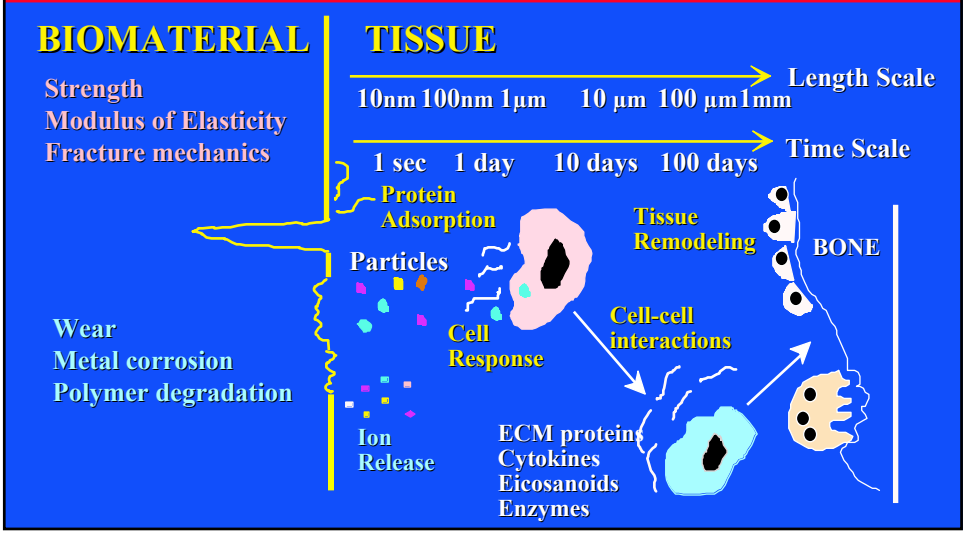
Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System

2.782J/3.961J/BEH.451J/HST524J

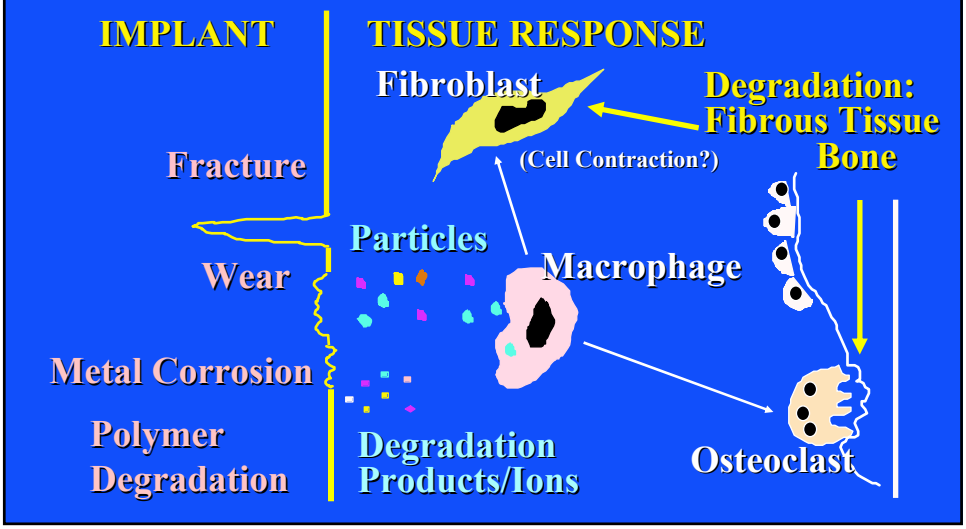
BIOCOMPATIBILITY: LOCAL AND SYSTEMIC EFFECTS

