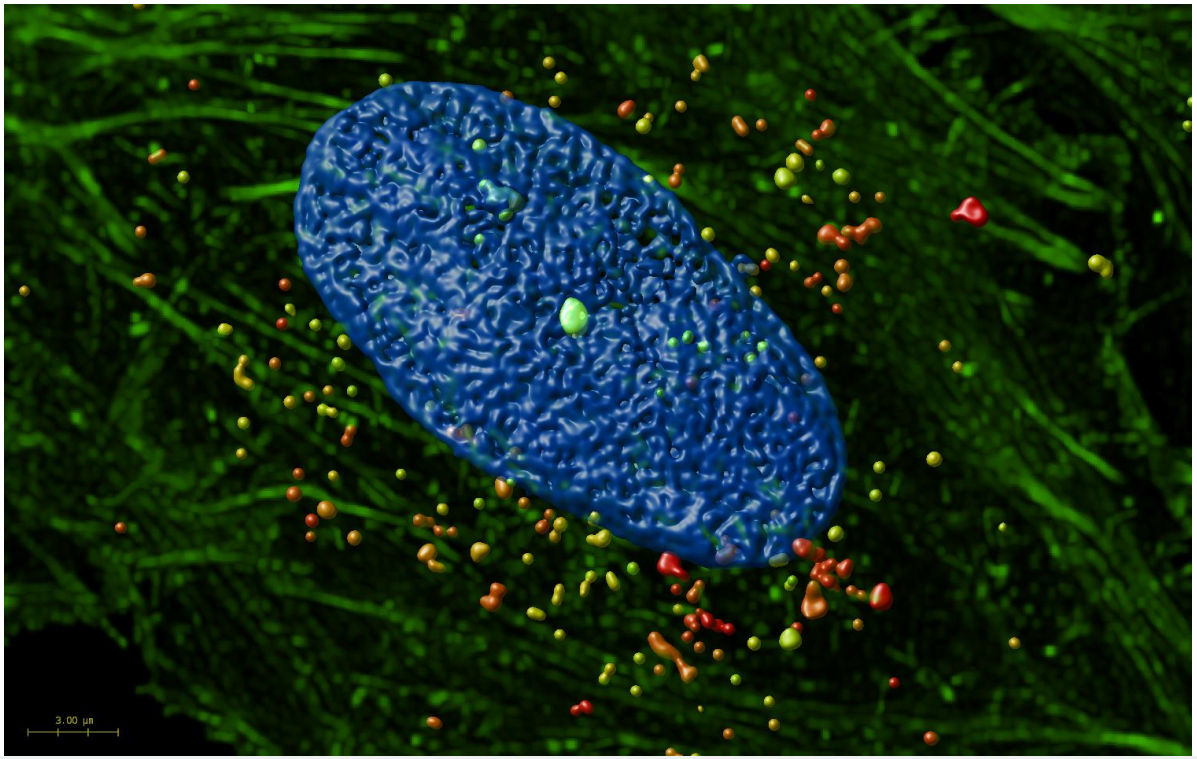
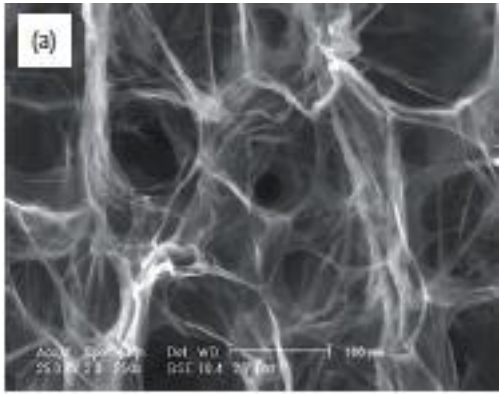


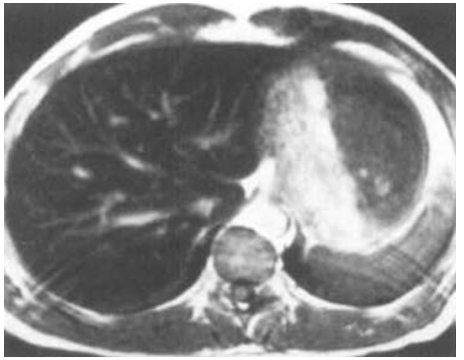
Biomaterials
May 17, 2019

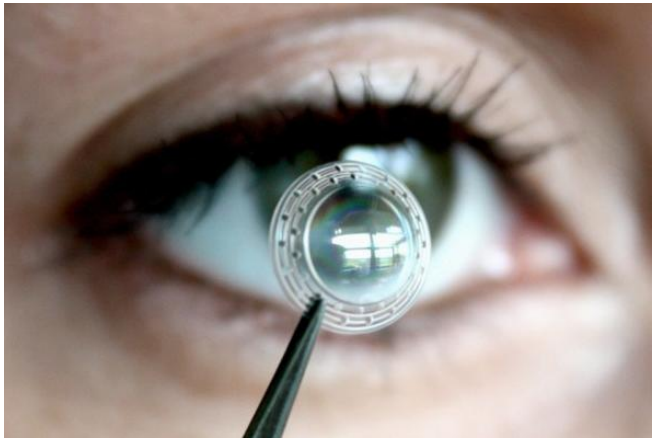
Dr. Annette Kraegeloh
INM - Leibniz Institute for New Materials

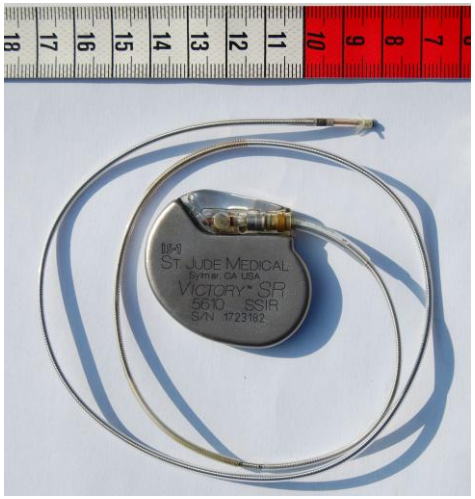
Biomaterials

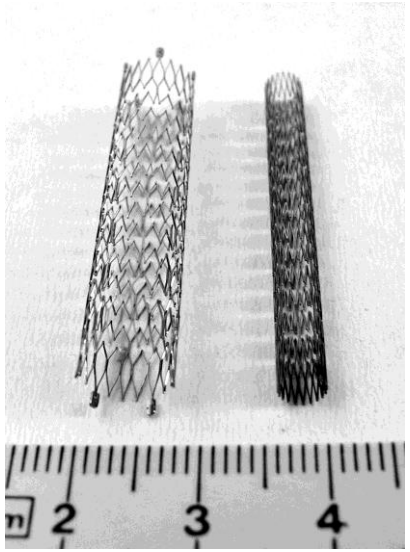
Biomaterials are synthetic or natural non-living materials that are used for therapeutic or diagnostic purposes and come into contact with biological tissues within the body.





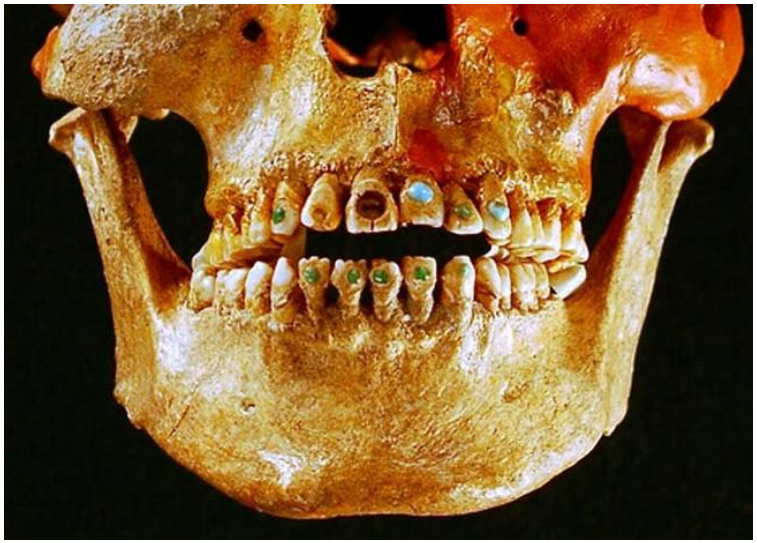






(Nuno Nogueira; Steven Fruitsmaak; ; biomaterial2009.de; Hamm et al., 1994; Frank C. Müller; O'Brien 2011)

Biomaterials in History



Prosthetic toe of an egypt mummy dates back 1,000 BC.

For cosmetic reasons, Mayans replaced their teeth with false teeth carved out of nacre (600 BC).

Sutures may have been used as long as 32,000 years to close large wounds (e.g. linen, catgut, metals).

