Massachusetts Institute of Technology
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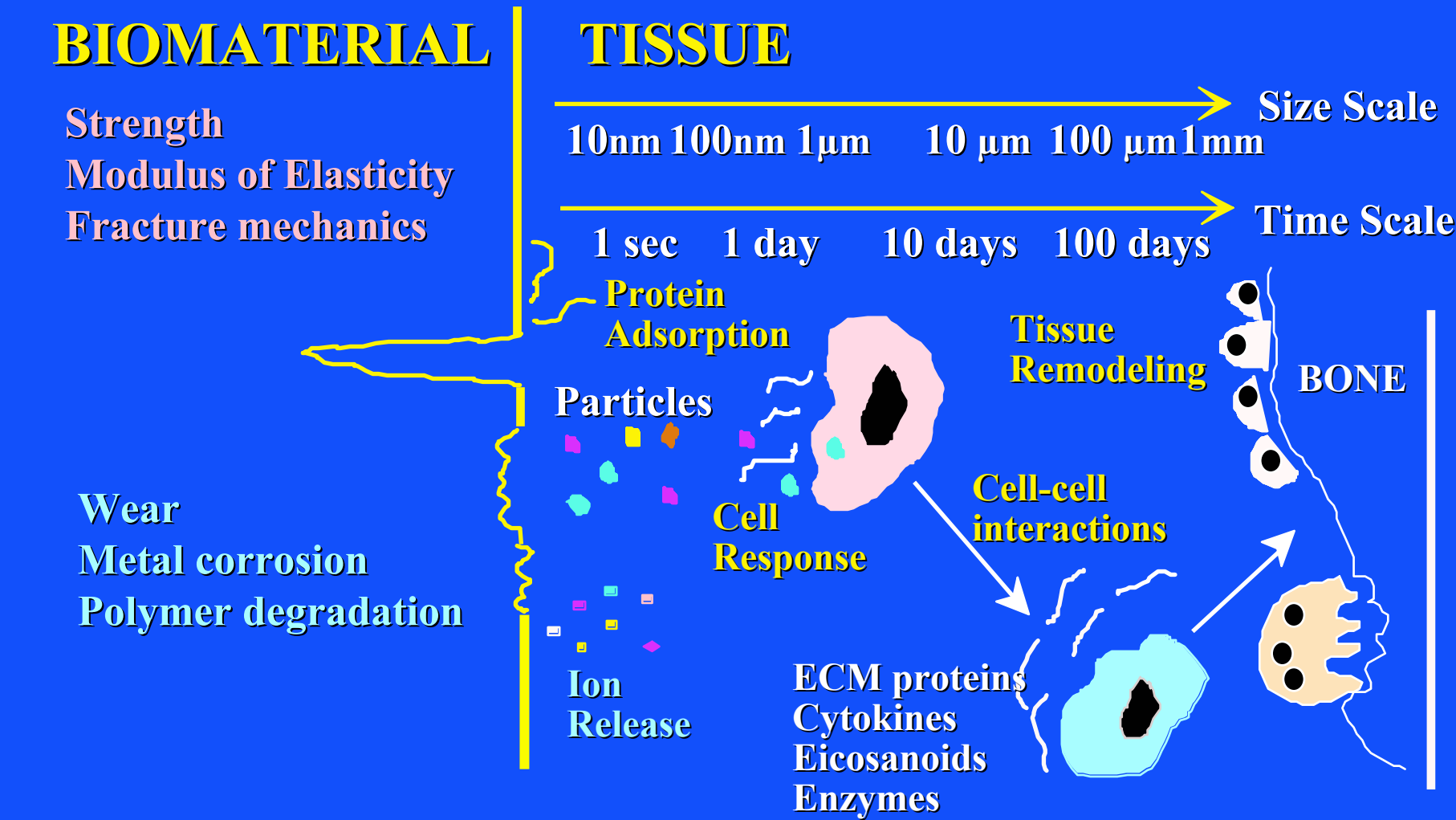
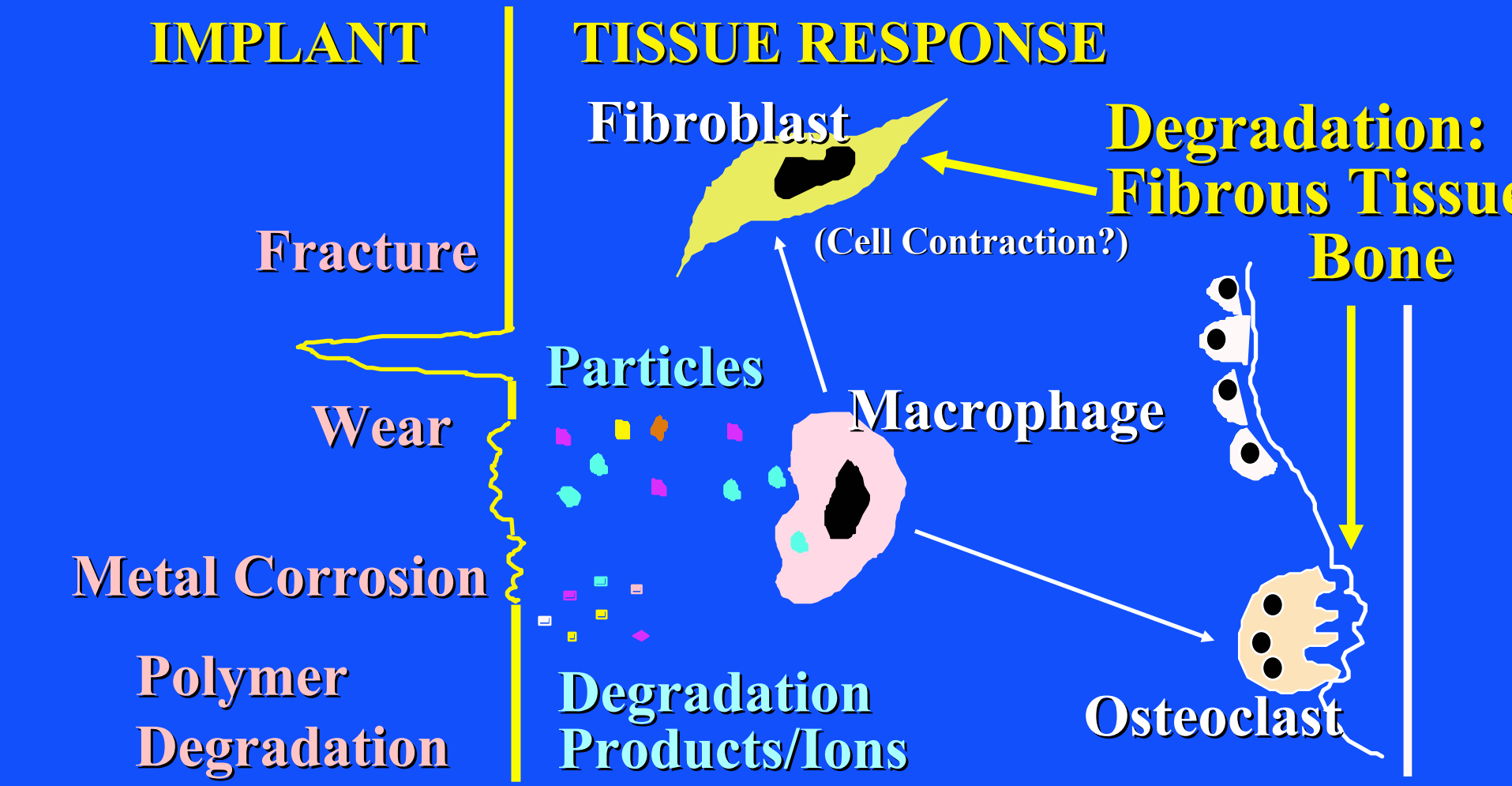
RESPONSE TO PARTICLES

