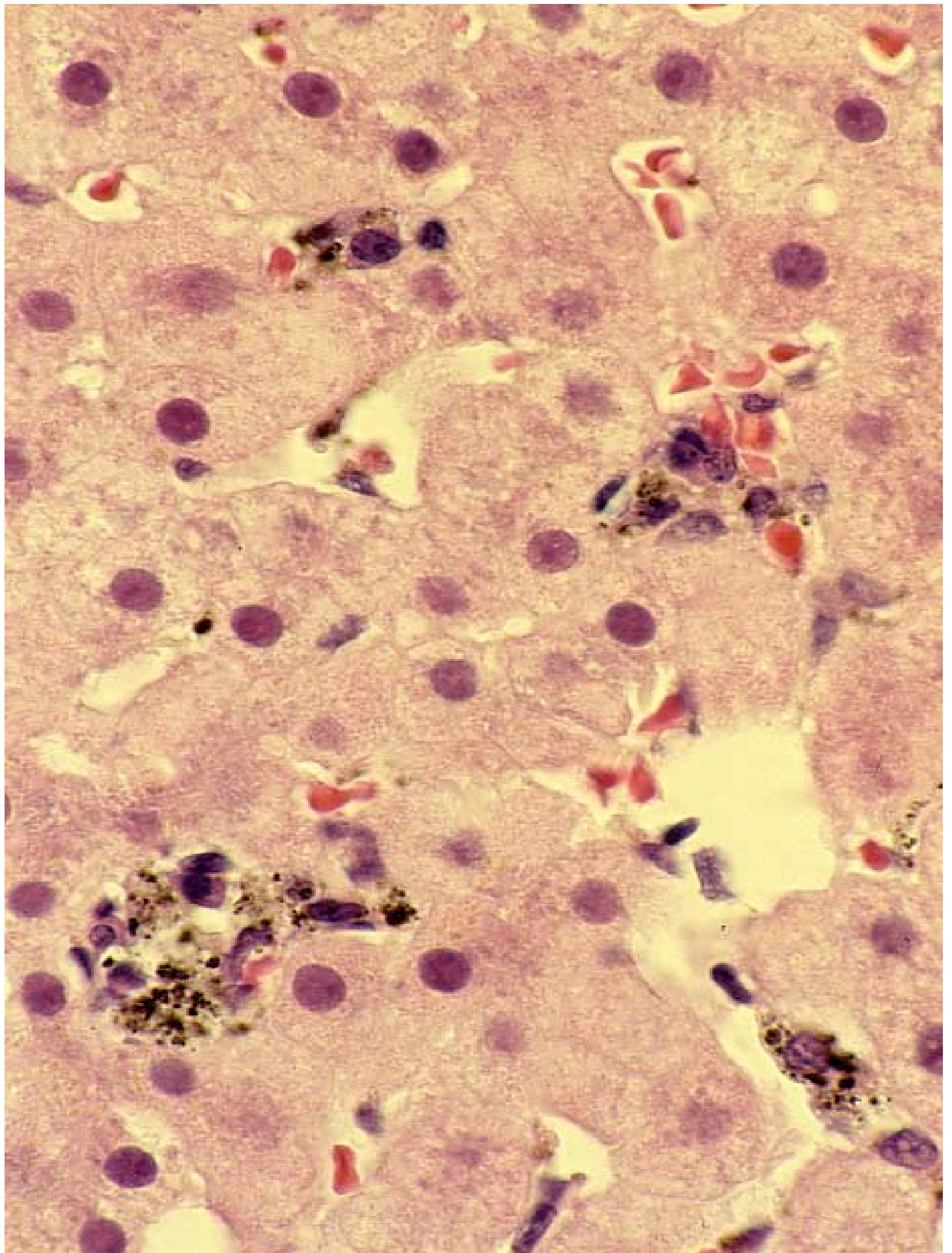
**Are there systemic markers of
prosthetic performance?**

SERUM CHROMIUM (ng/ml)









Serum Titanium (ng/ml or ppb)

■ Subject	1203
■ Primary Ti-alloy THR	4
■ Control	< 2

Serum Titanium > 8 ppb

- **> 750 measurements THR and TKR**
- **Aseptic Loosening**
- **Multiple Implants**
- **Accelerated Wear Against CFRPE**
- **PE “Wear-Through”, Including
Delaminated Metal-Backed Patellae**

Normal THR < 4 ppb; Controls < 2 ppb

Leopold et. al.

J Arthrop 15:938, 2000

- **67 yo Male, cementless TKR 1988**
- **Excellent function for 10+ years
(HSS Knee Score 96 - 100)**
- **Presented in 1999 with effusion,
mild pain with standing**
- **No palpable or audible crepitus**

Leopold et. al.

