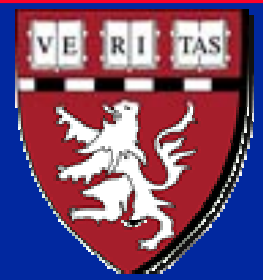
Massachusetts Institute of Technology
Harvard Medical School
Brigham and Women's Hospital
VA Boston Healthcare System



2.785j/3.97J/BEH.411/HST523J

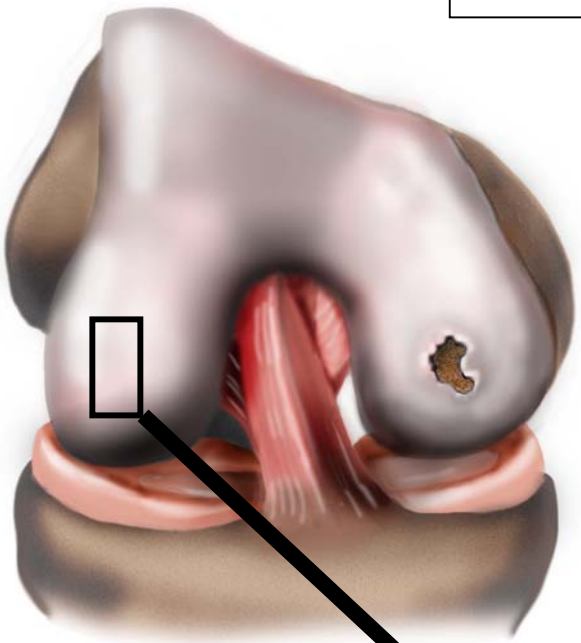
CELL-MATRIX MECHANICS

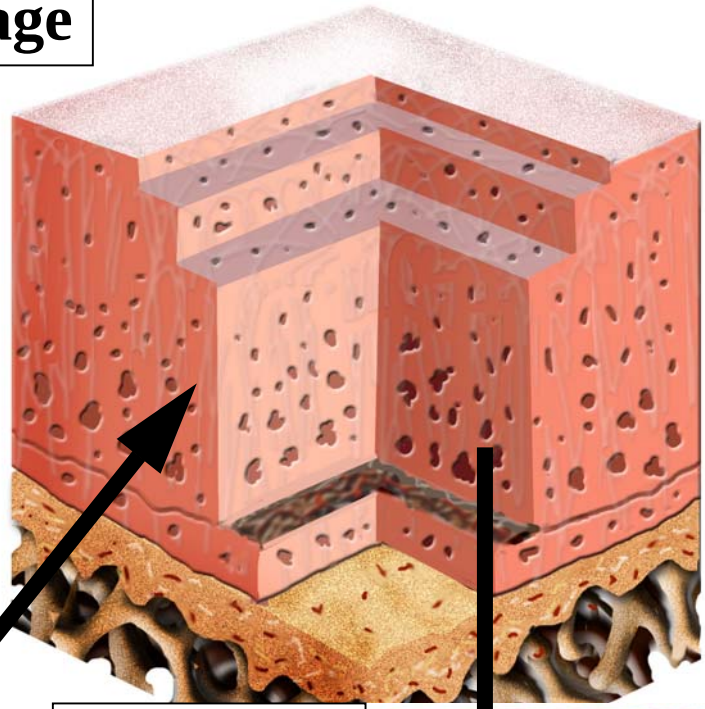
M. Spector, Ph.D. and I.V. Yannas, Ph.D.

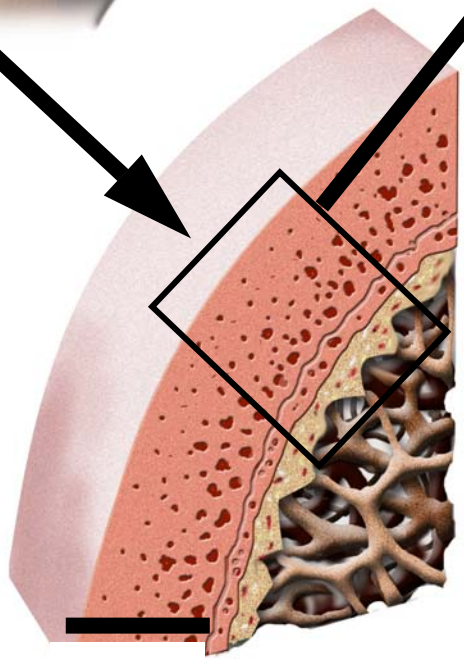
TISSUE

- **Tissue** is a biological structure made up of cells of the same type.
  - Cells of the same phenotype (*i.e.*, same genes expressed).
  - An aggregation of morphologically similar cells and associated extracellular **matrix** acting together to perform one or more specific functions in the body.
  - There are four basic types of tissue: muscle, nerve, epithelia, and connective.
  - An **organ** is a structure made up of 2 or more tissues.

Articular Cartilage

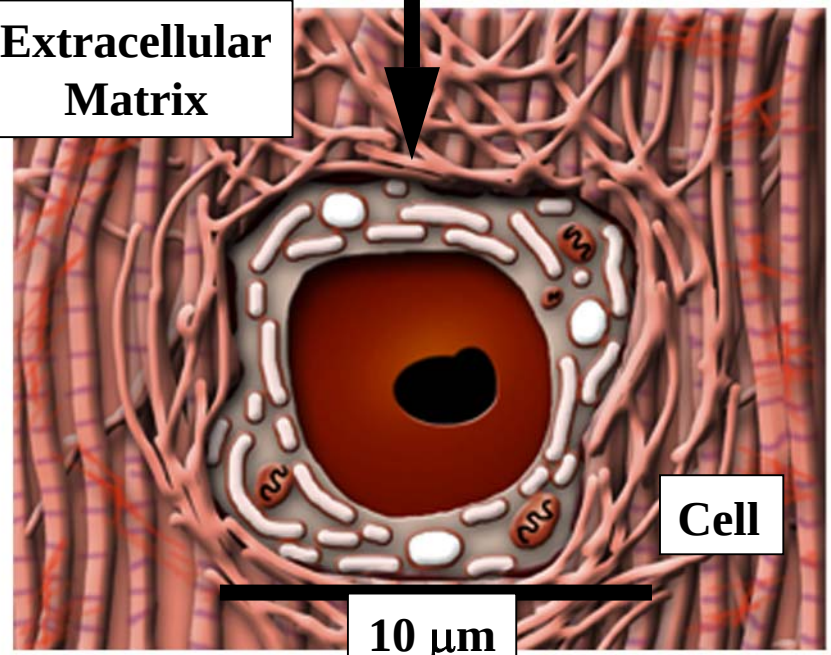






4 mm

Extracellular Matrix



Cell

10 μm

Figures by MIT OCW.