M. Spector, Ph.D

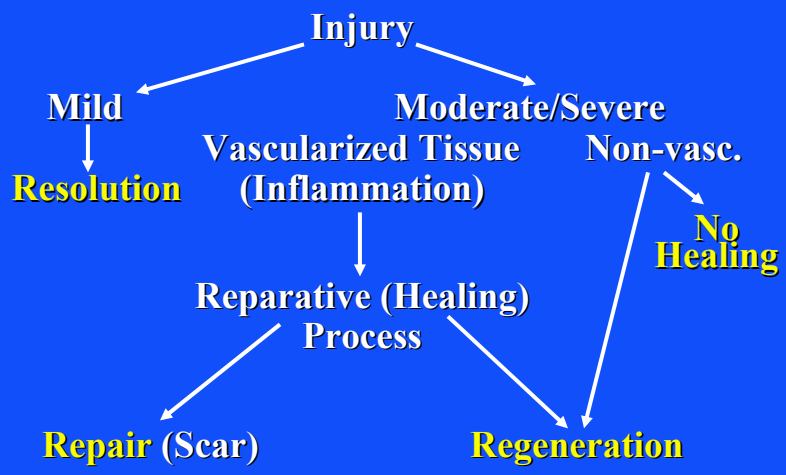
BIOMATERIALS-TISSUE INTERACTIONS

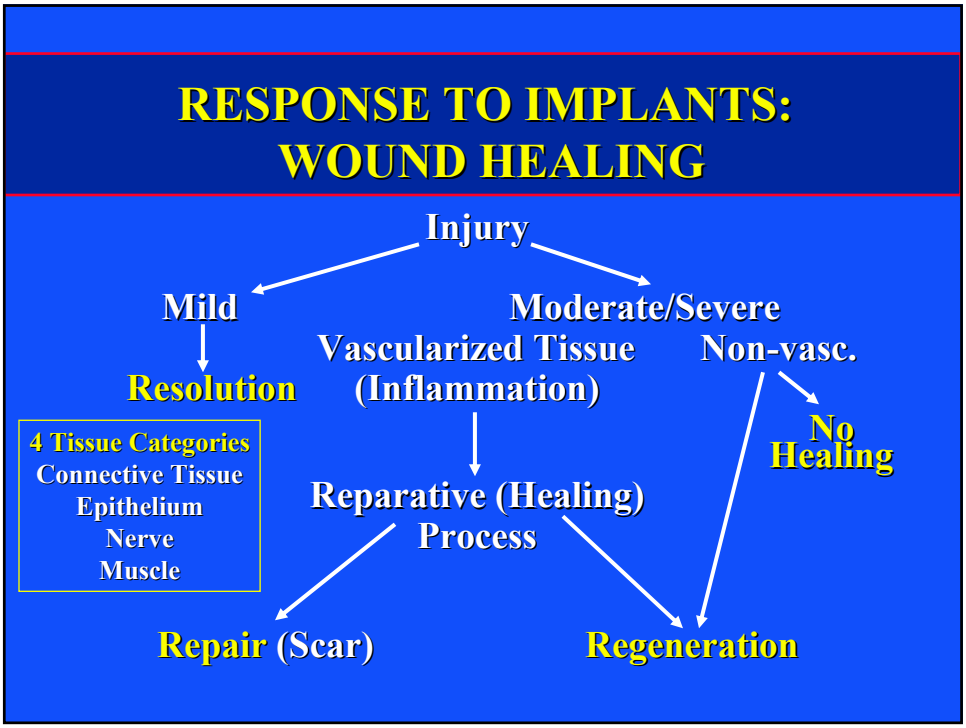


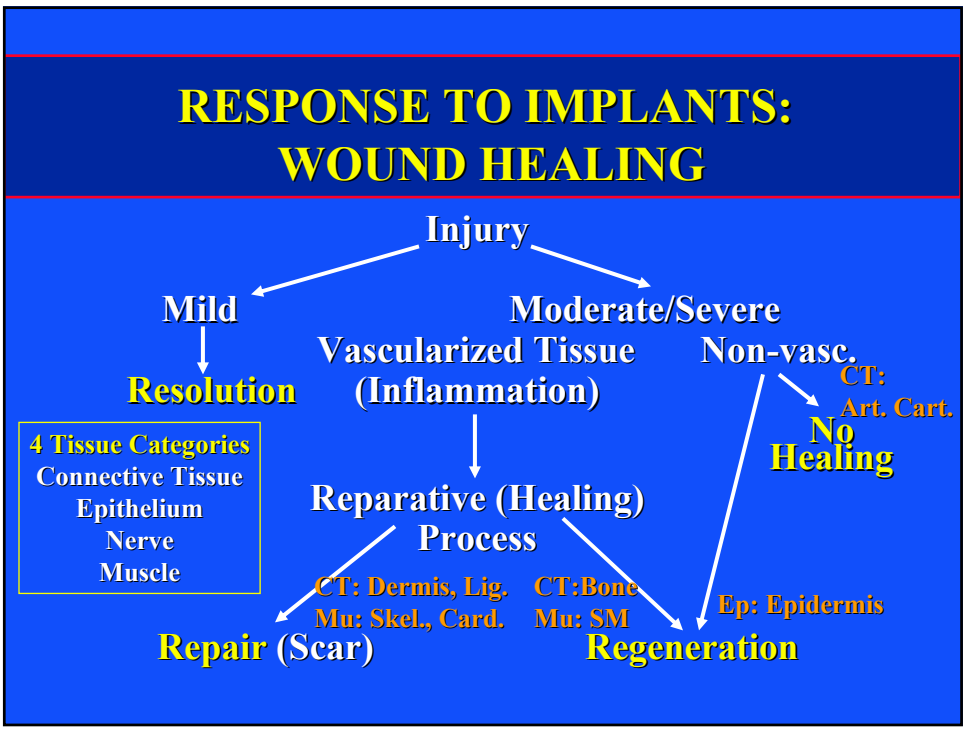
BIOMATERIALS-TISSUE INTERACTIONS: Tissue Response to Implant Breakdown