J Arthrop 15:938, 2000

- **X-rays: mild screw lysis, no loosening, skyline view unchanged from pre-op**
- **Ti levels:**
 - ◆ **1990 2.4 PPB**
 - ◆ **1998 5.5 PPB (contralateral TKR in 1992)**
 - ◆ **1999 536.8 PPB**

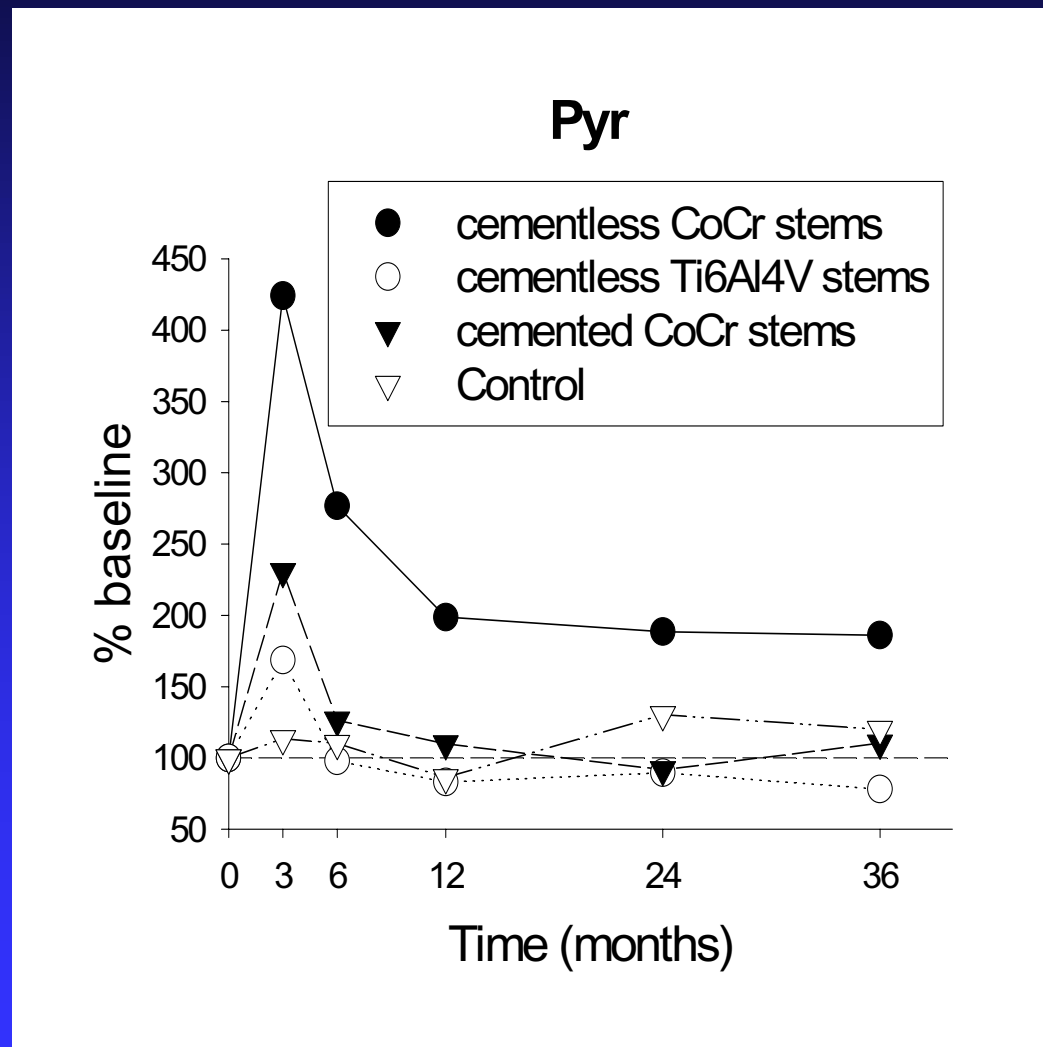
Well-Functioning MG TKR: 3.34 PPB (<2.1 - 5.28);

Failed Metal-Backed Patella: 135.6 PPB (24.1 - 716.9)

Markers of Bone Turnover and TJR

- Tauber et al. (1989): vitamin D metabolites and implant loosening
- Joering et al. (1993): serum collagen metabolites after THR and TKR
- Schneider et al. (1998): cross-links and implant loosening
- Granchi et al. (1998): serum cytokines and implant loosening

Qureshi et al J Bone Miner Res 2002



Wilkinson et al: JOR 2003

- **Subjects with femoral loosening had higher levels of the bone resorption marker N-telopeptides of type-I collagen**
- **? Early diagnosis of osteolysis/loosening**
- **? Response to pharmacological treatment of osteolysis**