The concept of contact lenses was developed by Leonardo da Vinci (1508), first glass lenses were developed by Adolf Fick (1860).

Biomaterials science became established in the 1940s-50s.

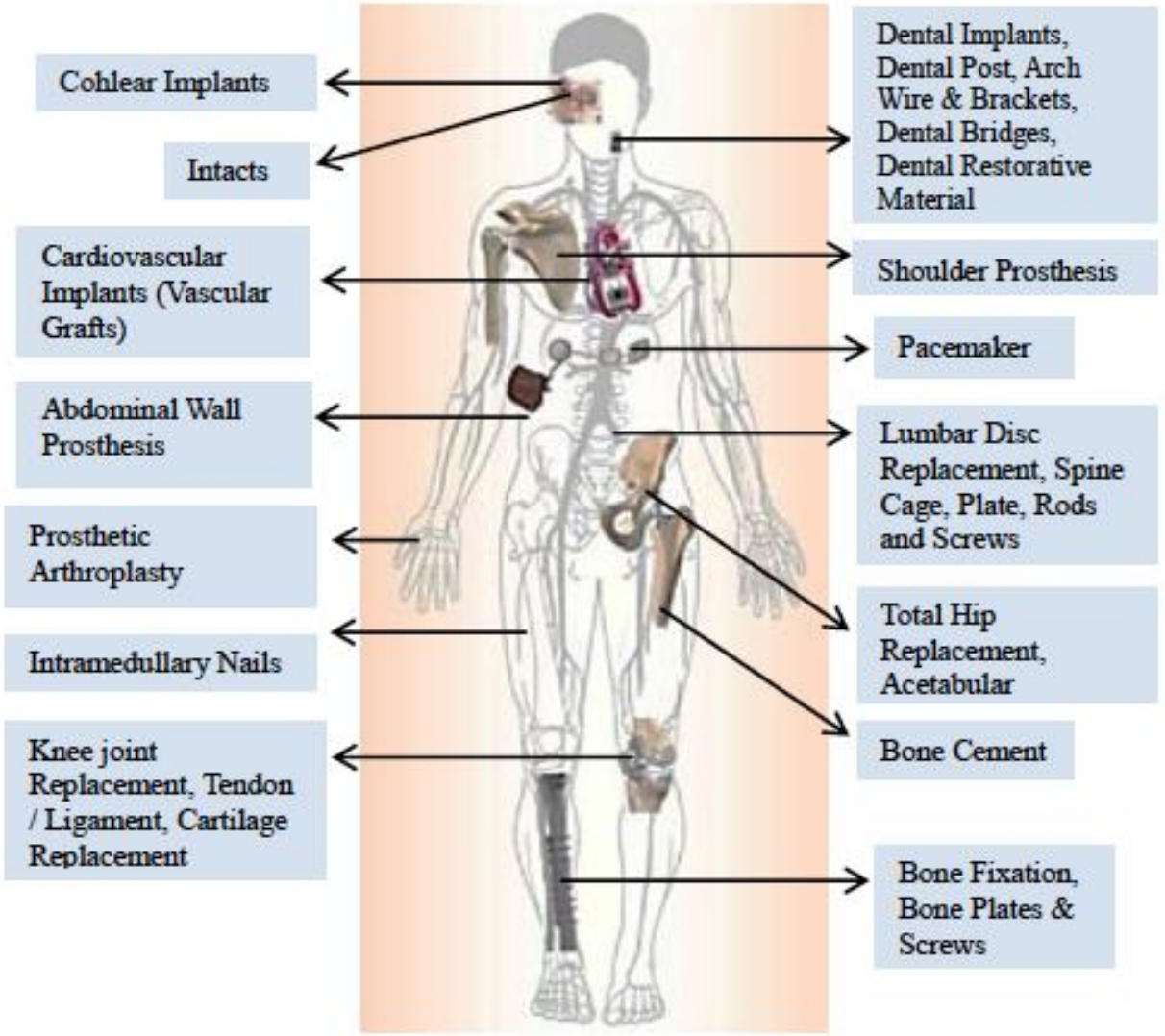
(livescience.com; allthingsbiomaterials.org/archives/89)

Classification of Biomaterials Applications

Biomaterials have to perform the desired function efficiently and for the intended duration, they must do the patient no harm and they have to be deliverable to the patient in an efficient and cost-effective way.

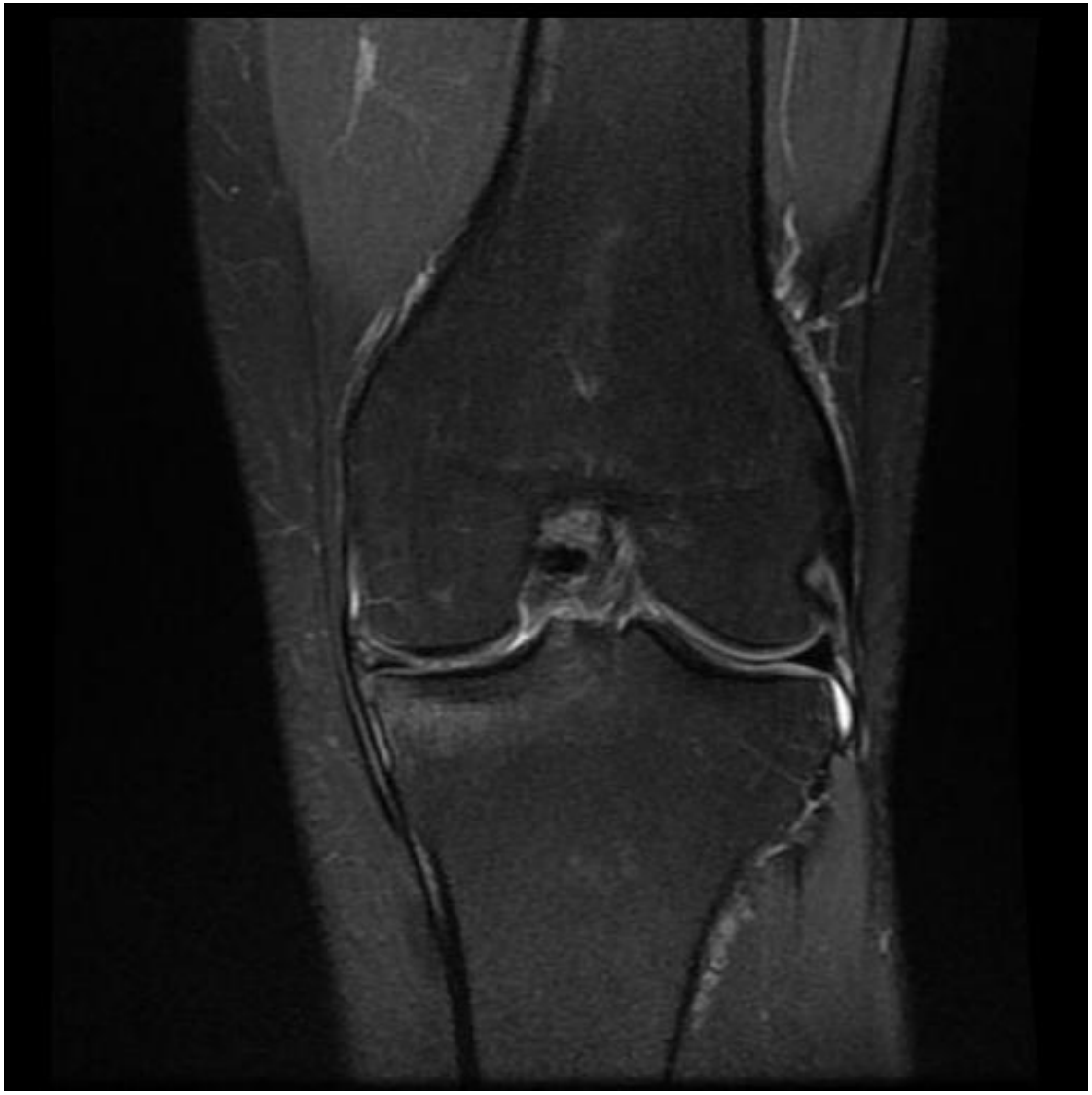
- **Permanent implantable devices** (degenerative diseases, cancerous tissue, deformities, injury, disease, cosmetic purposes)
- **Short-term implantable devices** (repair of broken bones or soft tissue)
- **Invasive but removable devices** (Catheters, shunts, contraceptive devices)
- **External artificial organs /organ assist devices** (bridge to transplant)
- **Surgical and clinical accessories** (wound dressing, catheters, drains)
- **Drug and gene delivery systems** (particulate systems, gene vectors, vaccine delivery, theranostics)
- **Tissue engineering systems** (cell or gene therapy, implanted scaffolds, cell sheet engineered constructs)
- ***In vivo* diagnostic systems** (contrast agents (MRI, CT, ultrasound), fluorescence imaging, implantable biosensors)