CELL-MATRIX MECHANICS

- How cells respond to mechanical force
  - Load-deformation of the matrix
- How cells generate mechanical forces

One effect that an exogenous mechanical force can have on cells (a and b; chondrocytes) and the generation of mechanical force by cells (c and d; chondrocytes).

Four images removed for copyright reasons.

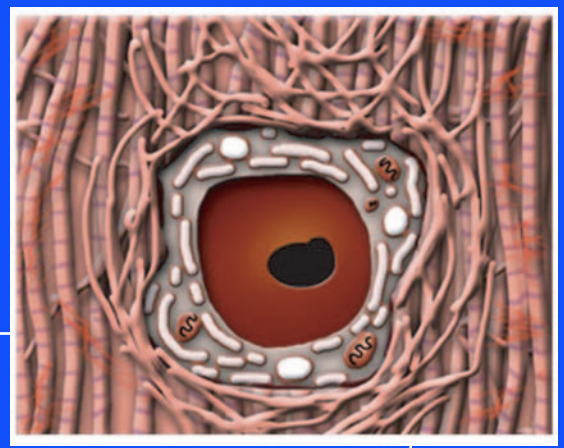
(a) A typical chondrocyte (approximately 10 micron in diameter) in articular cartilage viewed by a transmission electron microscopy. The application of a mechanical force to cartilage causes compression of a chondrocyte by 20%

(b) The compression results in a compaction and anisotropic organization of organelles such as the Golgi apparatus and the rough endoplasmic reticulum responsible for the synthesis of extracellular matrix molecules. Alterations in the organelles as a result of compression can change the structure of the matrix molecules that they synthesize.

(c) and (d). Light microscopy images of living chondrocytes seeded into a collagen-glycosaminoglycan scaffold, followed over a 300-min period after seeding.
(c) Up to 40 minutes after being seeded the chondrocytes show a rounded phenotype (the 2 cells on the horizontal strut in the middle of the image.
(d) After 5 hours the cells noticeably spread on the fine member to which they were attached and buckled the strut as a result of their contraction. Bending of the members to which the shortened strut was attached is noticeable. The strut to which the cells were attached reduced in length from approximately 144 micron (c) to 89 micron after 5 hours (d) representing a reduction of almost 40%.

Sources: (a) and (b) from M.A. DiMicco, et al., “Response of the chondrocyte to mechanical stimuli” in *Pathogenesis of Osteoarthritis*. (c) and (d) from J. Zaleskas, et al., Biomat. 2004;25:1299.

UNIT CELL PROCESSES
The "Control Volume" and Regulators



Chemical (Soluble) Regulator

Figure by MIT OCW.

Cell + Matrix Molecules (Insoluble Reg.) —UCP→ Product + Soluble Regulator

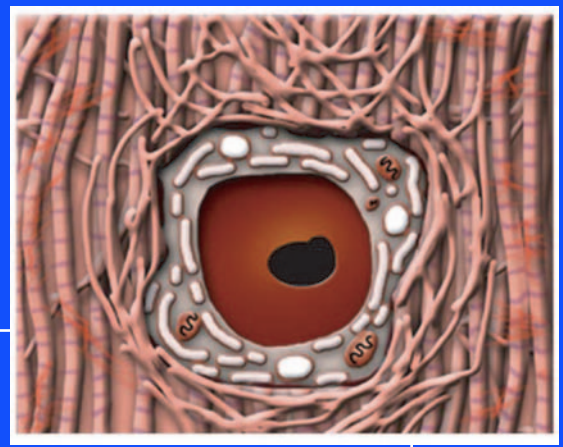
"Control Volume"

UNIT CELL PROCESSES
The "Control Volume" and Regulators

Chemical (Soluble) Regulator

Cell Biology Subjects

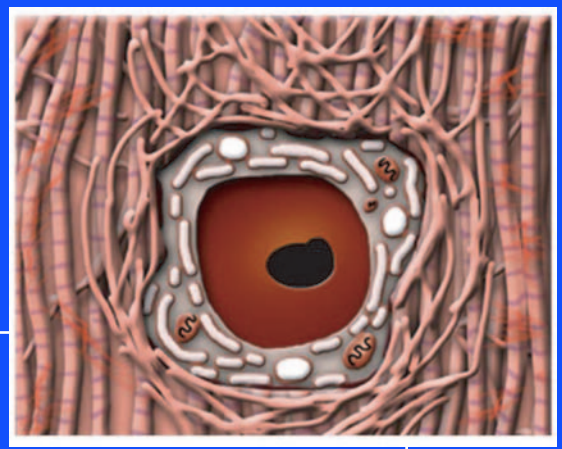
Figure by MIT OCW.



Cell + Matrix Molecules (Insoluble Reg.) —UCP→ Product + Soluble Regulator

"Control Volume"

UNIT CELL PROCESSES
The "Control Volume" and Regulators



Chemical (Soluble) Regulator

Figure by MIT OCW.