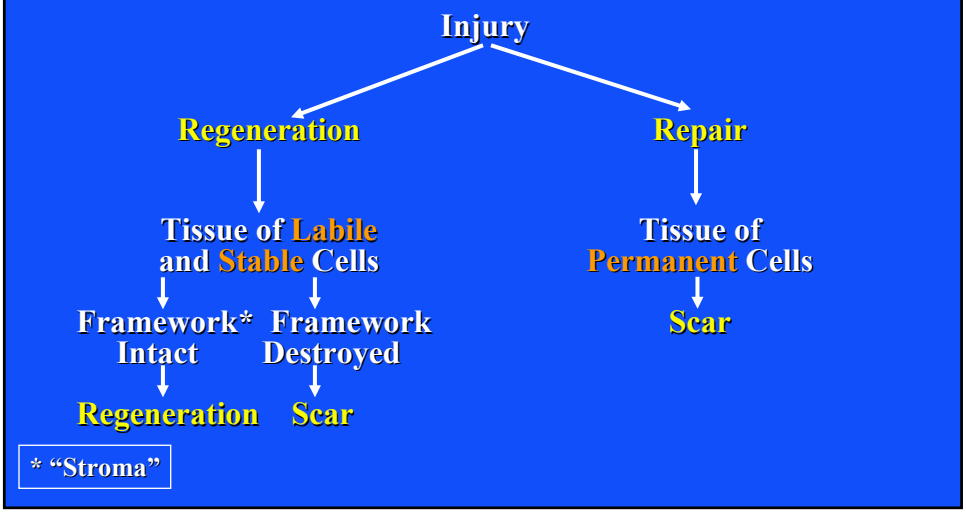
RESPONSE TO IMPLANTS: WOUND HEALING



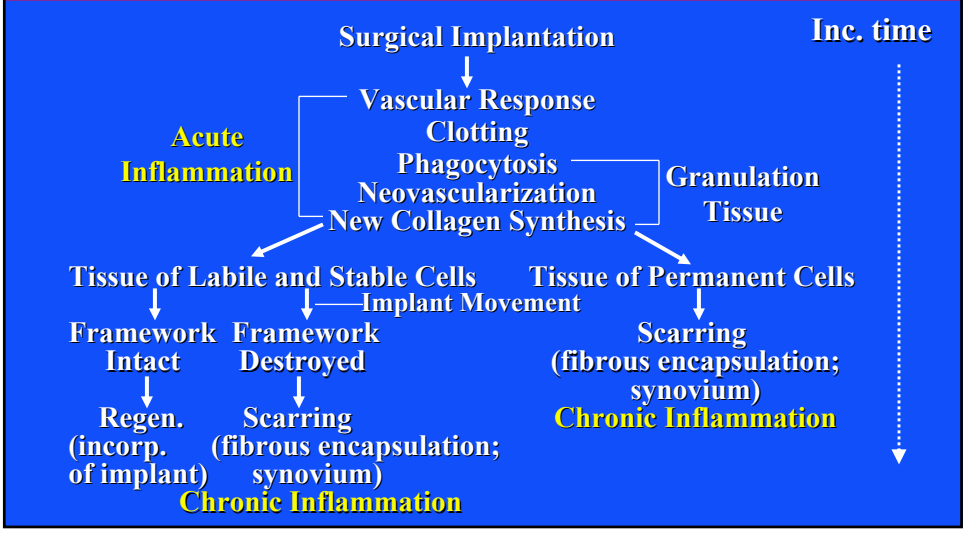

RESPONSE TO IMPLANTS:
WOUND HEALING
Injury
Mild
Moderate/Severe
Resolution
Vascularized Tissue
(Inflammation)
Non-vasc.
No
Healing
4 Tissue Categories
Connective Tissue
Epithelium
Nerve
Muscle
Reparative (Healing)
Process
Repair (Scar)
Regeneration

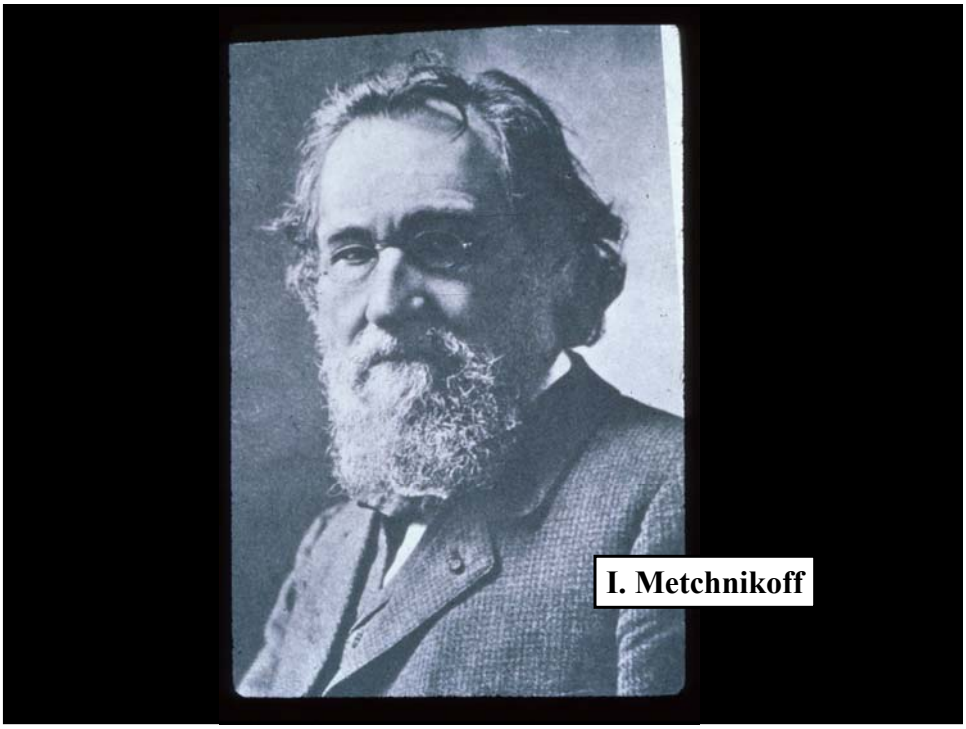

RESPONSE TO IMPLANTS:
WOUND HEALING
Injury
Mild
Moderate/Severe
Resolution
Vascularized Tissue
(Inflammation)
Non-vasc.
CT:
Art. Cart.
No
Healing
4 Tissue Categories
Connective Tissue
Epithelium
Nerve
Muscle
Reparative (Healing)
Process
CT: Dermis, Lig.
Mu: Skel., Card.
CT:Bone
Mu: SM
Ep: Epidermis
Repair (Scar)
Regeneration