Examples of Biomaterials



(Patel and Nohil, 2012)

Necessities for Biomaterials: Joints



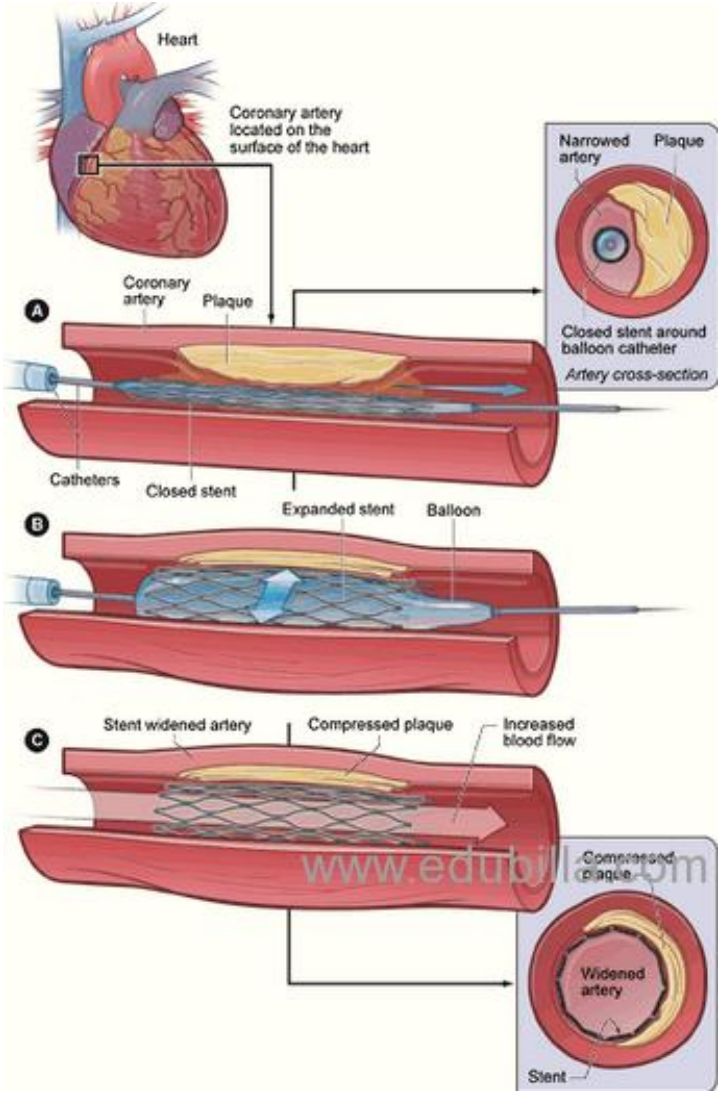
Joints (e.g. hip or knee) mediate rotational or sliding movements.

Cartilage carries part of the load.

Degeneration of the connective tissue and the bone might lead to osteoarthritis.

Early stages are treated with pain and anti-inflammatory medications, at later stages replacement or resurfacing might be necessary.

Necessities for Biomaterials: Blocking of blood vessels



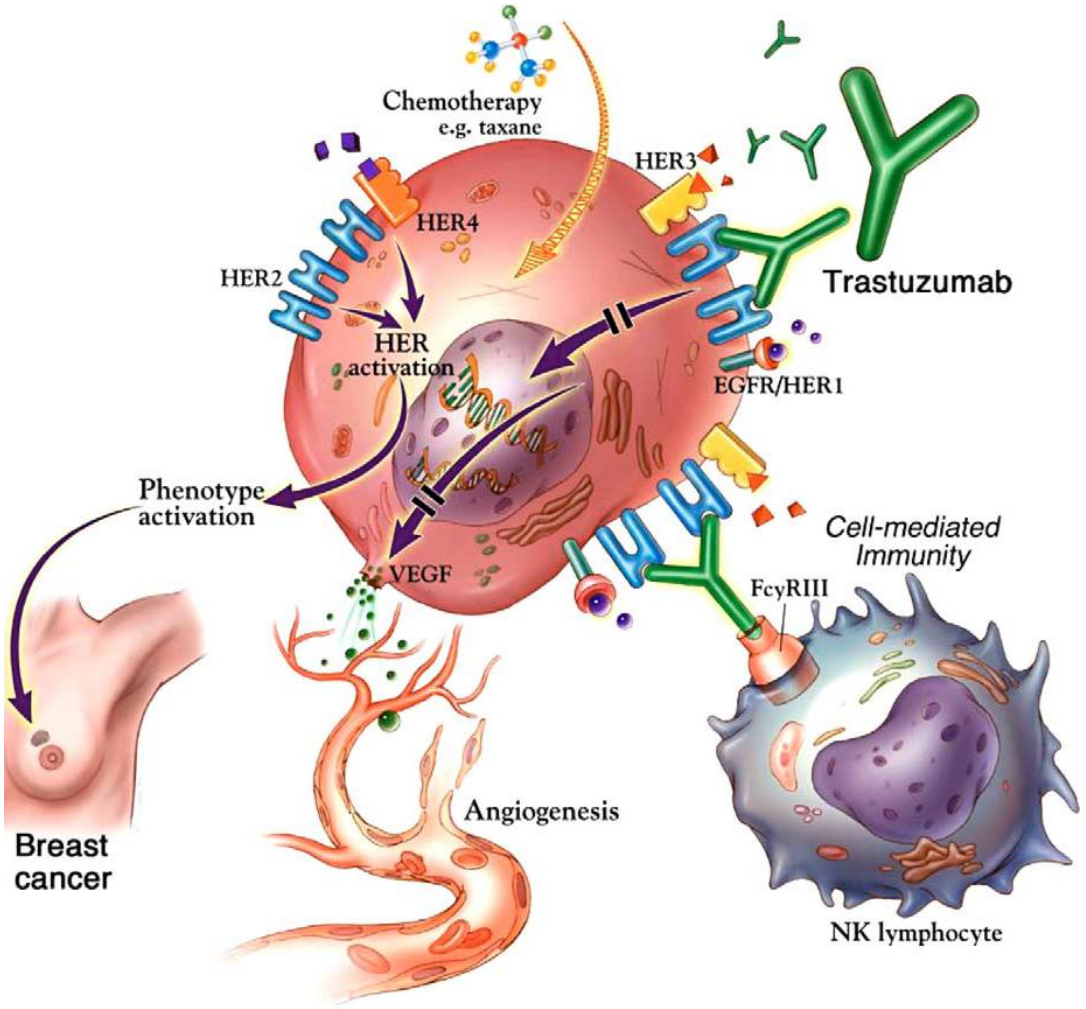
Blocking of arteries by plaque is called atherosclerosis.

Opening might be achieved by angioplasty: a balloon catheter is used to dislodge the plaque.

Intravascular stents are used to hold the vessel open.

A bypass is a further intervention, the blocked parts of arteries are bypassed by a tube.

Necessities for Biomaterials: Diagnosis and Treatment of Cancer



HER-2 receptors are overexpressed in some types of breast cancer, making the tumour aggressive (cell proliferation, angiogenesis).