Cell + Matrix Molecules (Insoluble Reg.) —UCP→ Product + Soluble Regulator

Biomaterials

"Control Volume"

2.79

UNIT CELL PROCESSES
The "Control Volume" and Regulators

Chemical (Soluble) Regulator

Mechanical Force (Strain); Physical Regulator

Exogenous MF

2.785

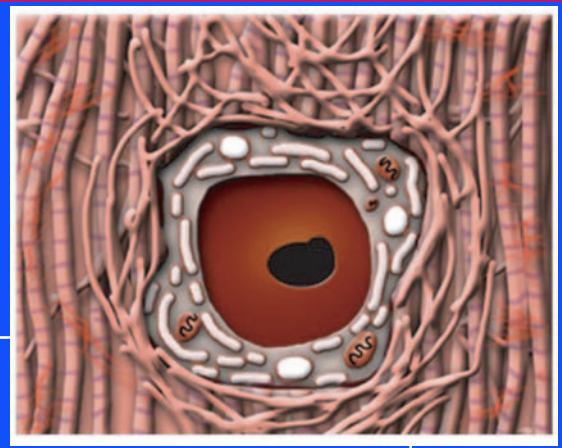
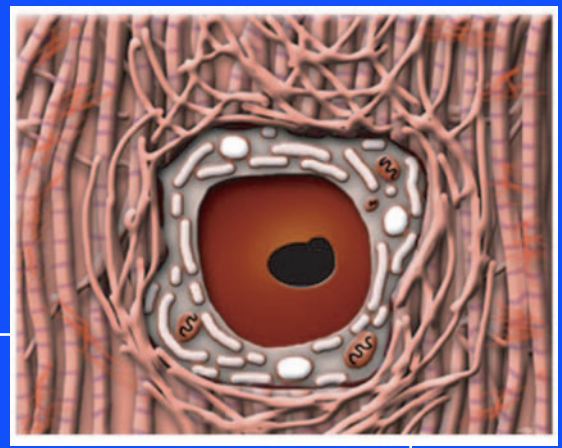


Figure by MIT OCW.

Cell + Matrix Molecules (Insoluble Reg.) —UCP→ Product + Soluble Regulator

"Control Volume"

UNIT CELL PROCESSES
The "Control Volume" and Regulators



Chemical (Soluble) Regulator

Mechanical Force (Strain); Physical Regulator

2.785

Figure by MIT OCW.

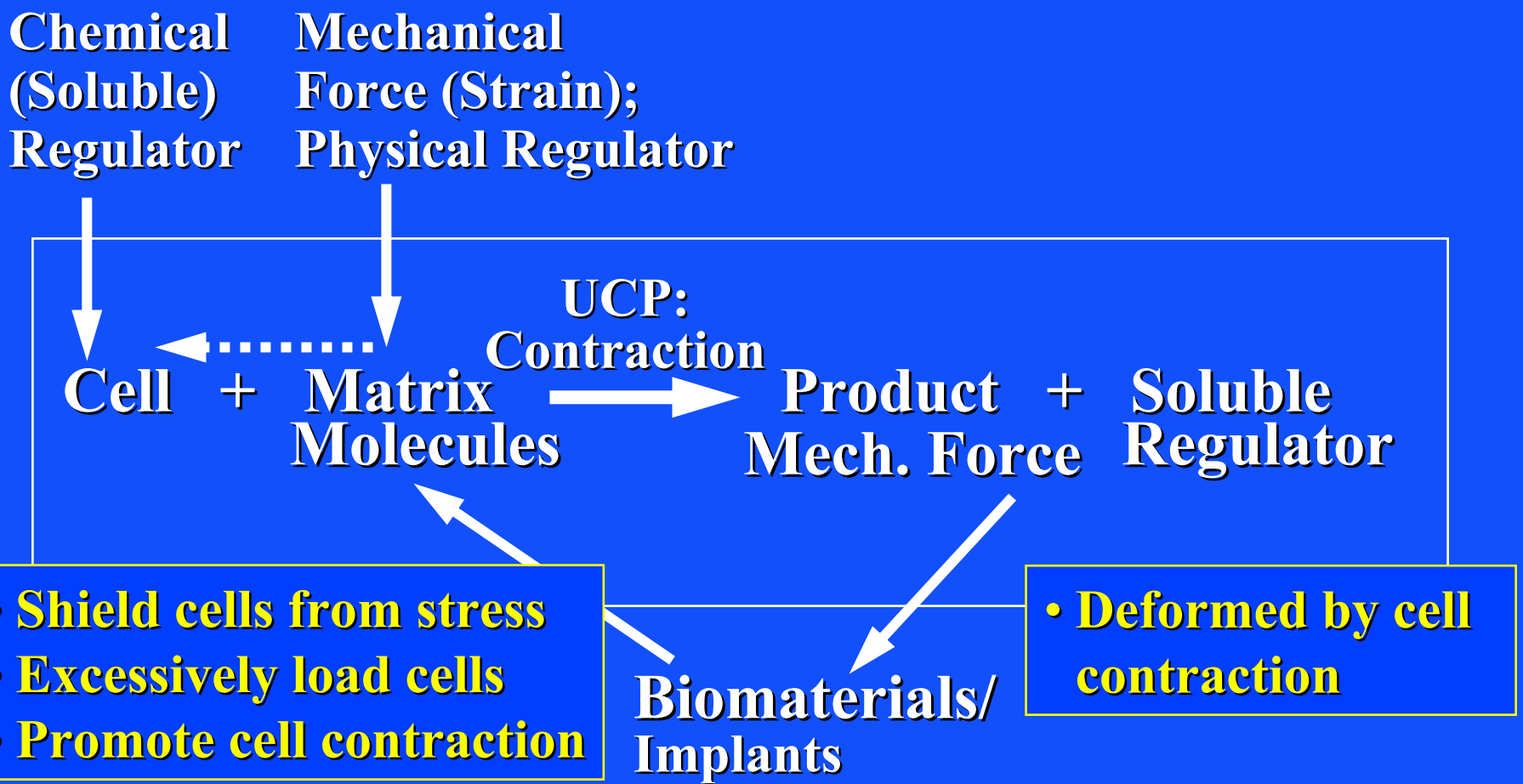
UCP: Contraction

Cell + Matrix Molecules (Insoluble Reg.) → Product Mech. Force + Soluble Regulator