M. Spector, Ph.D.

BIOMATERIALS-TISSUE INTERACTIONS



BIOMATERIALS-TISSUE INTERACTIONS:
Tissue Response to Implant Breakdown



LOCAL AND SYSTEMIC RESPONSES SMALL PARTICLE DISEASE

- **Local Component**

  Osteolysis - particle induced focal destruction of bone around the prosthesis

- **Systemic Component**

  Lymphadenopathy

PROGRESSION OF OSTEOLYSIS: "HYLAMER" CUP

Image removed due to copyright considerations

Why Artificial Joints Fail

Image removed due to copyright considerations

Spice, Byron. "Particle Disease Seen As Plague on Total Joint Replacement" Pittsburgh Post-Gazette.

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.

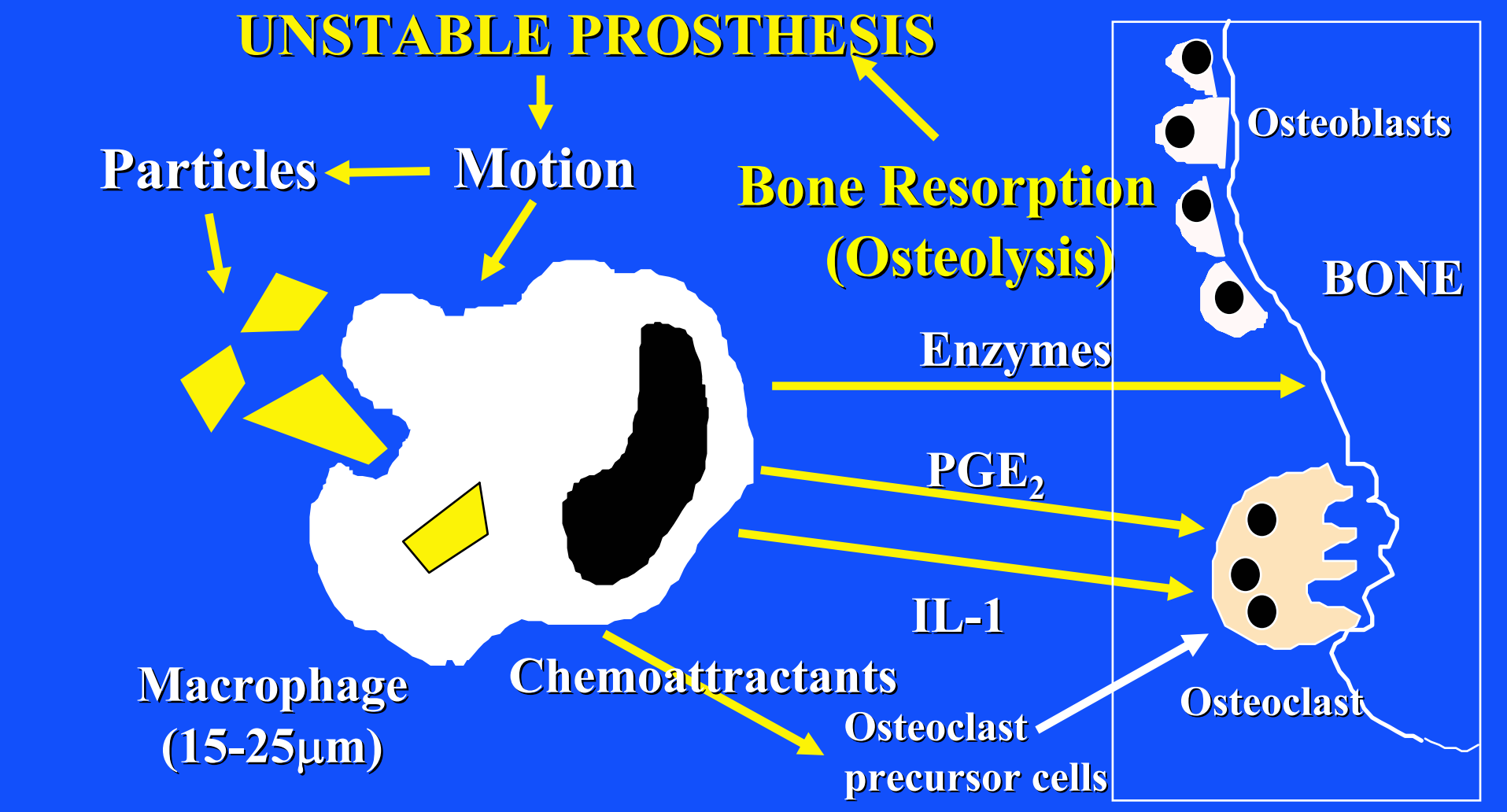
5×10^9 particles/yr.