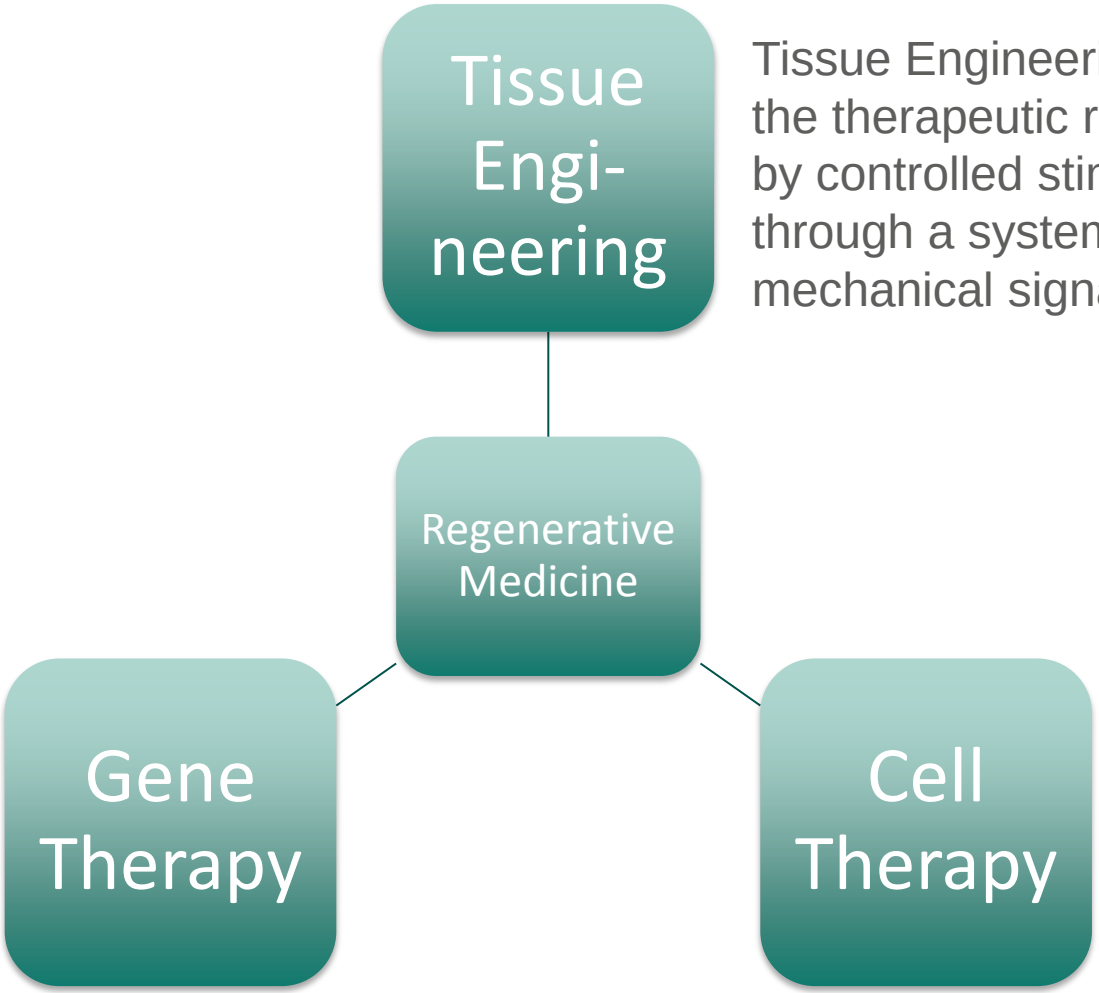
Trastuzumab is a monoclonal antibody directed against the HER-2 protein.

Bound antibody stimulates natural killer cell mediated cell-lysis.

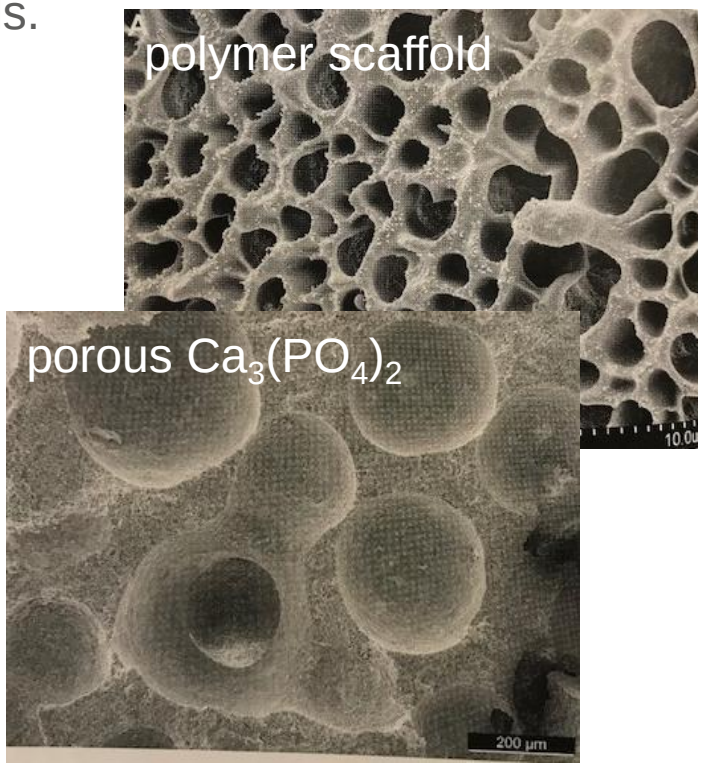
Targeted delivery of cytostatic agents (e.g. taxane) might improve the therapy.

(Nahta, 2006)

A Future Topic: Regenerative Medicine

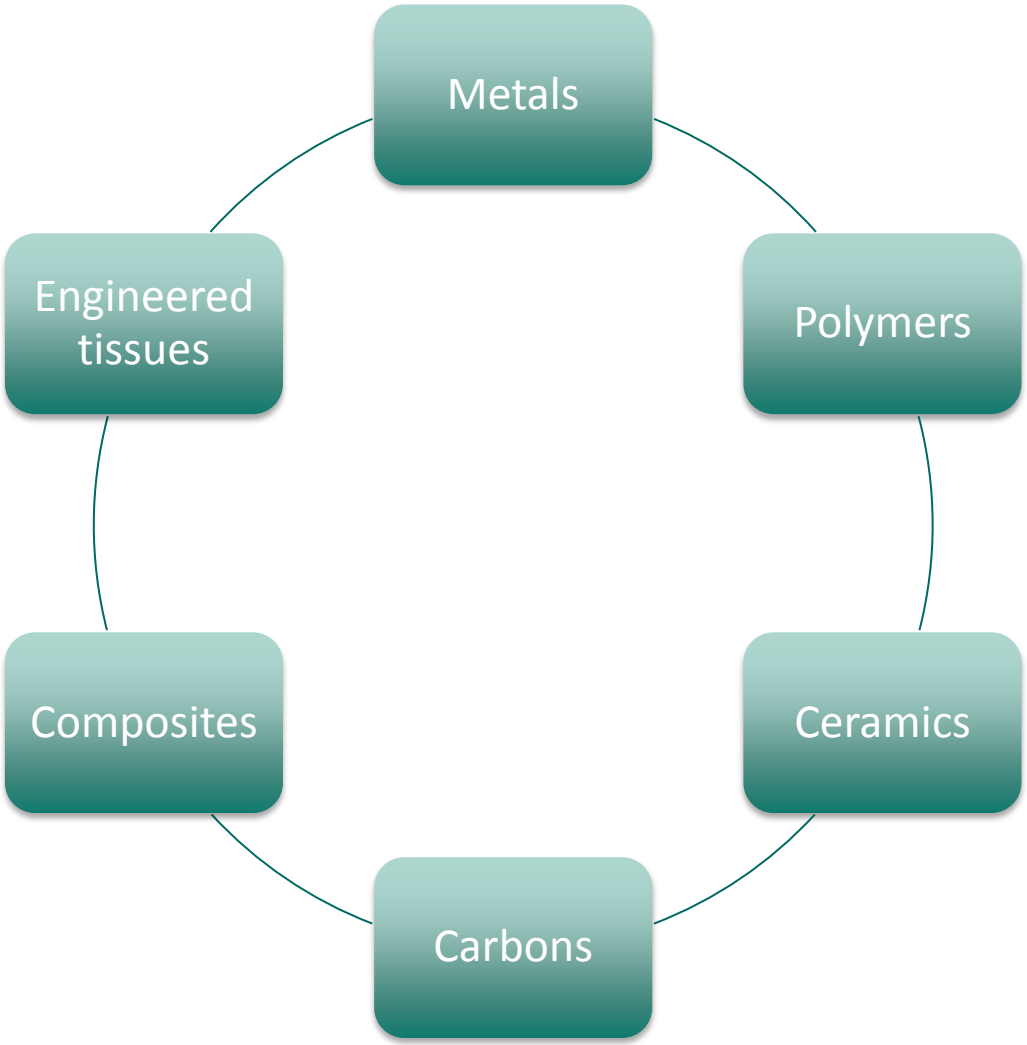


Tissue Engineering: The creation of new tissue for the therapeutic reconstruction of the human body, by controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals.