Other Putative Markers of Prosthetic Performance

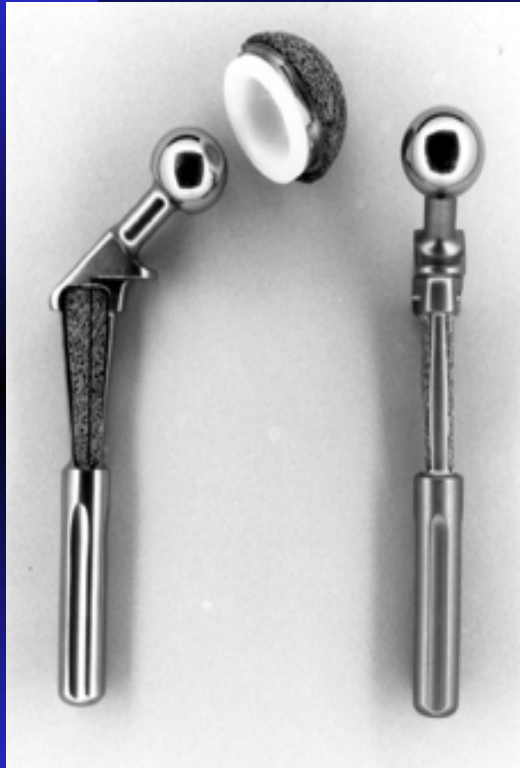
- Pro-inflammatory cytokines
 - ◆ IL-1, IL-6, TNF- α
- Chemokines
 - ◆ MCP-1, IL-8
- Matrix metalloproteinases
 - ◆ Collagenase, stromelysin
- Osteoclast activators
 - ◆ RANKL
- Gene microarrays

Challenges/Opportunities for the 21st Century: Diagnostics

- **Develop genetic databases on patients with TJR to correlate performance with genotype**
- **Develop reliable preoperative screening tests to dictate material selection in patients undergoing TJR**
- **Develop diagnostic tests which are reliable early surrogate markers for prosthetic performance**

THERAPEUTICS

Treatments to Inhibit Osteolysis



- Canine THR Model
 - ◆ Controls (n=8)
 - ◆ Debris (n=8)
 - ◆ Debris + Rx (n=8);
 - ◆ Alendronate (Fosamax, 5 mg/day)

Wear debris introduced intra-op



Rx started on post-op day 7



End-point: 24 weeks post-op

Inhibiting Osteolysis

- Alendronate (Fosamax, Merck)
 - ◆ (5 mg orally /day)
 - ◆ 24 weeks post-op.
 - ◆ Shanbhag et al. Clin Ortho (1997)