Titanium Wear Debris

Images removed due to copyright considerations

Co-Cr Particles

MACROPHAGE RESPONSE TO MOTION AND PARTICLES



Polyethylene Particles

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OSTEOLYSIS

Determinants

- Particles < 10 μm
- Movement of the prosthesis

  (*i.e.*, micomotion)

  – deformation (strain) of tissue

ROLE OF MICROMOTION IN OSTEOLYSIS

- Mechanical perturbation can provoke macrophages to release inflammatory agents that stimulate bone resorption

OSTEOLYSIS: ROLE OF IMPLANT MOVEMENT

Mechanical perturbation increases release of PGE_2 by (LPS-stimulated) macrophages *in vitro*

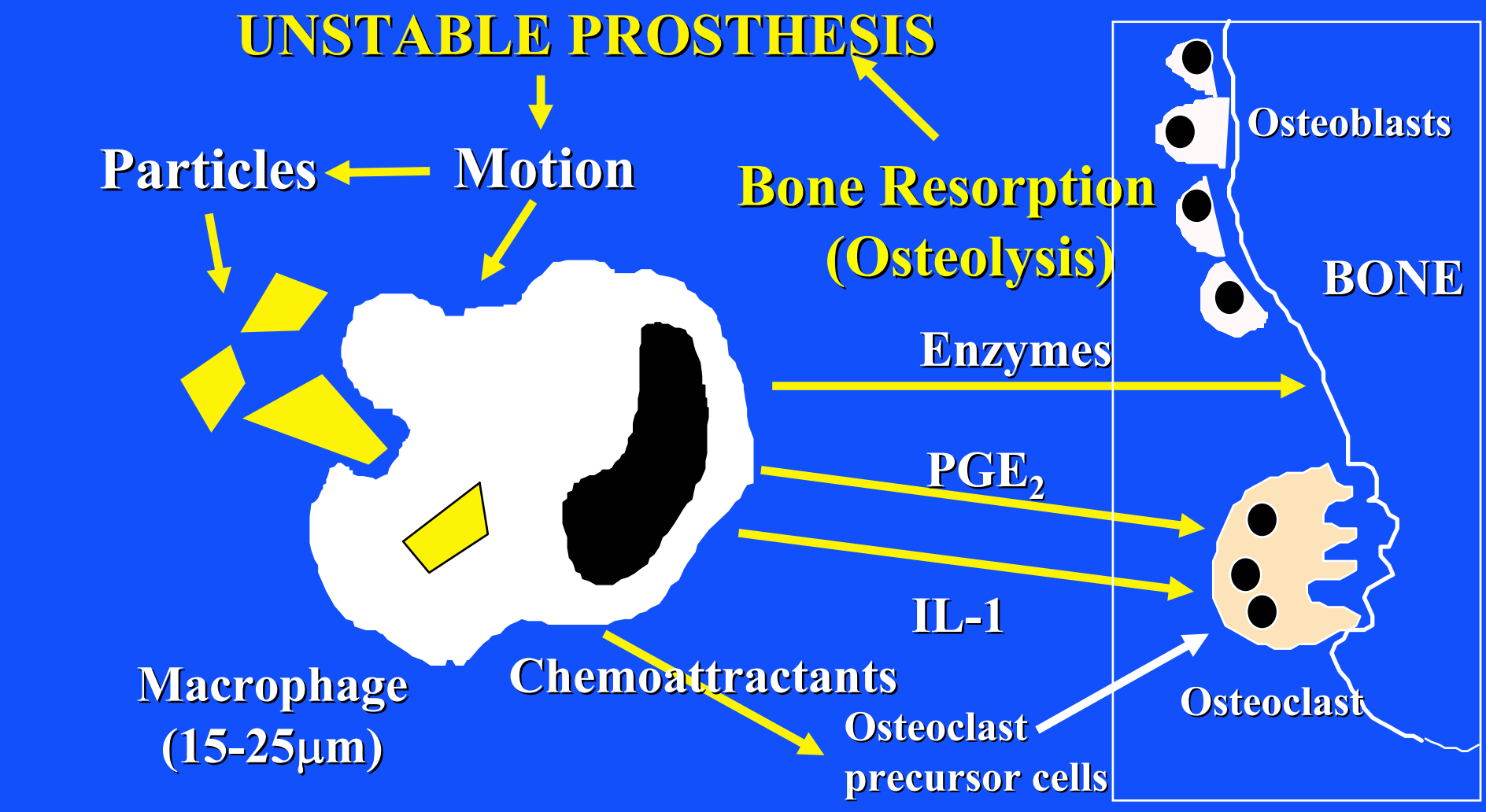
- **Macrophages on flexible membranes**
- **Cyclic strains of 4.0 and 7.7%**
- **Release of PGE_2 was approximately twice that of the unstretched controls**