(Williams, 2014))

Classes of Biomaterials



(Epple, 2003;

Metals

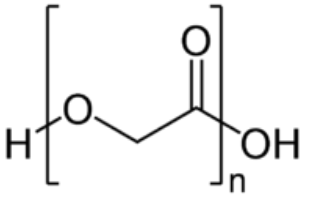
Material	Examples	Applications
Stainless steel	Cr-Ni-steel	Osteosynthesis, dental prostheses
Co-Cr alloys	Vitallium	Osteosynthesis, dental prostheses
Titanium and alloys	Ti-6Al-4V	Osteosynthesis, dental implants
Ni-Ti alloys	Nitinol	stents
Au, Ag, Cu..		Dental prostheses

Advantages:	Disadvantages:
Mechanical stability	Lacking biodegradability
Elasticity	Corroding
Ductility	Sensitizing

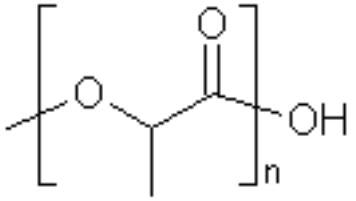
(Epple, 2003)

Polymers

Material	Biodegradability	Applications
Cellulose	+	Drug delivery
collagen	+	Suture material
polyester	+	Wound coverage
polyethylen	-	Joint socket, ligaments
polymethyl-methacrylat	-	Bone cement, intraocular lenses



PGA



PLA

Advantages:
Variable material properties
Surface functionalisation
Polymerisation within the body
Low density

Disadvantages:
Poorer mechanical properties than metals
Properties can change in contact with tissues
Degradability
Sterilisation might change material properties

(Epple, 2003)

Ceramics

Material	Biological Activity	Applications
Calcium phosphate	Biocompatible/bioactive, biodegradable	Bone replacement, implant coating
bioglass	Biocompatible/bioactive, biodegradable	Bone replacement
Aluminium oxide	Bioinert, not biodegradable	Joint socket, joint head
Zirconium oxide	Bioinert, not biodegradable	Dental materials

Advantages:
Hardness

Disadvantages:
Brittleness
Crack propagation

(Epple, 2003)

Joint Replacement Prostheses

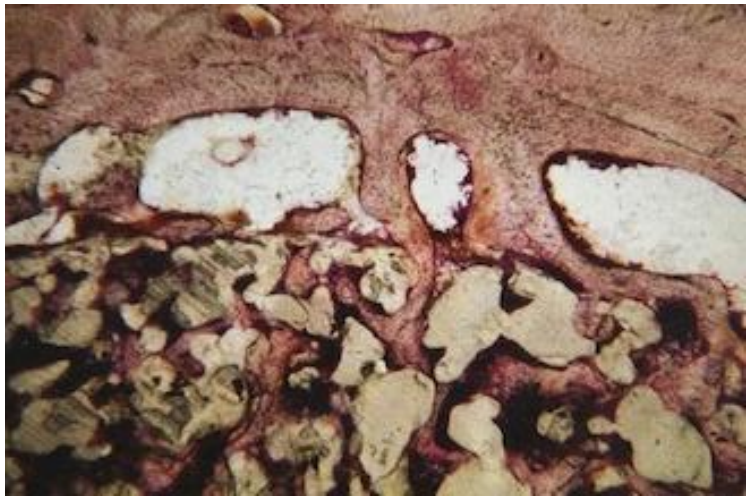
Material choices: wear resistance, low friction of the articulating surfaces

Material combinations	Coefficient of friction
Human articular joints	**0.01**
Alumina on alumina	**0.05**
Steel on polyethylene	**0.07**
Steel on steel	**0.80**

„elastohydrodynamic lubrication“ (cartilage with synovial fluid)

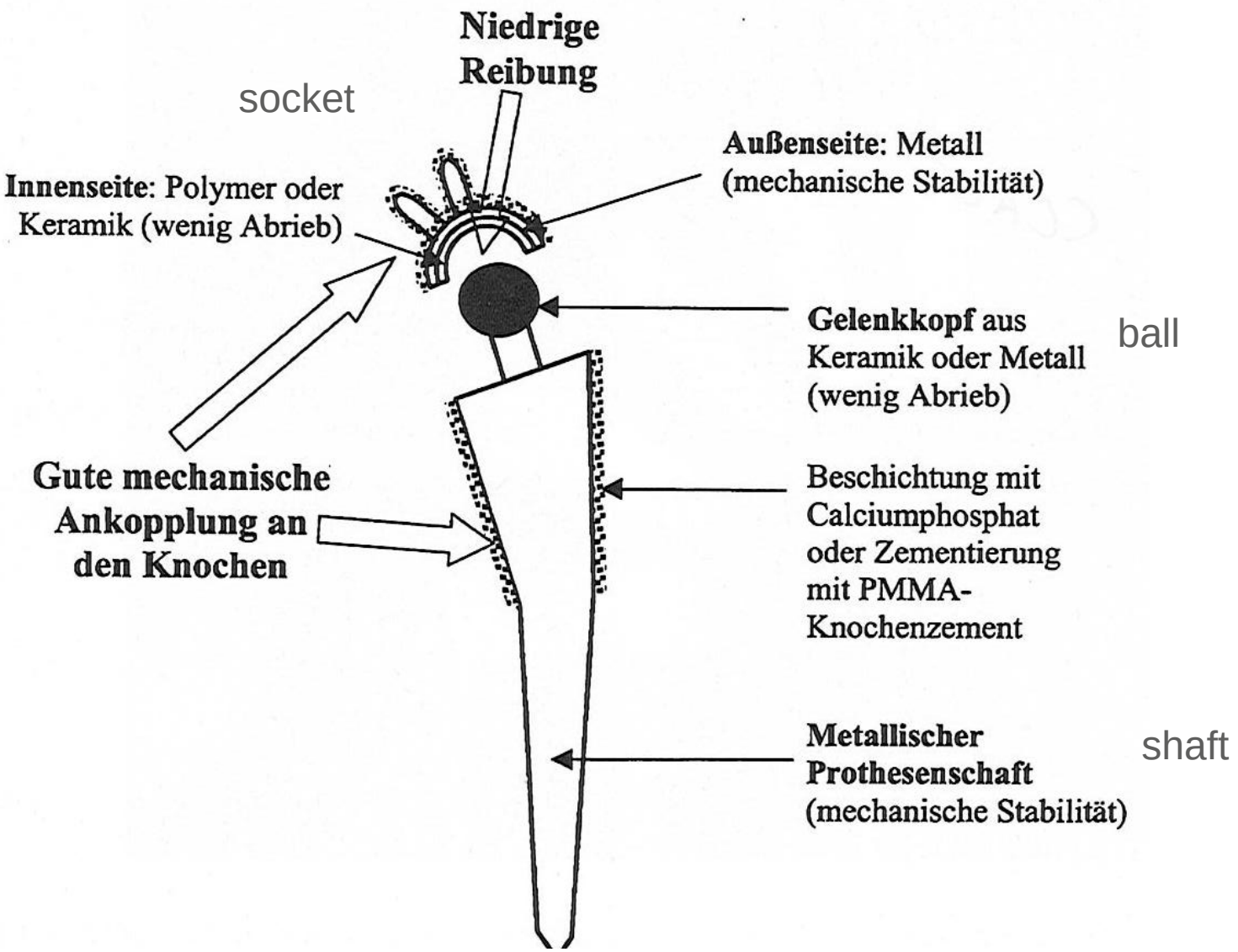
Attachment to bone:

- bone ingrowth into porous surfaces
- acrylic cements (amorphous polymer, exotherm polymerization reaction, toxicity of methylmethacrylate, no chemical bonds)



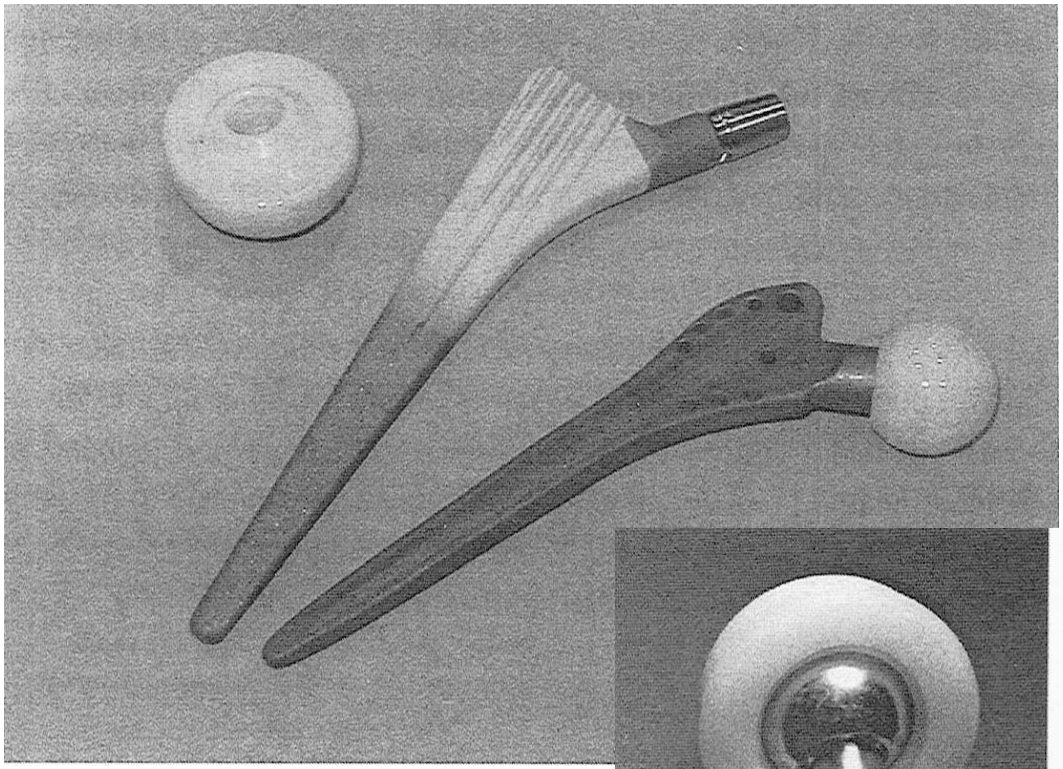
(Williams, 2014)