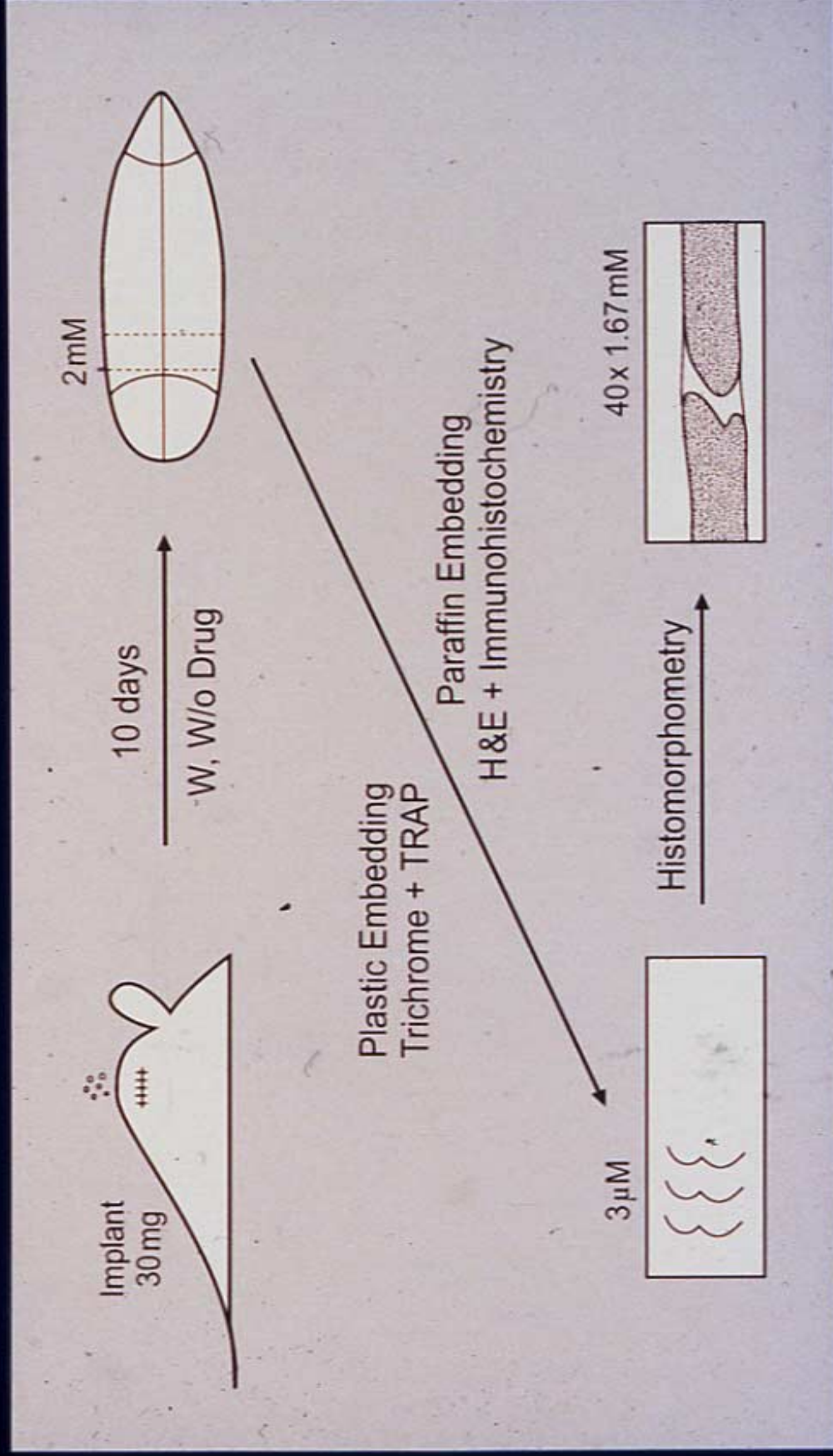


Debris



Debris+Rx

Mouse Calvaria Model of Wear Debris Induced Osteolysis



Drug Efficacy in Preventing Wear Debris-Induced Osteolysis in the Mouse Calvaria Model

<u>Drug</u>	<u>Anti-resorptive effects</u>	<u>Anti-osteoclastogenic effects</u>
Alendronate ¹	++	++
Pentoxifylline ¹	++	+
Celecoxib ²	++	++
Etanercept ³	++	+
RANK:Fc ⁴	++++	++++

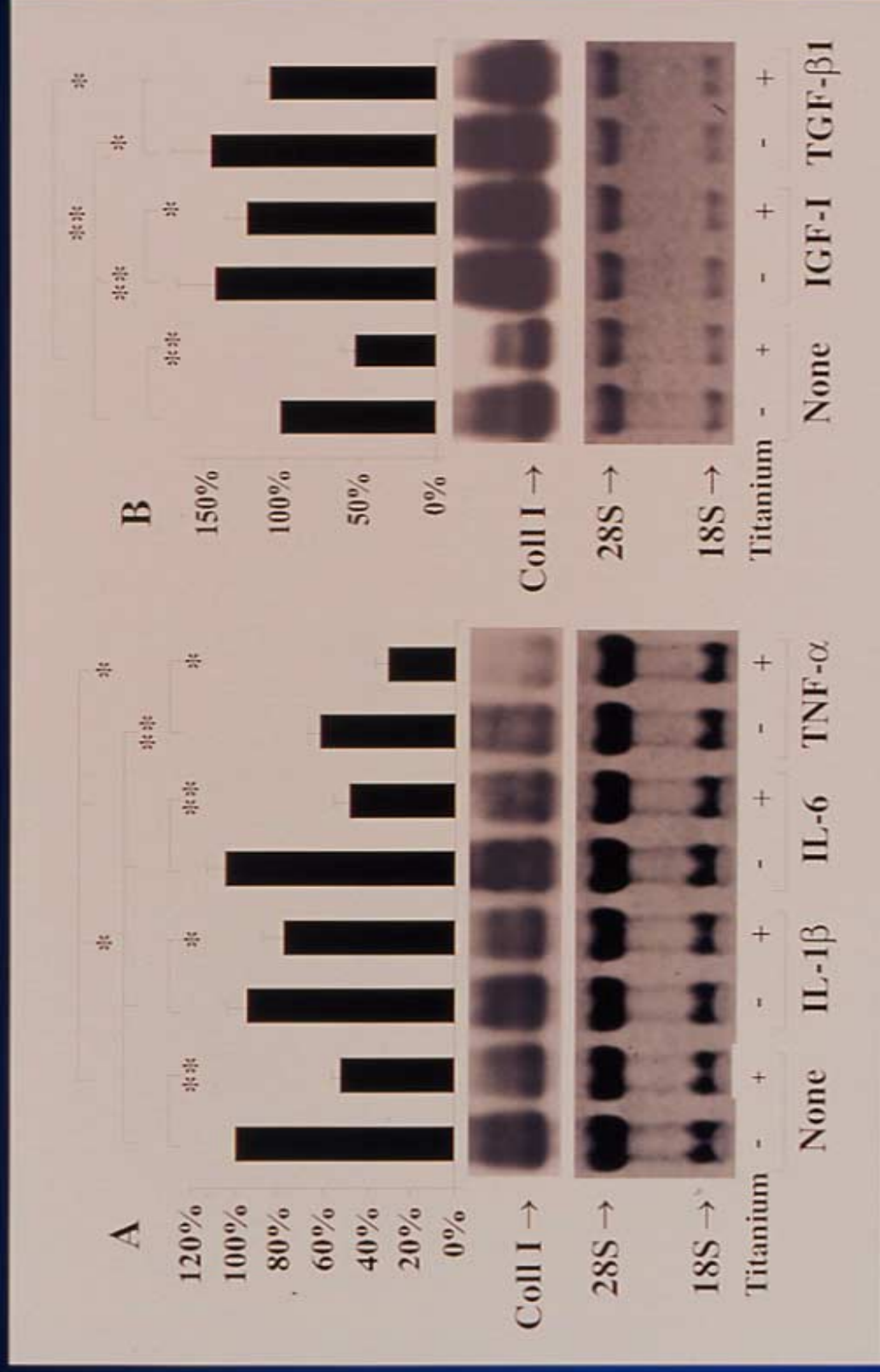
1) Schwarz, E.M. et al, *J. Ortho. Res.*, 18, 849-855 (2000).