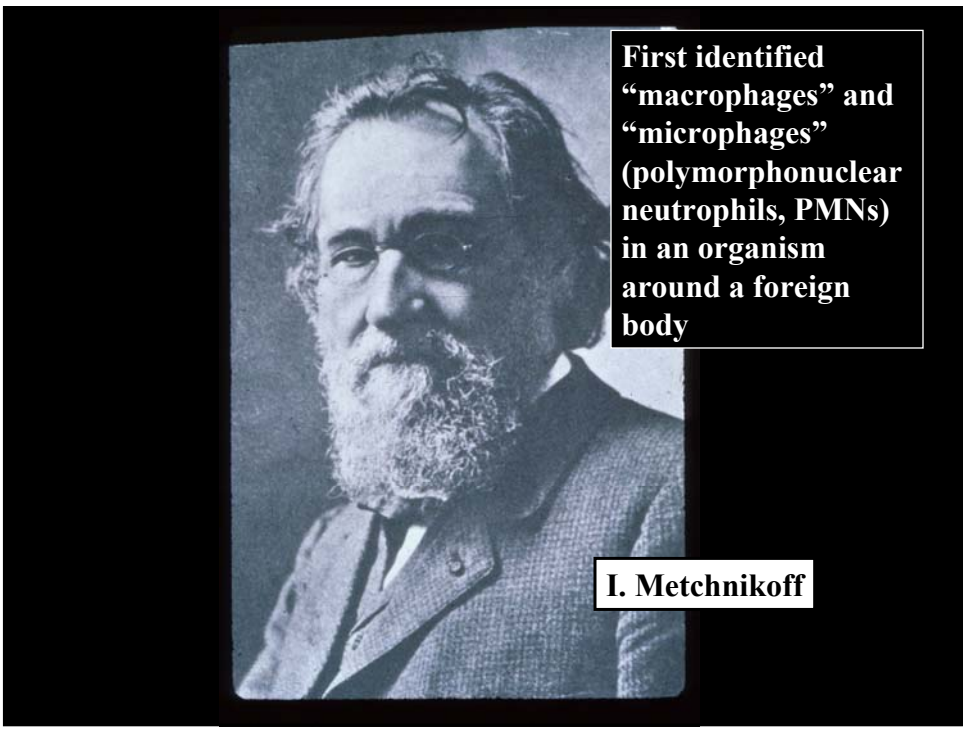
RESPONSE TO IMPLANTS: WOUND HEALING



RESPONSE TO IMPLANTS: WOUND HEALING




I. Metchnikoff


First identified "macrophages" and "microphages" (polymorphonuclear neutrophils, PMNs) in an organism around a foreign body
I. Metchnikoff

In 1923 a piece of glass was removed from a patient's back; it had been there for a year. It was surrounded by a minimal amount of fibrous tissue, lined by a glistening synovial sac, containing a few drops of clear yellow fluid.

Photo removed due to copyright restrictions.

Smith-Peterson

J. Bone Jt. Surg., 30-B:59 (1948)

Diagrams removed due to copyright restrictions.

I. Silver

Synovium:
Macrophage-like (Type A) and Fibroblast-like (Type B) Cells

Photo removed due to copyright restrictions.

Tissue response to a cylindrical implant of polysulfone in lapine skeletal muscle, 2 yrs. post-op

Fibrous tissue

Photo removed due to copyright restrictions.