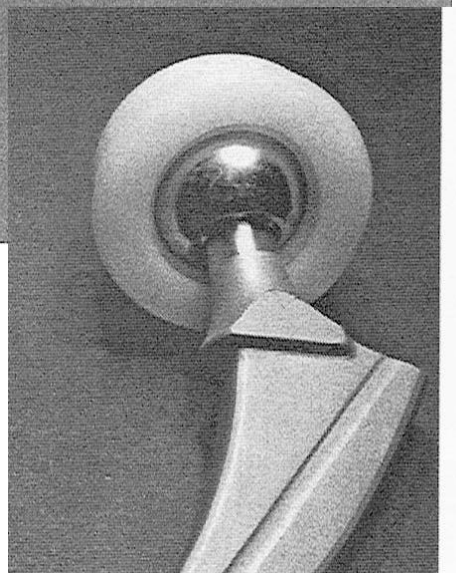
Hip Replacement Design

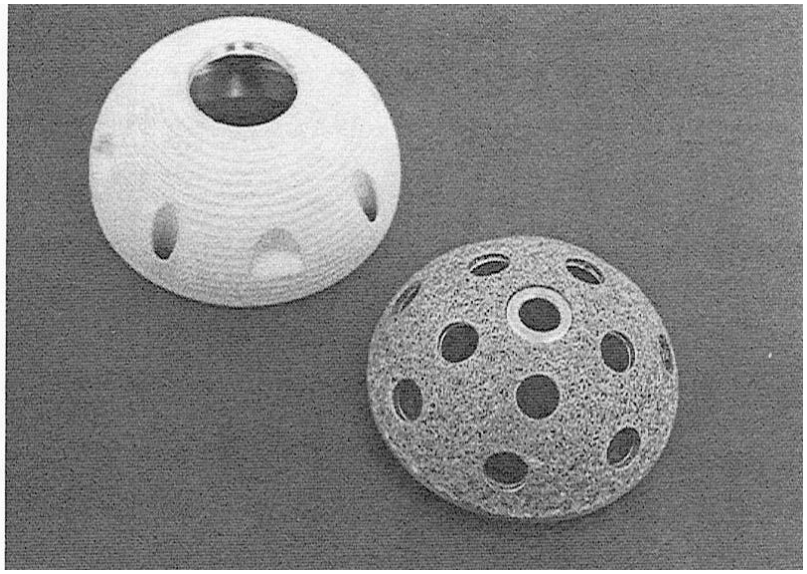


(Epple, 2003)

Hip Replacement Devices



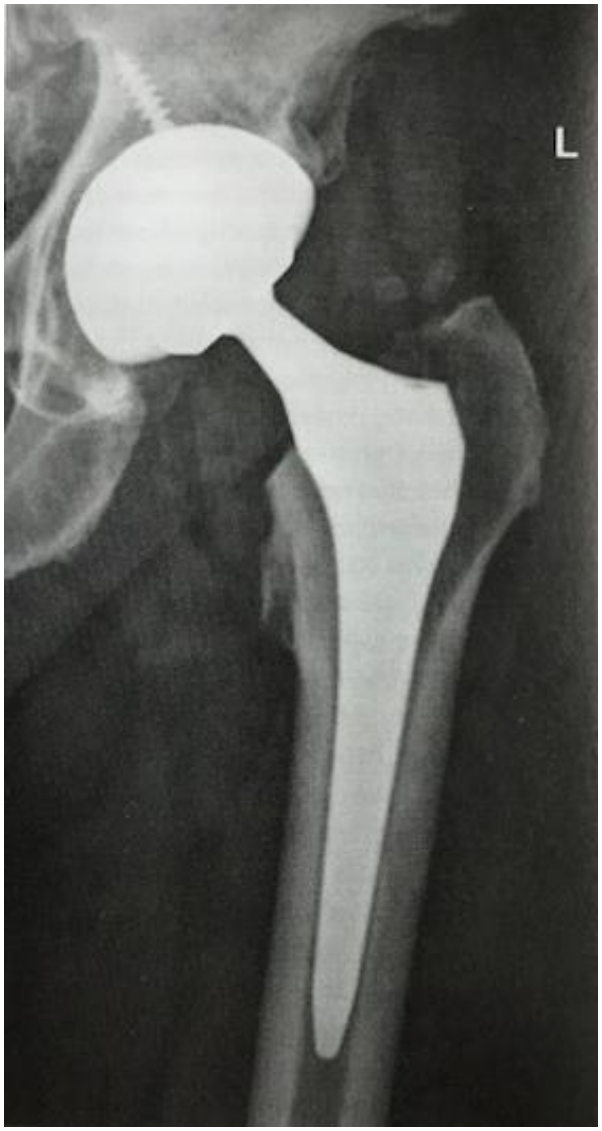


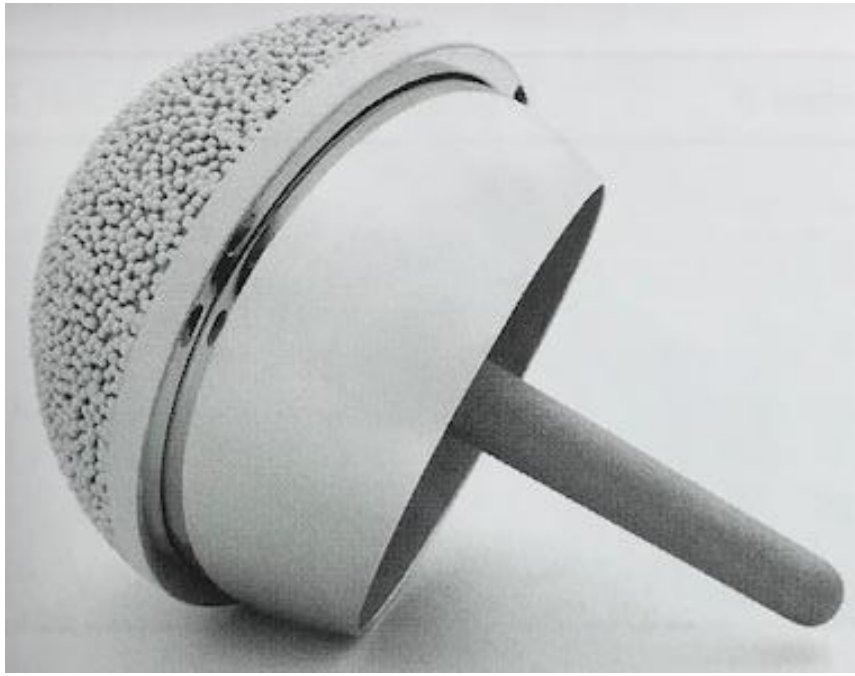


joint socket
ball
shaft

(Epple, 2003)

Hip Replacement and Hip Resurfacing





(Williams, 2014)

Hip Replacement

Cemented	Non-cemented
+ better fit	- danger of loosening
+ rapid resilience	- recovery necessary
+ simple implantation	- precise adjusment necessary
- local tissue damage	+ no tissue burden
- Bone loss during revision	+ less bone loss during revision
+ application of antibiotics	+ bioactive coating possible
older patients	younger patients

Clinical performance: 10 year survival 95%, 20 year survival 90%, uncemented 70%

Failure: loosening as result of wear, osteolysis, fractures, dislocation, infection (*Staphylococcus aureus*)

Complications: deep vein thrombosis, pulmonary embolism

(Epple, 2003, Williams, 2014)