Endogenous MF

"Control Volume"

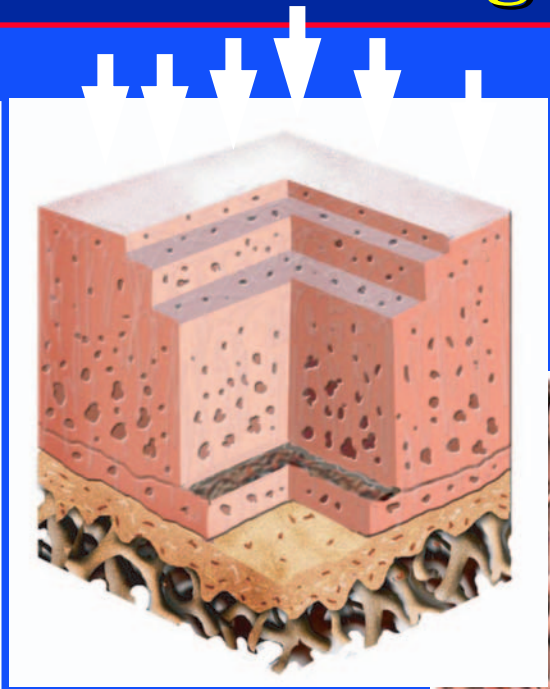
UNIT CELL PROCESSES
The "Control Volume" and Regulators

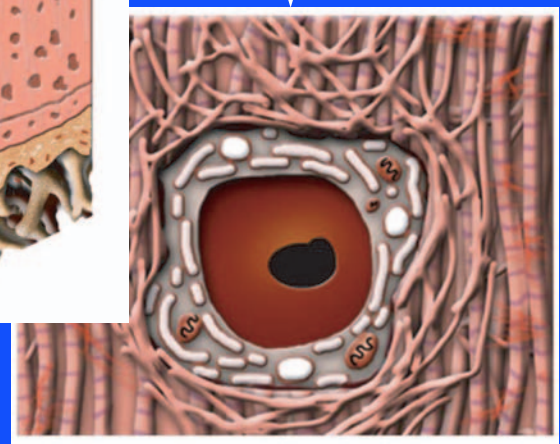


UNIT CELL PROCESSES
The "Control Volume" and Regulators

Mechanical
Force (Strain);
Physical Regulator

Cell + Matrix
Molecules
(Insoluble Reg.)





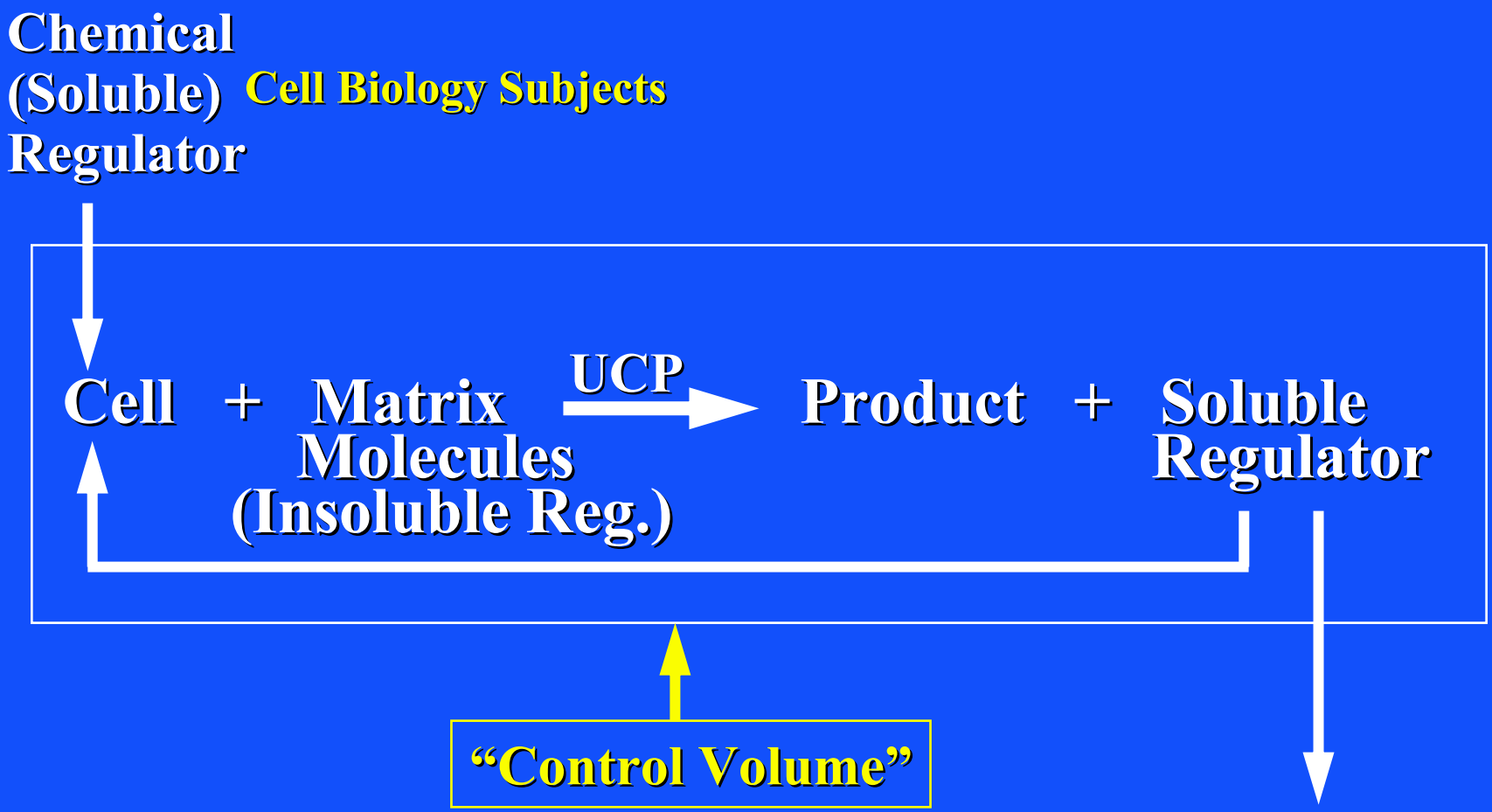
Figures by MIT OCW.