Skeletal muscle

Polyethylene implant, 6 mos. post-op

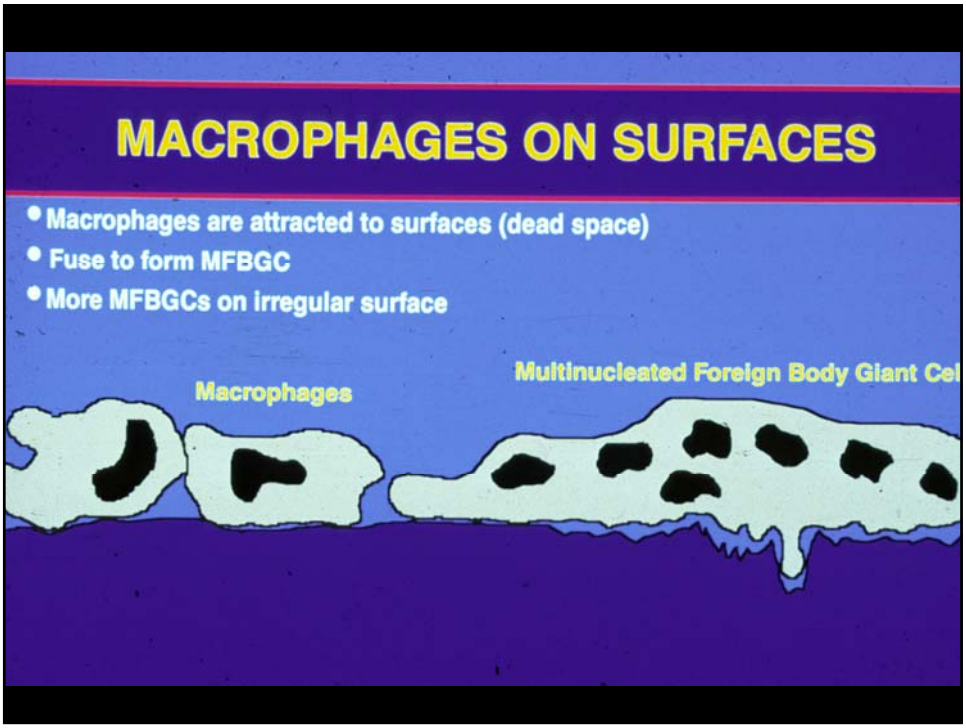
Polyethylene

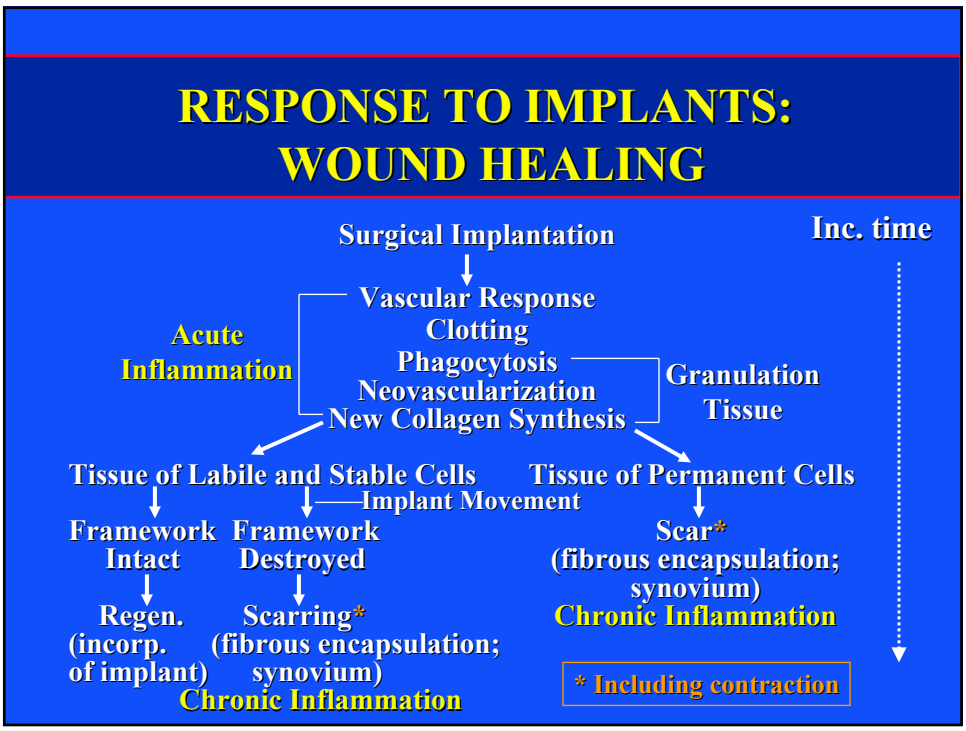
Photo removed due to copyright restrictions.

Polyethylene

Porous Coated Co-Cr Tibial Component
(retrieved 1 yr. post-op)

Photo removed due to copyright restrictions.


MACROPHAGES ON SURFACES
Macrophages are attracted to surfaces (dead space)
Fuse to form MFBGC
More MFBGCs on irregular surface
Macrophages
Multinucleated Foreign Body Giant Cel


RESPONSE TO IMPLANTS:
WOUND HEALING
Surgical Implantation
Inc. time
Vascular Response
Clotting
Phagocytosis
Neovascularization
New Collagen Synthesis
Acute Inflammation
Granulation Tissue
Tissue of Labile and Stable Cells
Tissue of Permanent Cells
Implant Movement
Framework Intact
Framework Destroyed
Scar*
(fibrous encapsulation; synovium)
Chronic Inflammation
Regen. (incorp. of implant)
Scarring*
(fibrous encapsulation; synovium)
Chronic Inflammation
* Including contraction

FIBROBLAST BEHAVIOR IN FIBROUS TISSUE AROUND IMPLANTS

- Proliferation and increased matrix synthesis of fibroblasts leads to an increase in the thickness and density of the scar tissue.
- Fibroblast contraction results in scar contracture.

BREAST IMPLANTS
Capsular Contracture

Photo removed due to copyright restrictions.

Photograph shows Grade IV capsular contracture in the right breast of a 29-year-old woman seven years after subglandular (on top of the muscle and under the breast glands) placement of 560cc silicone gel-filled breast implants.

http://www.implantforum.com/capsular-contracture/

BREAST IMPLANTS
Capsular Contracture

What is Capsular Contracture?
Scar tissue that forms around the implant which causes the breasts to harden (similar to what a contracted muscle feels like) as the naturally forming scar tissue around the implant tightens and squeezes it. While capsular contracture is an unpredictable complication, it is also the most common complication of breast augmentation.

How can Capsular Contracture be prevented?
Textured implants help deter contracture because of their rough surface which is intended to discourage a hard capsule from forming.
Under the muscle (sub-pectoral or 'partial sub-muscular') placement of the implant reduces risk of capsular contracture by an average of 8 - 10%. Whereas over the muscle (in front of the muscle or 'sub-mammary') has 10 - 25% or more chance of capsule contracture.

CAUSE OF CAPSULAR CONTRACTION

Myofibroblasts, and the regulatory protein TGF-β, were found in the contracted capsules around silicone breast implants but not in non-contracted capsules. Mature skin scar tissue did not contain TGF-β or myofibroblasts.

Lossing C, and Hansson HA,
Plast Reconstr Surg 91:1277 (1993)

α-smooth muscle actin-fusion peptide (SMA-FP) inhibits the tension exerted by lung fibroblasts on silicone substrates. After washing our of the FP, cells contract again.