Mechanical Properties of Biomaterials: Elastic Deformation

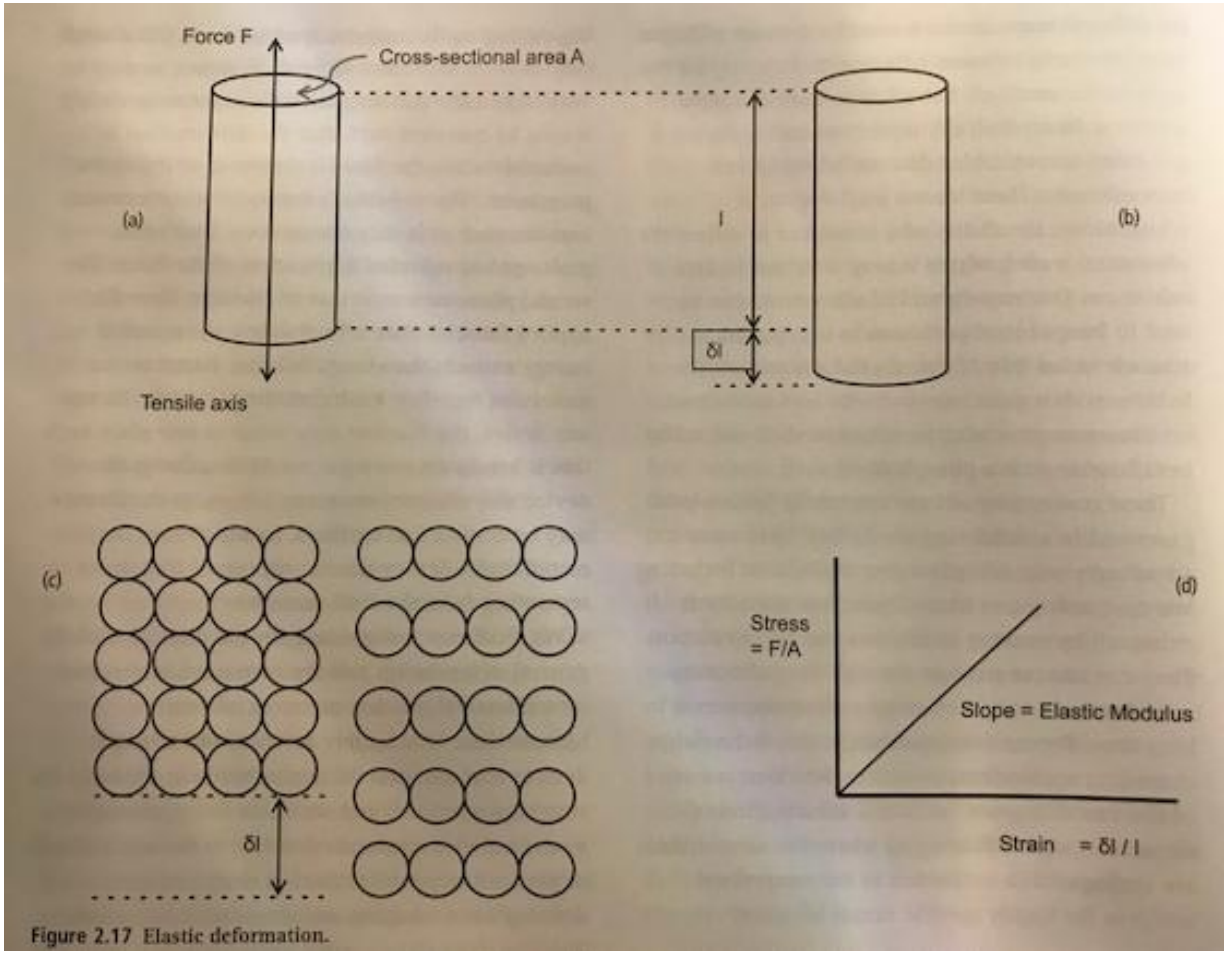


Figure 2.17 Elastic deformation.

a) the tensile stress is given by F/A.

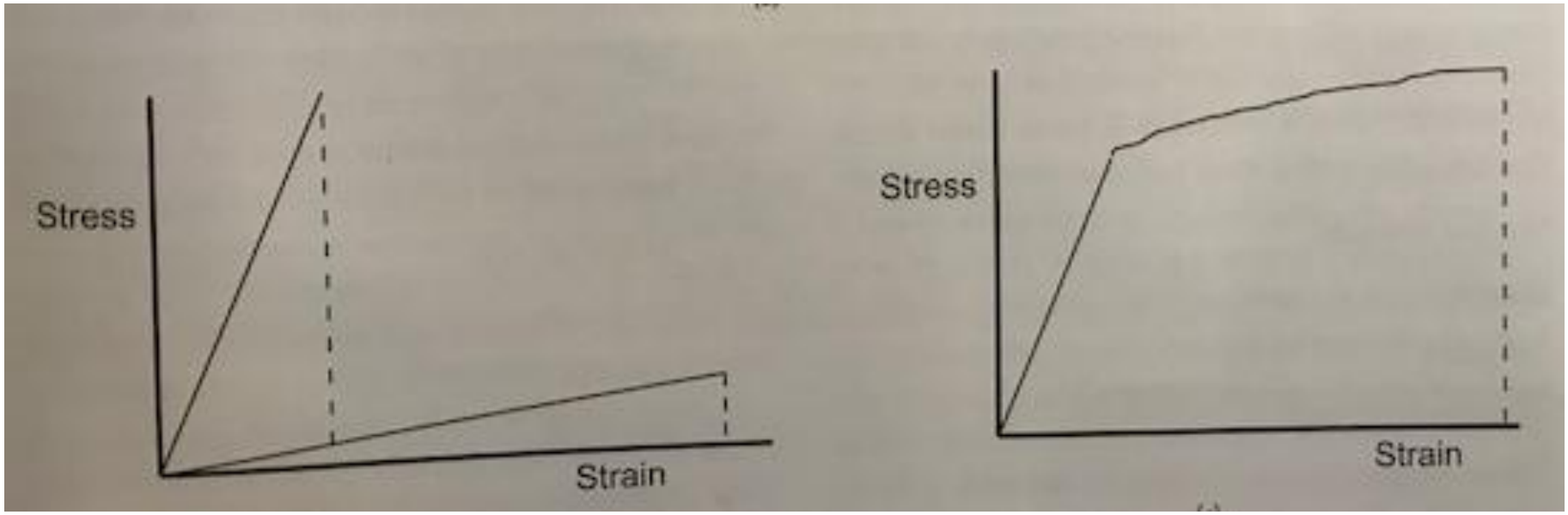
b) application of this stress results in deformation δl.

c) movement of atoms results in deformation, which is reversible.

d) stress strain curve for elastic deformation.

(Williams, 2014)

Mechanical Properties of Various Material Classes



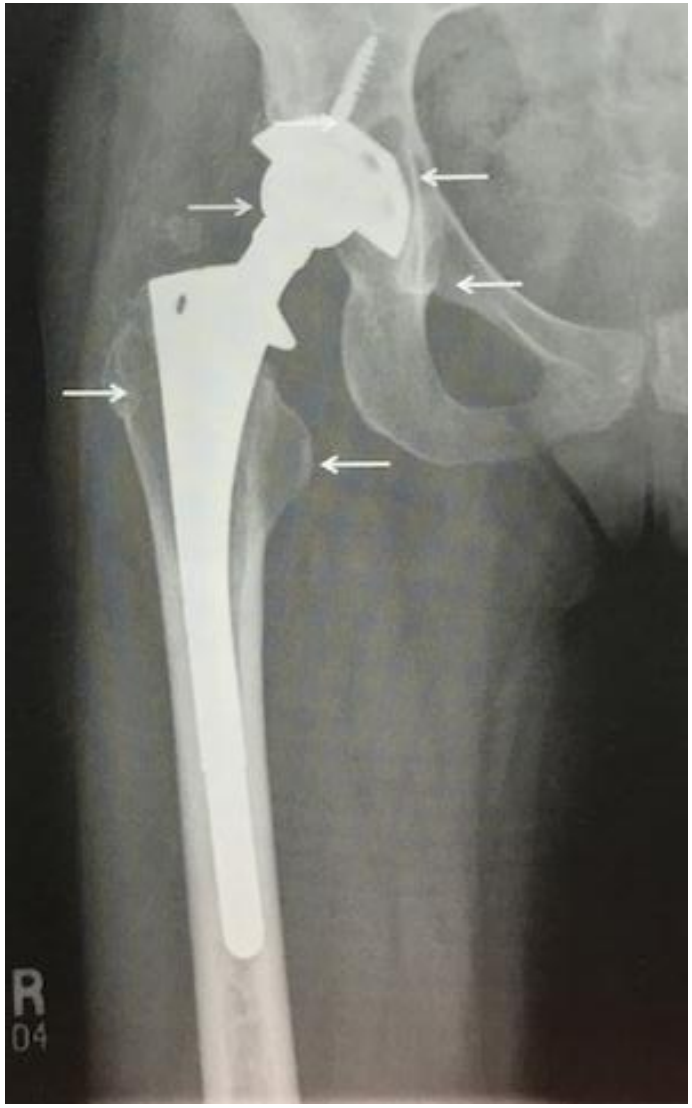
-Ceramics can withstand high stresses but not high strains (rigid, brittle)

-Many polymers can withstand high strains but not high stresses (flexible)

-Metals (alloys) sustain both: high stress and high strain, such materials are „tough“

(Williams, 2014)