2) Zhang, X. et al, *J. Bon. Min. Res.*, 16, 4 (2001)

3) Childs, L. M. et al, *J. Bon. Min. Res.*, 16, 338-347 (2001)

4) Childs, L. M. et al, *Arth. Rheum.*, 43, S206 (2000)

The expression of procollagen $\alpha 1[I]$ mRNA in human osteoblasts



Challenges/Opportunities for the 21st Century: Therapeutics

- Establish translational research protocols to determine if putative therapeutic/preventive agents are effective in animal models of TJR
- Establish clinical research protocols to determine if agents effective in animal models are effective in humans
- Develop novel methods of periprosthetic drug delivery, including gene therapy, to minimize systemic impact of treatment

ASTM Committee F04:Divisions

- **I. Resources**
- **II. Orthopaedic Devices**
- **III. Medical/Surgical Devices**
- **IV. Tissue Engineered Medical Products**
- **IX. Administrative**

Division I: Resources

- **Polymeric Materials**
- **Metallurgical Materials**
- **Ceramic Materials**
- **Composite Materials**
- **Materials Test Methods**
- **Biocompatibility Test Methods**
- **Device Retrieval Analysis**

Division II: Orthopaedic Devices

- **Osteosynthesis**
- **Arthroplasty**
- **Spinal Devices**

Division III: Medical/Surgical Devices

- **Cardiovascular Standards**
- **Neurosurgical Standards**
- **Plastics and Reconstructive Surgery**
- **Medical/Surgical Instruments**
- **Urological Materials and Devices**
- **GI Endoscopes**
- **Cotton Products for Medical Use**

Division IV: Tissue Engineered Medical Products

- **Classification and Terminology for TEMP_s**
- **Biomaterials and Biomolecules**
- **Cells and Tissue Engineered Constructs**
- **Assessment**
- **Safety**

Division IX: Administration

- **Executive**
- **Awards**
- **Planning**
- **US TAG ISO/TC 150**
- **Finance**
- **ISO/TC 168**
- **ISO/TC 194**
- **Editorial**

Classification & Balance



Technical Committees are balanced. There are no more Producer voters than User & General Interest voters. This ensures the development of fair, consensus, technically sound documents. It protects the documents from bias.