The strain experienced by the cell will depend on the load-deformation behavior (modulus of elasticity) of the Matrix

CELL-MATRIX MECHANICS

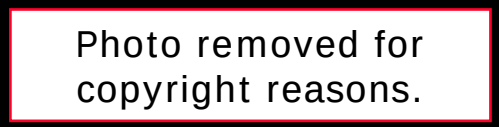
- **How cells respond to mechanical force**
  - **Load-deformation of the matrix**
- **How cells generate mechanical forces**

UNIT CELL PROCESSES
The "Control Volume" and Regulators

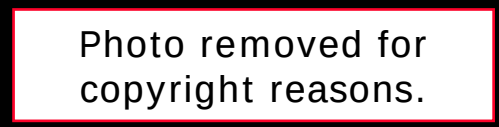


Bone (Trabecular) Structure

Normal

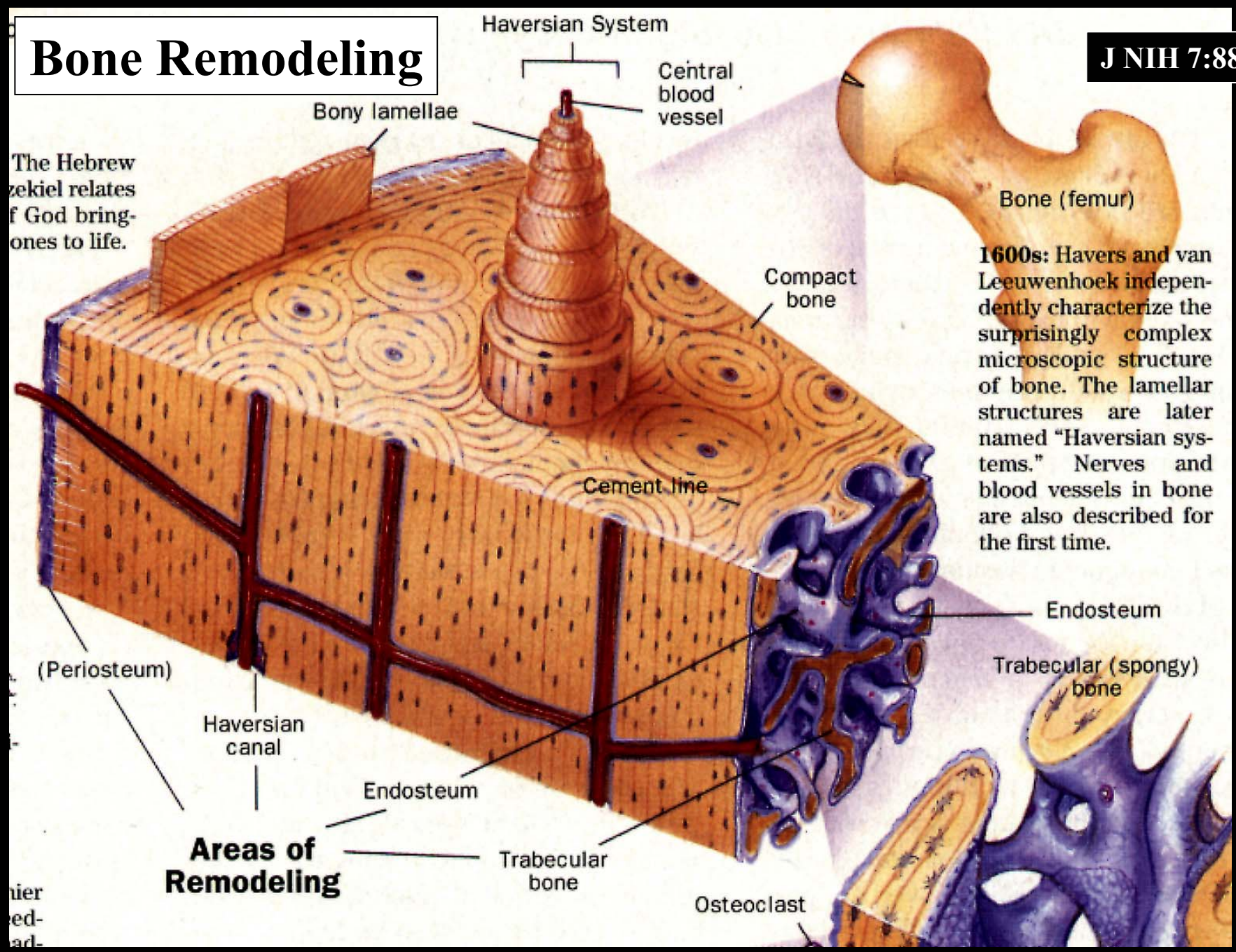


**Osteoporotic:
Postmenopausal**



Bone Remodeling

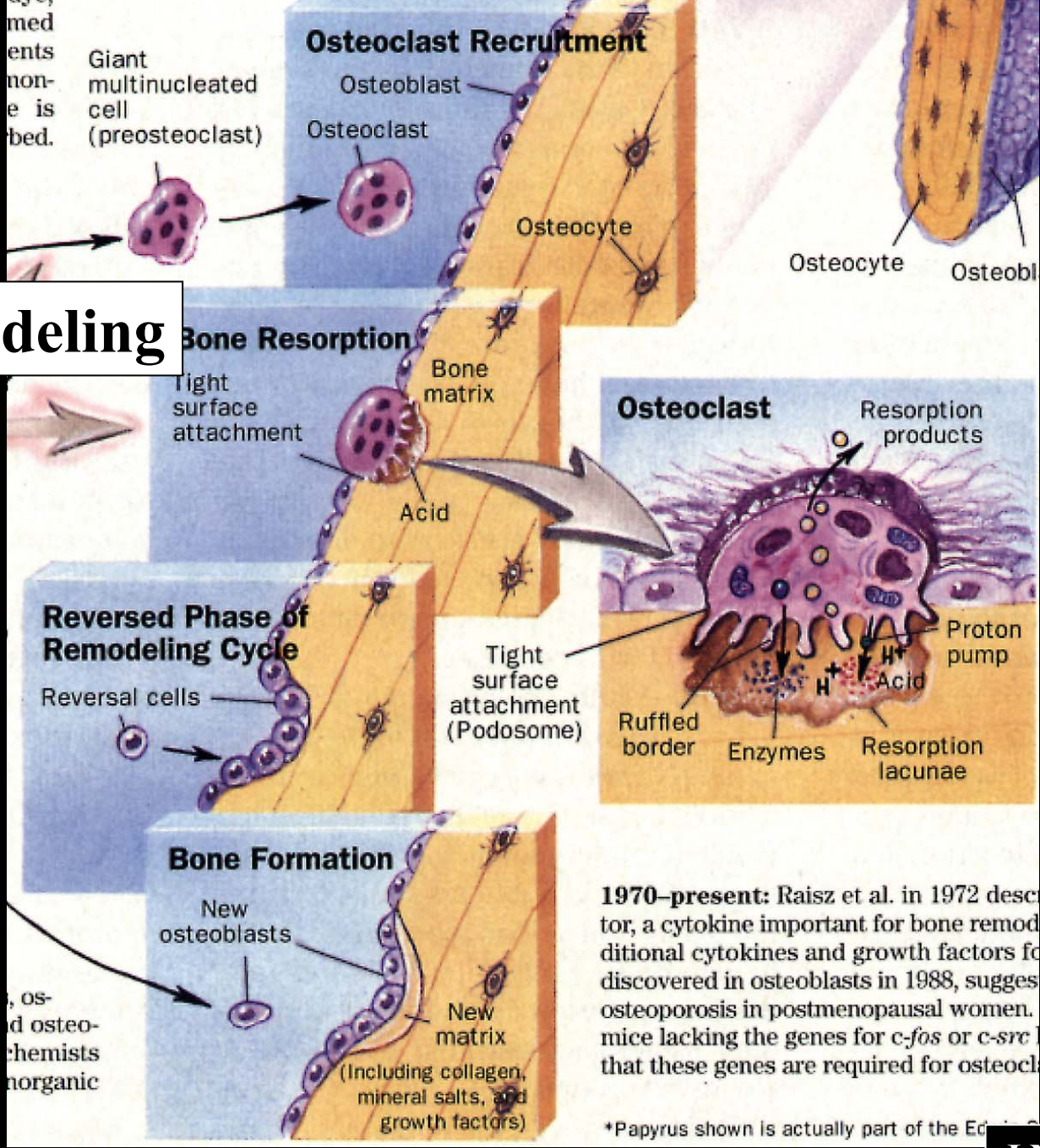
J NIH 7:88 (1995)



The Hebrew ezekiel relates f God bring- ones to life.