Video removed due to copyright restrictions.

Hinz B, *et al*., J Cell Biol 157:657 (2002)

http://www.implantforum.com/capsular-contracture/

BREAST IMPLANTS
Capsular Contracture

How can Capsular Contracture be prevented?
Massage and or compression. This is usually only done with smooth implants and may be suggested for a period between a few weeks to as long as you have your implants. Do not massage bruises!

The "no-touch" technique. This method includes meticulously rewashing surgical gloves before handling any instrument and implants. Only the head surgeon touches the implant, using a unique Teflon cutting board and immediately inserting the implant underneath the muscle. All of these measures help ensure that no foreign substance attach themselves to the implant, which could inflame the surrounding tissue and cause complications such as capsular contracture.

Chondrocytes (P2 Canine) in a Type I Collagen-GAG Matrix: Contraction

Photo removed due to copyright restrictions.

40 min

B Kinner

Non-Seeded: 8 days **Cell-Seeded: 8 days**

Photo removed due to copyright restrictions.

Non-Seeded and Cell-Seeded Collagen-GAG Scaffolds

S. Vickers

Human Articular Chondrocytes in Monolayer Culture

IH - Green: α-smooth muscle actin; Orange: type II collagen

Photo removed due to copyright restrictions.

Chondrocytes express the gene for α-smooth muscle actin and this enables them to contract

B. Kinner, *et al*. JOR 2001;19:233

MUSCULOSKELETAL CELLS THAT CAN EXPRESS α-SMOOTH MUSCLE ACTIN AND CAN CONTRACT

- Articular chondrocyte
- Osteoblast
- Meniscus fibroblast and fibrochondrocyte
- Intervertebral disc fibroblast and fibrochondrocyte
- Ligament fibroblast
- Tendon fibroblast
- Synovial cell
- Mesenchymal stem cell

M. Spector, Wound Repair Regen. 9:11-18 (2001)

POSSIBLE ROLES FOR α-SMOOTH MUSCLE ACTIN-ENABLED CONTRACTION

Musculoskeletal Connective Tissue Cells

• Tissue engineering	Contracture of scaffolds
• Healing	Closure of wounds (skin wounds and bone fractures)
• Disease processes	Contracture (Dupuytren's)
• Tissue formation and remodeling	Modeling of ECM architecture (*e.g.*, crimp in ligament/tendon?)

IMPLANT MATERIALS/BIOMATERIALS TISSUE RESPONSE

Soft Tissue (that does not regenerate)

- Fibrous capsule (scar)
  - Synovium: fibrous tissue interspersed with macrophages
  - Wound healing response of repair (scar formation) coupled with macrophage accretion at the "dead space" - chronic inflammation

Bone

- Tissue integration and tissue bonding

TISSUE INTEGRATION TISSUE BONDING

- Tissue Integration (Osseointegration)
  - Apposition of tissue (bone) to the implant (contact of bone with the surface but not necessarily bonding)
  - Regeneration of tissue up to the surface of the implant
- Tissue Bonding (Bone Bonding)
  - Chemical bonding of tissue (*viz.*, bone) to the surface
  - Protein adsorption and cell adhesion
  - Biomaterials: calcium phosphates and titanium (?)

Photos removed due to copyright restrictions.

Why are there no macrophages on the surface of the implant?

Hydroxyapatite-Coated Implants

Photos removed due to copyright restrictions.

Plasma-Sprayed Hydroxyapatite Coating

Photos removed due to copyright restrictions.

Photos removed due to copyright restrictions.

Plasma-sprayed HA coating on a canine femoral stem, 6 mos. post-opc

Photos removed due to copyright restrictions.

PROGRESSION OF OSTEOLYSIS: "HYLAMER" CUP

Photos removed due to copyright restrictions.

J. Charnley, 1979

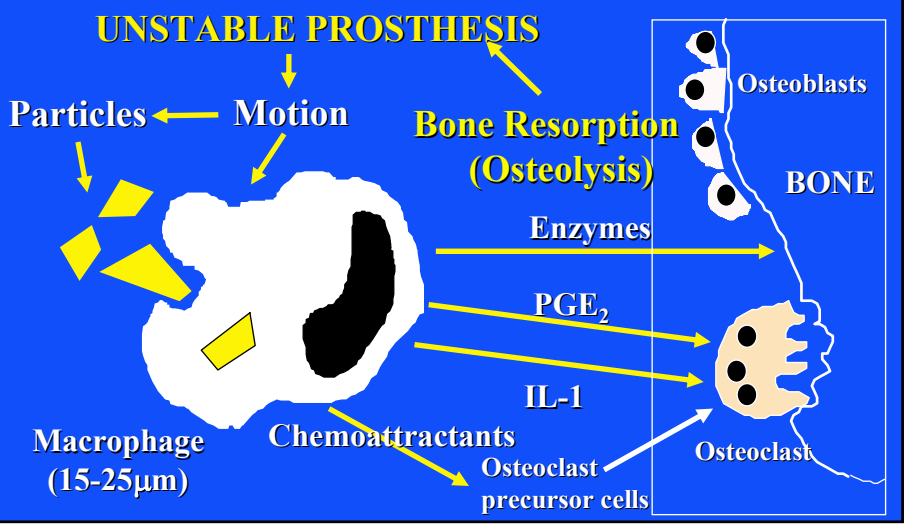
Photos removed due to copyright restrictions.