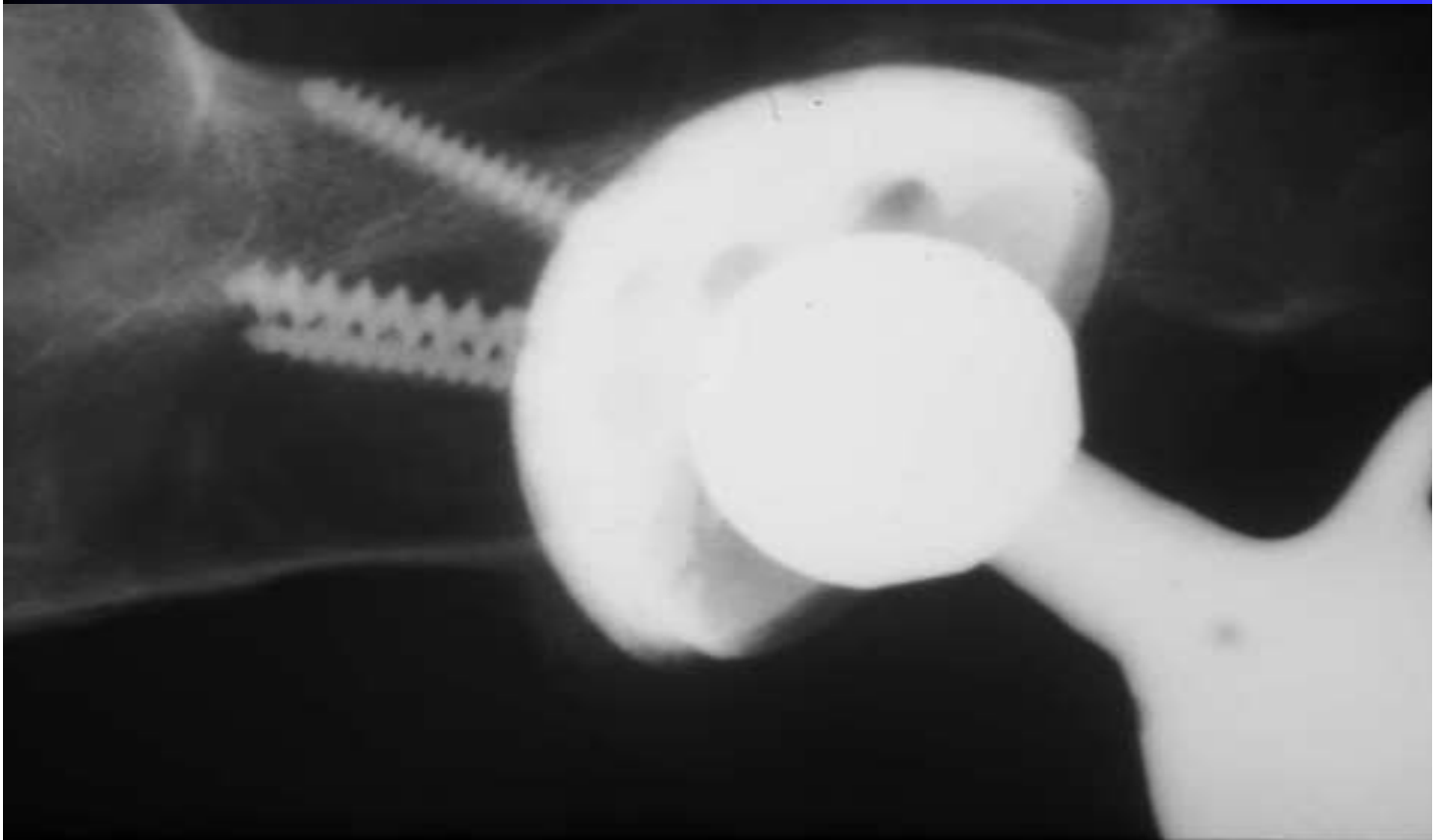
FDAMA (1997)

- **SEC. 204. DEVICE STANDARDS.**

“...the Secretary shall, by publication in the Federal Register, recognize all or part of an appropriate standard established by a nationally or internationally recognized standard development organization for which a person may submit a declaration of conformity in order to meet a premarket submission requirement or other requirement under this Act to which such standard is applicable”.