1600s: Havers and van Leeuwenhoek independently characterize the surprisingly complex microscopic structure of bone. The lamellar structures are later named "Haversian systems." Nerves and blood vessels in bone are also described for the first time.

Bone Remodeling



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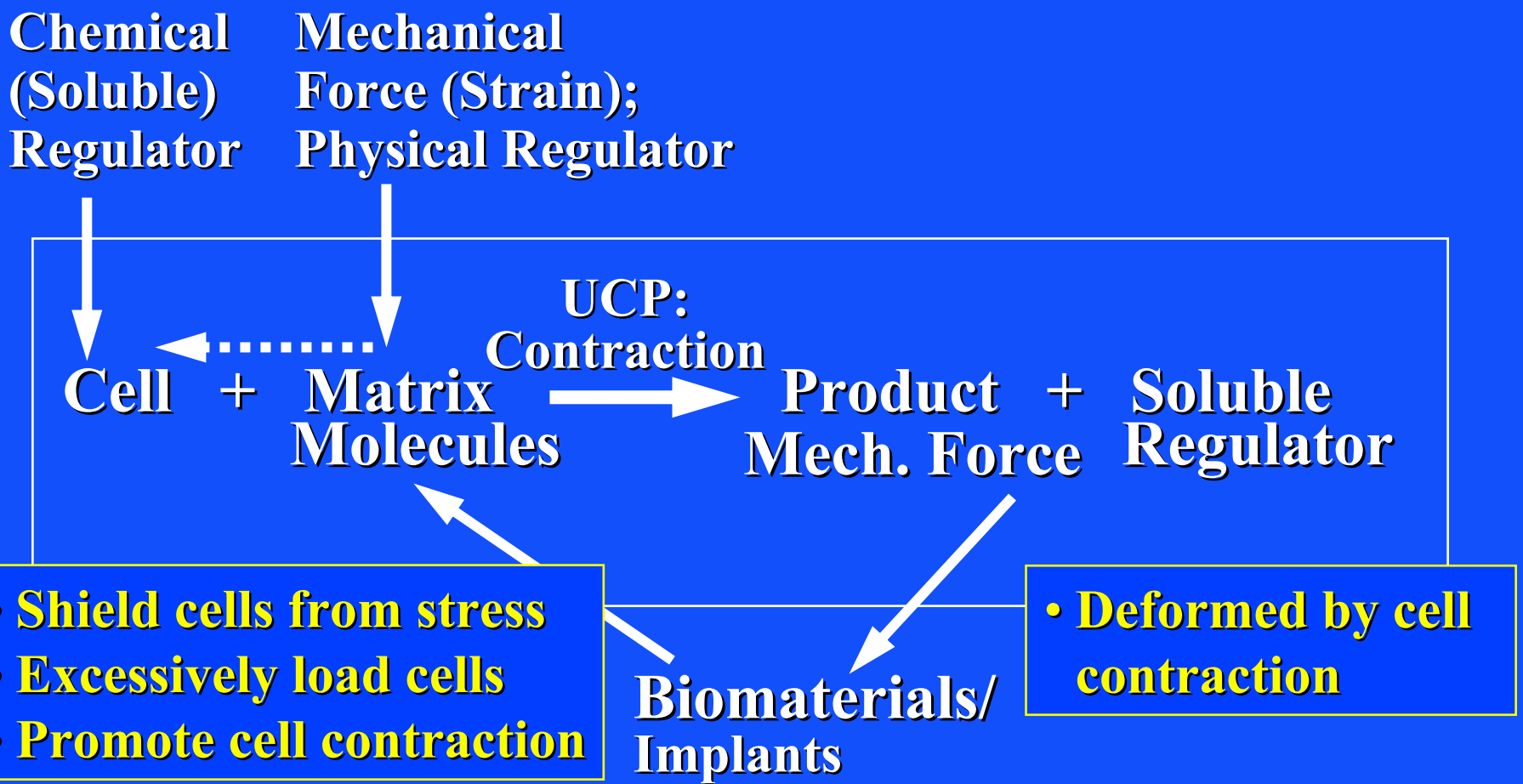
1970–present: Raisz et al. in 1972 desc
tor, a cytokine important for bone remod
ditional cytokines and growth factors fo
discovered in osteoblasts in 1988, sugges
osteoporosis in postmenopausal women.
mice lacking the genes for c-*fos* or c-*src*
that these genes are required for osteocl