Titanium Wear Debris

Co-Cr Particles

Photos removed due to copyright restrictions.

MACROPHAGE RESPONSE TO MOTION AND PARTICLES



POLYETHYLENE WEAR PARTICLES

H. McKellop, 1994 Hip Society

The number of particles generated by a hip prosthesis

7×10^{11} particles/yr.

700,000 particles/step

NUMBER OF INHALED PARTICLES

Avg. particle burden of urban atmosphere:

10^5 particles/liter

Respired volume in man = 1 liter/min.

Therefore, 10^5 particles are inhaled/min.

10% of the inhaled particles are deposited in the lungs.

Therefore, 10^4 particles are deposited in the lungs per min.

5×10^9 particles/yr.

RESPONSE TO PARTICLES

- Type of material
- Size
  - mm, μm, nm
- Location
  - Joint fluid
  - Peri-prosthetic tissues
  - Synovium
  - Lymphatic system
- Number

RESPONSE TO PARTICLES

- **Size**
  - **mm** No adverse response.
  - **μm** Able to be phagocytosed by macrophages; macrophages release molecules that stimulate bone resorption.
  - **nm** Sub-micrometer (nanoparticles) interfere with function of cell organelles; enter into the nucleus and interfere with genetic functions.

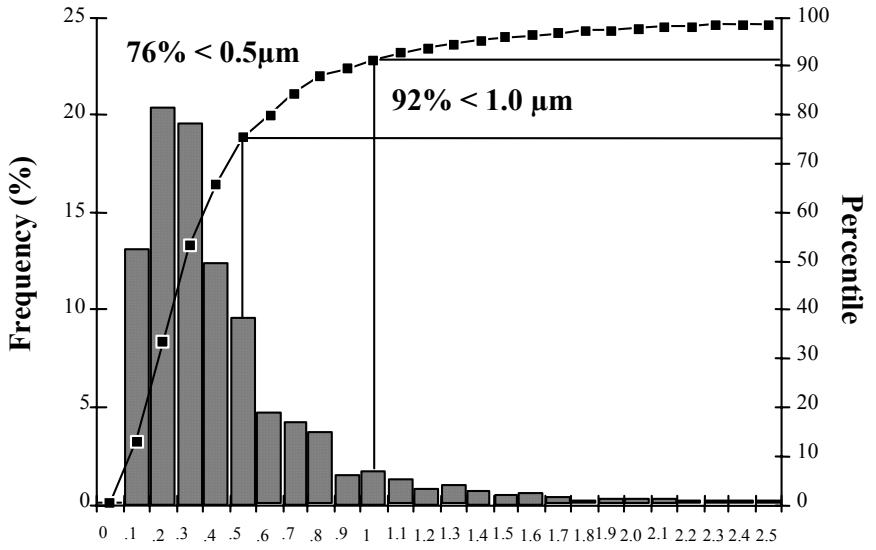
Light Microscopy

Polyethylene Particles in Peri-prosthetic Tissues

Photos removed due to copyright restrictions.

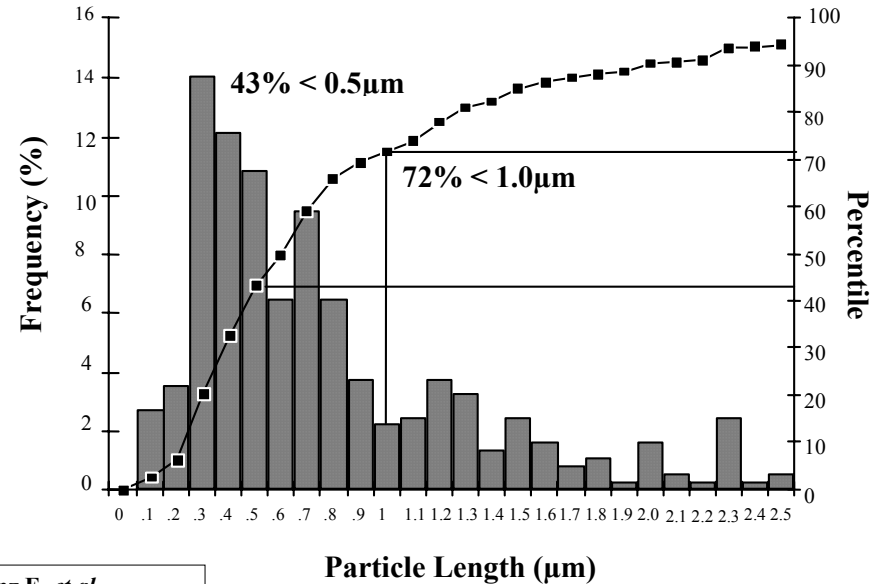
Transmission Electron Microscopy, TEM

The total of 15 cemented and uncemented total hip replacement prostheses.



Benz E, *et al.*,
Biomat. 2001;22:2835

The total of 3 total knee replacement prostheses.