Types of ASTM Documents

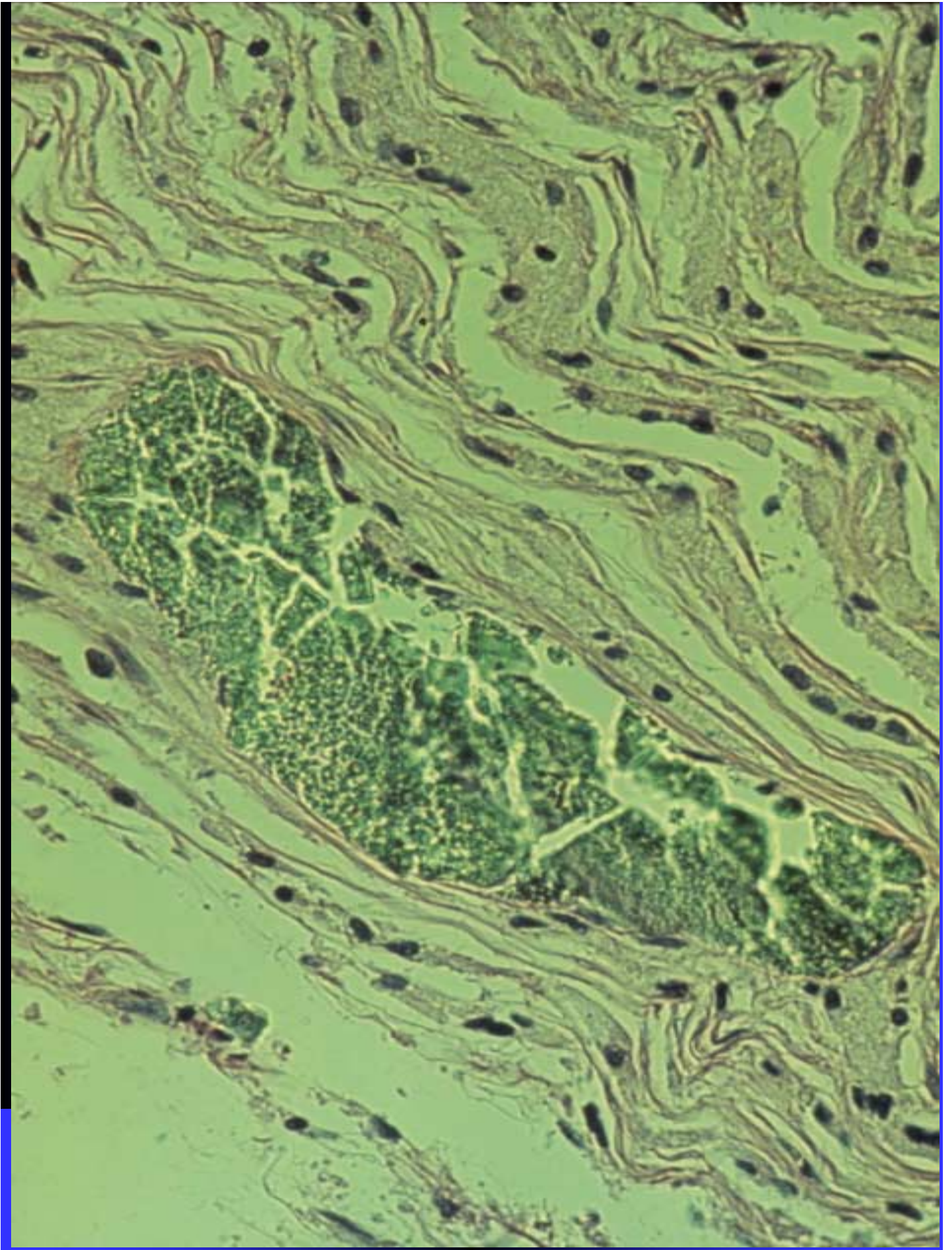
- **Classification**
- **Guide**
- **Practice**
- **Specification**
- **Terminology**
- **Test Method**



ASTM F 561-97

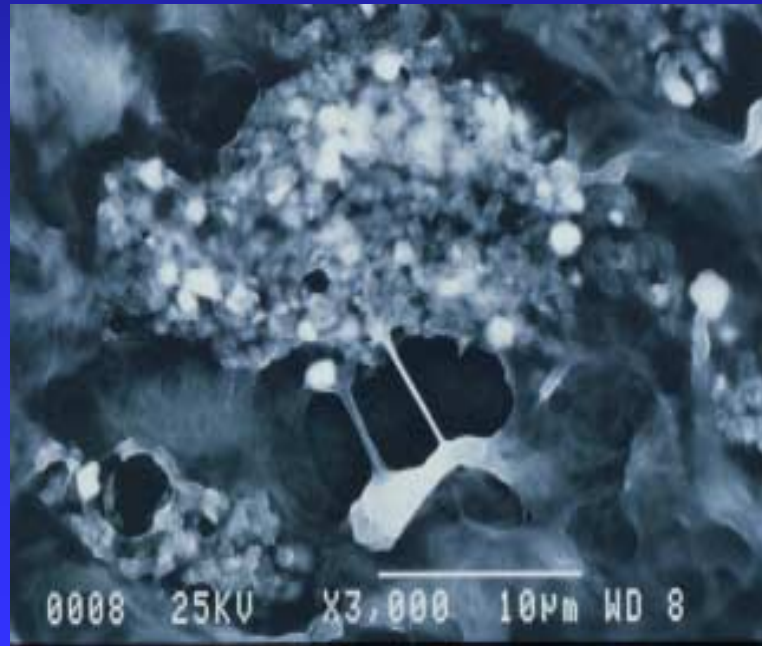
- Practice for Retrieval and Analysis of Implanted Medical Devices, and Associated Tissues