*Papyrus shown is actually part of the Ed

J NIH 7:88 (1995)

UNIT CELL PROCESSES
The "Control Volume" and Regulators



CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Shielding cells from stress
  - Excessively loading cells
  - Promoting cell contraction
- How cells generate mechanical forces
  - Deformation of biomaterials/implants

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Shielding cells from stress

    Joint replacement prostheses

Knee and Hip Replacement with Prostheses

Photos removed for copyright reasons.

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Excessively loading cells

    Tissue expanders (soft tissue)

    Distraction osteogenesis (bone lengthening)

    Ultrasound stimulation of fracture healing

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Excessively loading cells

    Tissue expanders (soft tissue)

http://www.breastreconstruction.ca/implant.htm

Tissue Expanders for Breast Reconstruction

Tissue expansion is a process that stretches the skin in preparation for the placement of a permanent implant later. Depending on whether one is dealing with an immediate or a delayed reconstruction, the tissue expander is either placed at the time of the mastectomy or during a subsequent procedure.

Photo removed for copyright reasons.

Photo removed for copyright reasons.

Schematic showing the position of the tissue expander under the pectoralis major muscle.

Intraoperative view of the tissue expander placed underneath the pectoralis major muscle.

Photo removed for copyright reasons.

Photo removed for copyright reasons.

Schematic shows the position of the tissue expander and three stages in its expansion. At the completion of expansion the permanent breast implant will be inserted in a similar location.

Photo removed for copyright reasons.

Intraoperative view of the tissue expanders being inflated.

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Excessively loading cells

    Distraction osteogenesis (bone lengthening)

Limb Lengthening
Distraction Osteogenesis

Photos removed for copyright reasons.

Gavriel Illizarov, M.D., Russian Orthopaedic Surgeon

http://www.ilizarov.com/english/limb_lenghtening.asp

Insertion of the intramedullary nail and osteotomy; The corticotomy is completed percutaneous with a corticotome.

Application of the external fixator

Photo removed for copyright reasons.

Photo removed for copyright reasons.

Distraction (the method of taking the bony fragments away from each other) is started in the tenth day. The rate of the distraction should be 0.25 mm four times a day.

Rat Model

Sacrifice 5 days after a 13-day distraction period

Photos removed for copyright reasons.

Kinner B, et al. *J. Orthop. Res.* 2003;21:20

Cranial Deformation

Photos removed for copyright reasons.

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Excessively loading cells

    Ultrasound stimulation of fracture healing

Sonic Accelerated Fracture Healing System
Exogen 2000®

- **Low-intensity ultrasound (lower than a fetal sonogram)**
  - **Accelerates fracture healing by 38%**
  - **Prescribed by physicians**
  - **Used by patients at home or work**
  - **20 minute treatment time once per day**

- **Osteoporosis Studies**
  - **New and unique mechanical stress technology**
  - **Non-pharmaceutical therapy**
  - **Subject of pre-clinical studies**
  - **Demonstrated prevention of bone loss and increase in bone mass (animal studies)**
  - **Currently being studied in post-menopausal women**

- **Clinical Use**
  - **Prescribed for more than 15,000 fractures**
  - **Prescribed by over 6,000 physicians**
  - **Reimbursed by more than 800 insurers**

Source: http://ortho.smith-nephew.com/au/Category.asp?NodeId=2480

The Role of Ultrasound in Fracture Healing

See Smith & Nephew slide presentation online at
http://ortho.smith-nephew.com/nl/Category.asp?NodeId=1453
(last accessed 25 January 2005)

CELL-MATRIX MECHANICS

Clinical Examples/Medical Devices

- How cells respond to mechanical force
  - Promoting cell contraction
- How cells generate mechanical forces
  - Deformation of biomaterials/implants

    Tissue contracture

Scar Contracture after a Burn Injury

Photos removed for copyright reasons.

What cells are responsible for this?
Treatments?

Food and Drug Administration
Breast Implant Complications

Photographs of
Breast Implant Complications

http://www.fda.gov/cdrh/breastimplants/breast_implants_photos.html

FDA has developed this website for displaying photographs and/or illustrations of breast implant complications.

This website is not intended to be photographic representation of all breast implant complications. FDA will continue to add photographs and/or illustrations of complications associated with saline-filled and silicone gel-filled implants as they become available.

You should refer to the breast implant consumer handbook, which is available on the FDA breast implant website at

http://www.fda.gov/cdrh/breastimplants/

for a description of potential breast implant complications.

http://www.fda.gov/cdrh/breastimplants/breast_implants_photos.html

BREAST IMPLANTS
Capsular Contracture

Capsular contracture occurs when the scar tissue or capsule that normally forms around the implant tightens and squeezes the implant. It may be more common following infection, hematoma (collection of blood), and seroma (collection of watery portion of blood). There are four grades of capsular contracture.