B.E. Grottkau, *et al.*
Brigham & Women's Hospital

THERAPEUTIC STARTEGIES TO MANAGE SMALL PARTICLE DISEASE

- Inhibitors of inflammatory cytokines and eicosanoids
  - *e.g.*, NSAIDs to reduce PGE_2
- Gene therapy to up-regulate the synthesis of antagonists of receptors for inflammatory molecules
  - *e.g.*, IL-1 receptor antagonist
- Agents to block osteoclastic bone resorption

MACROPHAGE RESPONSE TO PARTICLES AND MOTION



Canine Model for Prosthesis Loosening

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6 mos. continuous treatment with Naproxen

EFFECT OF NAPROXEN ON PGE_2 LEVELS IN A CANINE MODEL

Naproxen *In Vivo* Treatment Period (Mos.)	PGE_2 Naproxen *In Vitro* Without	With
0	314±236	177±177
3	112±63	7±6
6	84±51	0

BIOLOGIC RESPONSE TO PARTICLES

- Systemic response: lymphadenopathy

Drainage of Particles by the Lymphatics

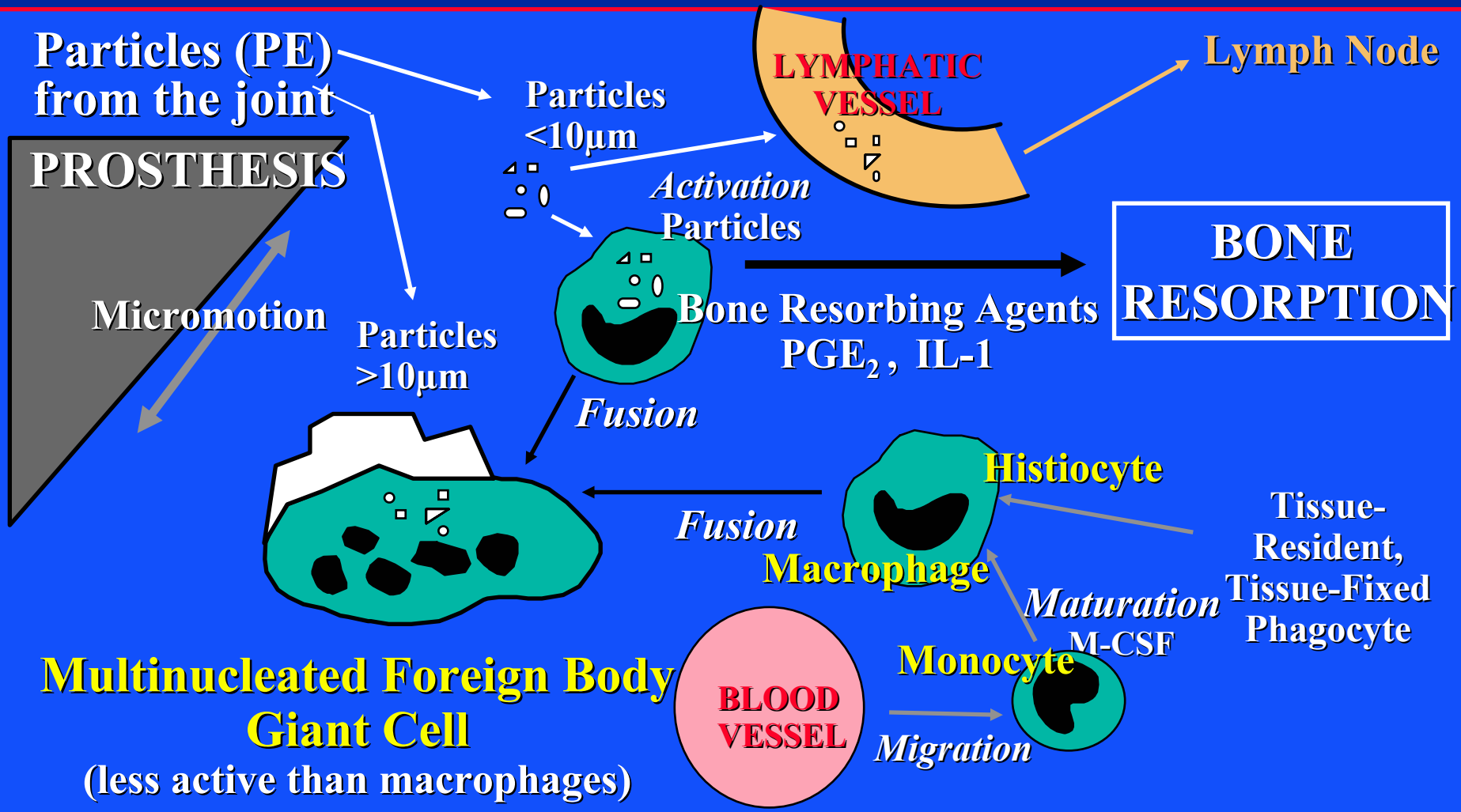
Image removed due to copyright considerations

H. Willert, *et al.*

SMALL PARTICLE DISEASE: LYMPHADENOPATHY

- Enlargement of the node
- Particles drained from tissue by the lymphatic system are phagocytosed by macrophages in the nodes
  - histiocytes derived from cells that line the sinuses of the node and macrophages derived from circulating monocytes
- Sinus histiocytosis
- No adverse clinical sequelae yet noted

MIGRATION OF PARTICLES AND CELLULAR RESPONSES



Lymphadenopathy

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BIOLOGICAL RESPONSE TO METAL DEBRIS

- Cell response to metal particles and ions

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.

IMMUNE RESPONSE TO METAL IONS

K. Merritt and S.A. Brown (1985)

"The incidence of metal sensitivity in the normal population is high, with up to 15% of the population sensitive to nickel and perhaps up to 25% sensitive to at least one of the common sensitizers Ni, Co, and Cr. The incidence of metal sensitivity reactions requiring premature removal of an orthopedic device is probably small (less than the incidence of infection). Clearly there are factors not yet understood that caused one patient but not another to react."

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 an unusually adverse response