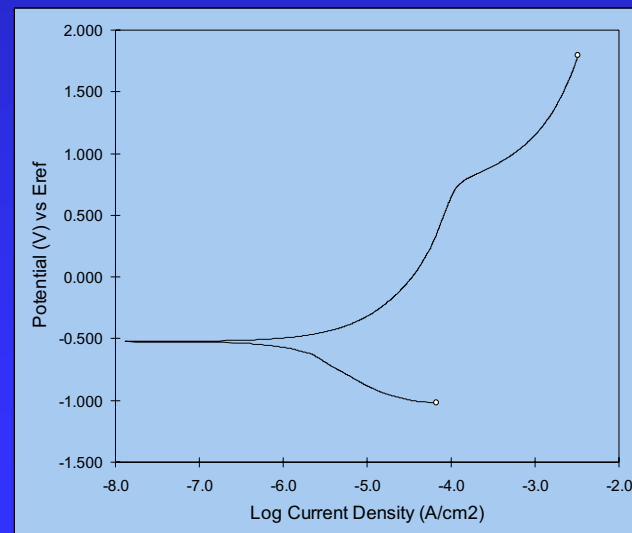
ASTM F 1877-98

■ Standard Practice for Characterization of Particles

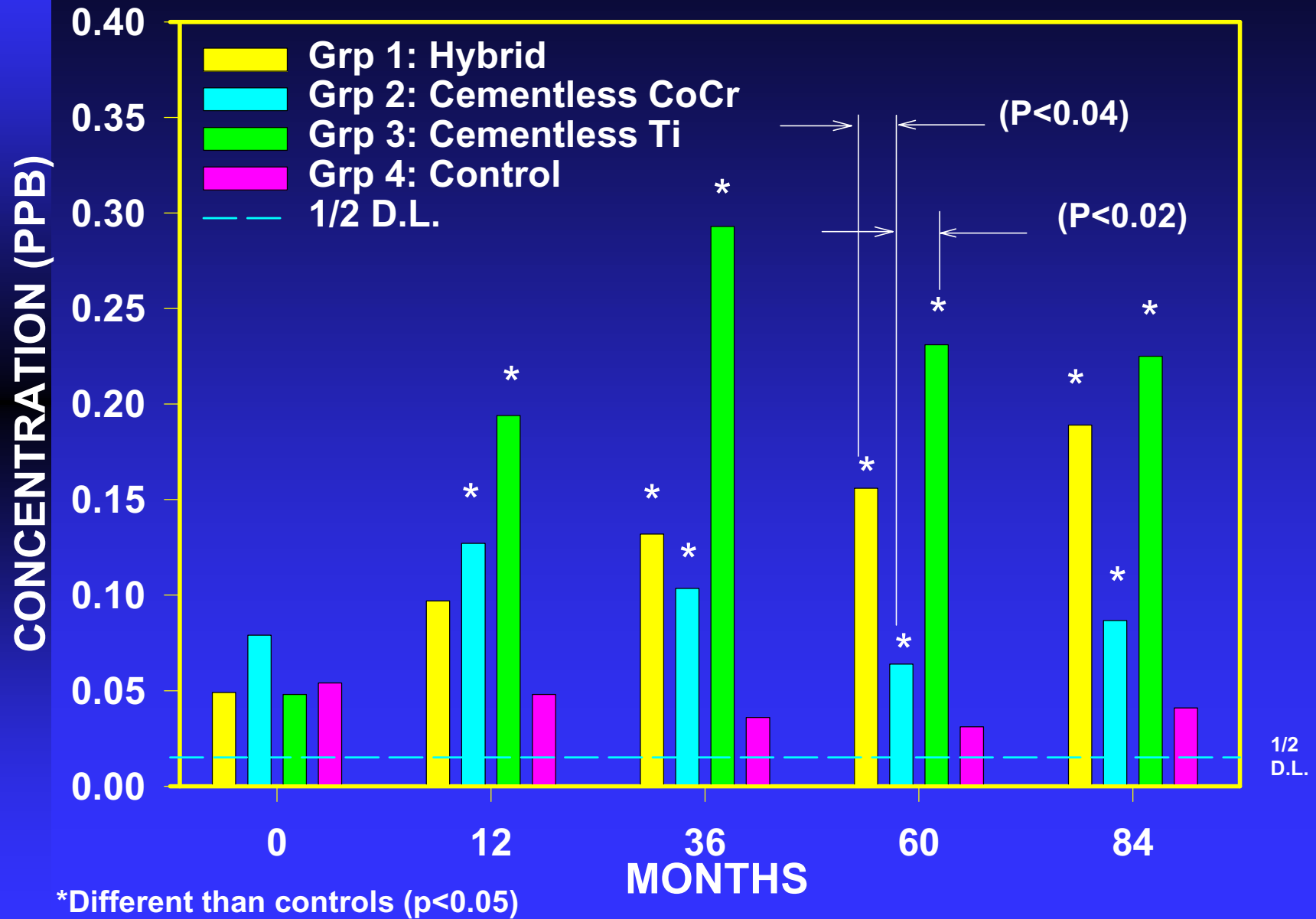


ASTM F 1875-98

■ Standard Practice for Fretting Corrosion Testing of Modular Implant Interfaces: Hip Femoral Head-Bore and Cone Taper Interface



SERUM CHROMIUM



ASTM F 1537-00

- **Standard Specification for Wrought Cobalt-28 Chromium-6 Molybdenum Alloys for Surgical Implants**

Benefits of Standards for Biomedical Engineering Materials and Devices

- **Regulatory**
- **Legal**
- **Commerce**
- **Research**
- **Development**
 - ◆ **Technology Transfer**
- **Clinical Practice**
 - ◆ **Patient Safety**

Acknowledgements

- **NIH/NIAMS AR39310**
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100 YEARS
OF
INDEPENDENCE