Benz E, *et al.*,
Biomat. 2001;22:2835

PARTICLE SIZE

- A large percentage of polyethylene particles in periprosthetic tissues are of nanometer size
  - less than 200 nm
- These nanometer size particles would go through the filters often used to capture particles from joint fluid
  - 200 nm diameter pores in the filter

ISOLATION OF PARTICLES FROM JOINT FLUID

J Biomed Mater Res Part B: Appl Biomater 71B: 1–6, 2004

Characteristics of Polyethylene Wear Particles Isolated from Synovial Fluid After Mobile-Bearing and Posterior-Stabilized Total Knee Arthroplasties

Yukihide Minoda,[1] Akio Kobayashi,[1,2] Hiroyoshi Iwaki,[3] Masatsugu Miyaguchi,[1] Yoshinori Kadoya,[1] Hirotsugu Ohashi,[1] Kunio Takaoka[1]

solutions were filtered through a 0.2-μm pore nylon filter

NANOPARTICLE TOXICITY

- Particles from prostheses have become smaller (from micrometer to nanometer).
- Introduction of nanotechnolgy into medicine (*i.e.*, engineered nanoparticles for various applications) has raised questions about the biological response to nanoparticles.
- Several federal agencies (NIH, EPA) are looking into this issue.
- 2 major causes of death are cancer and heart disease; there are indications that nanoparticles can adversely contribute to these processes

NANOPARTICLE TOXICITY

"Nano's Troubled Waters:"

"Latest toxic warning shows nanoparticles cause brain damage in aquatic species and highlights need for a **moratorium on the release of new nanomaterials.**

- A new study revealing that engineered carbon molecules cause brain damage in fish is one more brick in the wall of evidence suggesting that **manufactured nanoparticles are harmful to the environment and to health.**
- How many warnings do government regulators require before they take action to ensure that uses of nanoparticles are safe before workers in production facilities are harmed and before consumers are further exposed? "

http://online.sfsu.edu/~rone/Nanotech/nanobraindamage.htm
Genotype; Thursday, 1 April 2004; www.etcgroup.org

RESPONSE TO PARTICLES

- Type of material
- Size
  - mm, μm, nm
- Location
  - Joint fluid
  - Peri-prosthetic tissues
  - Synovium
  - Lymphatic system
- Number

LYMPHATIC SYSTEM

- Filters out organisms and particles.
- The lymphatic vessels are present wherever there are blood vessels.
- More than 100 tiny, oval structures (called lymph nodes).
  - scattered all along the lymph vessels.
  - filter out particles
- Particles that pass through the lymph node enter into the blood circulation.

Lymphadenopathy

Photos removed due to copyright restrictions.

Benz EB, *et al*., J. Bone Jt. Surg. 1996;78-A:588

Photos removed due to copyright restrictions.

Benz EB, *et al*., J. Bone Jt. Surg. 1996;78-A:588

SMALL PARTICLE DISEASE: LYMPHADENOPATHY

- Enlargement of the node.
- Particles drained from tissue by the lymphatic system are phagocytosed by macrophages in the nodes.
- No adverse clinical sequelae yet noted, but can confound differential diagnosis of other diseases.
- Concern about the clinical sequelae of nanoparticles that gain access to the vascular system.

LOCAL AND SYSTEMIC RESPONSES SMALL PARTICLE DISEASE

- **Local Component**

  Particle induced focal destruction of tissue around the imlant
- **Systemic Component**

  Lymphadenopathy

BIOLOGICAL RESPONSE TO METAL DEBRIS

- Immune responses

PATIENT CONCERNS ABOUT METAL DEBRIS

Am I allergic to my metal implant?

IMMUNE RESPONSE TO METAL IONS

- "Metal allergy" has been incriminated as the cause of failure in certain patients.
- However, results obtained to date are not definitive.

METAL SENSITIVITY IN PATIENTS

- 10-15% of population have dermal sensitivity to metal (14% to Ni)
- Metal ions bind to proteins to form immunogenic complexes
- Metals known as sensitizers:
  - Ni > Co and Cr >>> Ti and V
- 60% of pts. with failed TJRs were metal sensitive vs. 25% with well-functioning implants
  - Did metal sensitivity cause failure or did the failed implant cause metal sensitivity?

Hallab, Merritt, Jacobs, JBJS 83-A:428 (2001)

METAL SENSITIVITY IN PATIENTS

- "May exist as an extreme complication in only a few highly susceptible patients (< 1%), or it may be a more common subtle contributor to implant failure."
- "It is likely that cases involving implant-related metal sensitivity have been underreported because of the difficulty of diagnosis."
- Patients who have displayed sensitivity to metal jewelry are at higher risk.

Hallab, Merritt, Jacobs,
JBJS 83-A:428 (2001)

CELL RESPONSE TO METAL PARTICLES

- Macrophages *in vitro*
- Particles of Ti alloy not toxic; Co-Cr highly toxic
- Ti induced more release of PGE_2 than Co-Cr
- Exp. to Ti increased the release of PGE_2, IL-1, TNF, and IL-6; exp. to Co-Cr decreased release of PGE_2 and IL-6 and had little effect on IL-1 and TNF
- "release of Ti....worse than....Co-Cr"

D.R. Haynes, *et al.*,
JBJS 75-A: 825 (1993)

CELL RESPONSE TO METAL PARTICLES

- Bovine articular chondrocytes
- Co was toxic to cells at all conc.
- At high conc. Cr, Ti, and Ti alloy were toxic
- At high conc. all metals decreased enzyme activity
- PGE_2 increased with conc., except for Ti alloy

W.J. Maloney, et al.,
J. Appl. Biomat. 5: 109 (1994)

BIOLOGICAL RESPONSE TO METAL PARTICLES AND IONS

Summary

- Metal particles and ions are released from TJR prostheses; the amounts can be reduced by careful design and manufacturing
- Cellular response to metal particles has some of the same elements as the response to particles of other materials
- No indication yet that metal particles and ions are responsible for profound adverse responses