The Baker grading is as follows

Grade I	the breast is normally soft and looks natural
Grade II	the breast is a little firm but looks normal
Grade III	the breast is firm and looks abnormal (visible distortion)
Grade IV	the breast is hard, painful, and looks abnormal (greater distortion)

Additional surgery may be needed to correct the capsular contracture. This surgery ranges from removal of the implant capsule tissue to removal (and possibly replacement) of the implant itself. Capsular contracture may happen again after this additional surgery.

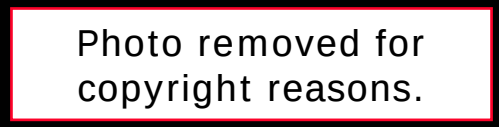
Breast Implant Position and “Capsular Contraction”

Diagrams removed for copyright reasons.

Boston Globe, July 22, 1991

Fibroblasts with contractile capacity cause contracture of the fibrous tissue

BREAST IMPLANTS
Capsular Contracture



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.

BREAST IMPLANTS Capsular Contracture

Removed implant: viewing the outside of the fibrous capsule

Photo removed for copyright reasons.

Photo removed for copyright reasons.

Inside of the fibrous capsule

Implant

Photo removed for copyright reasons.

Photo removed for copyright reasons.

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.

BREAST IMPLANTS
Capsular Contracture

How can Capsular Contracture be prevented?

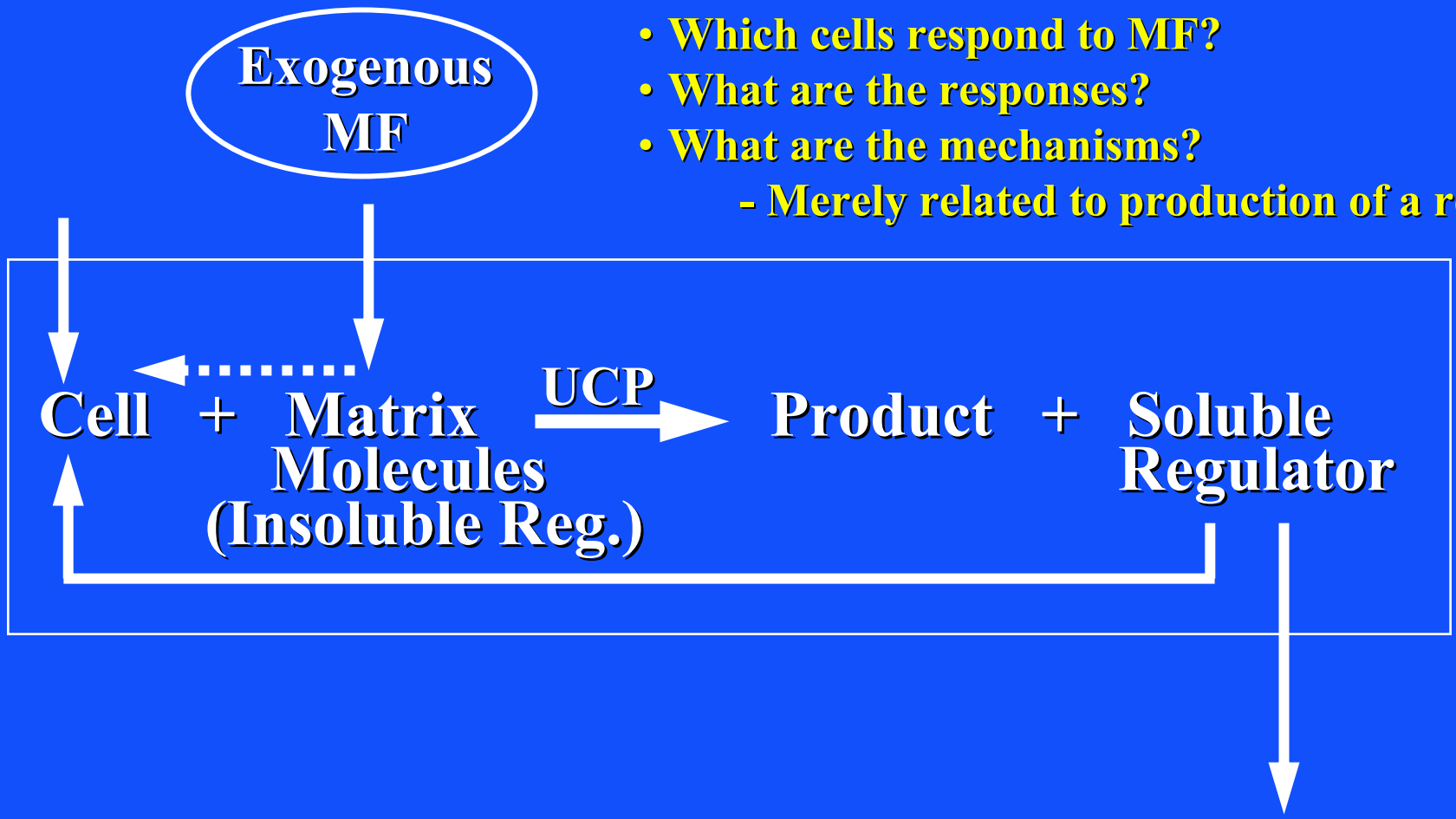
Massage and or compression. This is usually only done with smooth implants and may be suggested for a period between a few weeks to as long as you have your implants. Do not massage bruises!

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.

CELL-MATRIX MECHANICS

- How cells respond to mechanical force
  - Load-deformation of the matrix
- How cells generate mechanical forces

UNIT CELL PROCESSES
The "Control Volume" and Regulators



UNIT CELL PROCESSES
The "Control Volume" and Regulators

- Which cells are capable of contraction?
- What are the regulators?
- What are the mechanisms of contraction?