Degradation of Biomaterials: Wear



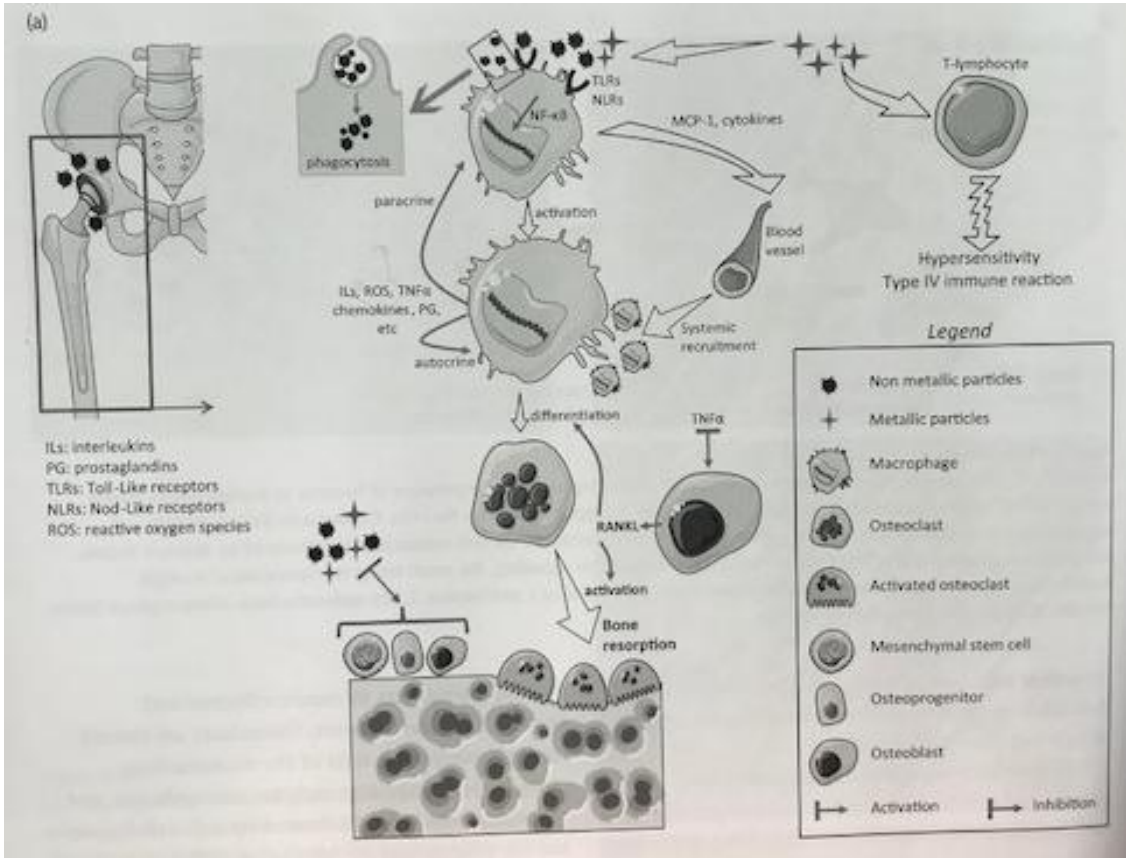
Wear is the removal and relocation of material arising from the contact of two solids.

- proportional to the load across the interface and to the distance of sliding
- inversely proportional to the hardness of the surface

- corrosive wear (surface oxide films)
- surface fatigue wear (repeated loading and sliding results in crack formation)
- abrasive wear (rough hard surface slides over a softer one)
- adhesive wear (fragmentation within the area of contact)

(Williams, 2014)

Release of Wear Causes Osteolysis



Bone resorption following release of wear debris from hip replacement prosthesis.

The wear particles activate macrophages, in turn causing activation and differentiation of osteoclasts.

Acidification and protease release causes loss of bone.

(Williams, 2014)

Corrosion

physiological fluids: Na^+, K^+, Ca^{2+}, Mg^{2+}
dissolved oxygen
pH 7,4
proteins, low molecular weight organic species

Corrosion of metals: M ➔ $M^{(n+)} + n(e^-)$

$2H^+ + 2e^- \rightarrow H_2$

$O_2 + 4H^+ + 4e^- \rightarrow 2H_2O$ (in acidic environment)
$O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$ (in neutral or basic environment)

Displacement of the equilibrium, e.g. by removal of metal ions from the immediate vicinity causes sustained corrosion.

Galvanic corrosion occurs when two metals with different potentials are placed in electrical contact (in an electrolyte).
Regional variations in electrode potential over an alloy surface are responsible for surface corrosion in metallic components.

Passivation is the formation of a protective oxide layer adherent to metal surfaces
(Ti, Cr, Al are strongly passivated)

(Biomaterials Science, 2004)

Corrosion and Toxicity of Metal Ions

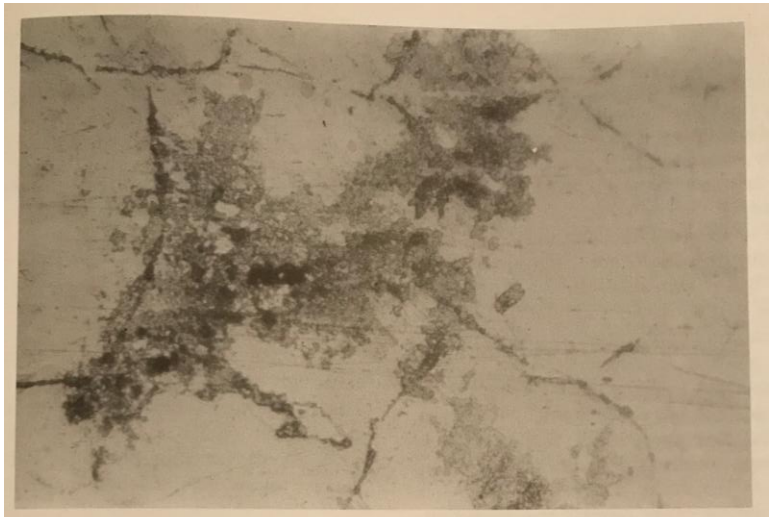


FIG. 4. Intergranular corrosion is demonstrated on this etched stainless steel specimen.

Ni induces allergic contact dermatitis via activation of pro-inflammatory processes

Cr(VI) is toxic and can easily pass through cell membranes, whereas Cr(III) is poorly absorbed. Inside cells, Cr species attack macromolecules and disrupt the cellular integrity.

Co is an essential element, toxic at higher concentrations

Al is absorbed through the skin and is discussed to be a relevant factor in the development of Alzheimer‘s disease

V as vanadate (VO_4^{3-}) competes with phosphates and interferes with many biological processes

Fe is an essential element but it is also involved in formation of reactive oxygen species, causing inflammation

(Biomaterials Science, 2004)

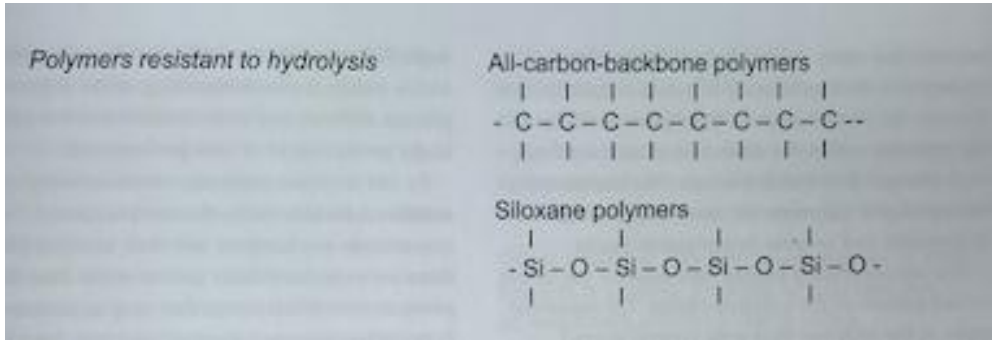
Degradation of Polymers

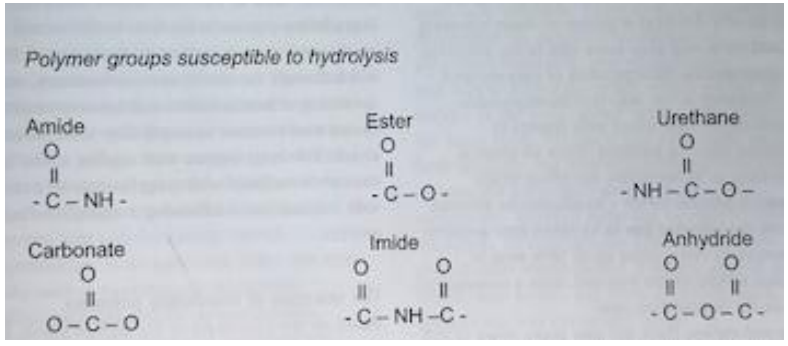
Bioresorption is the process of removal by cellular activity and/or dissolution of a material in a biological system.

Polymers are generally susceptible to degradation through heat, light, radiation or in certain chemical environments
Hydrolysis is the main mechanism relevant for polymers in the body.

Hydrophilic hydrolysable polymers show bulk degradation.

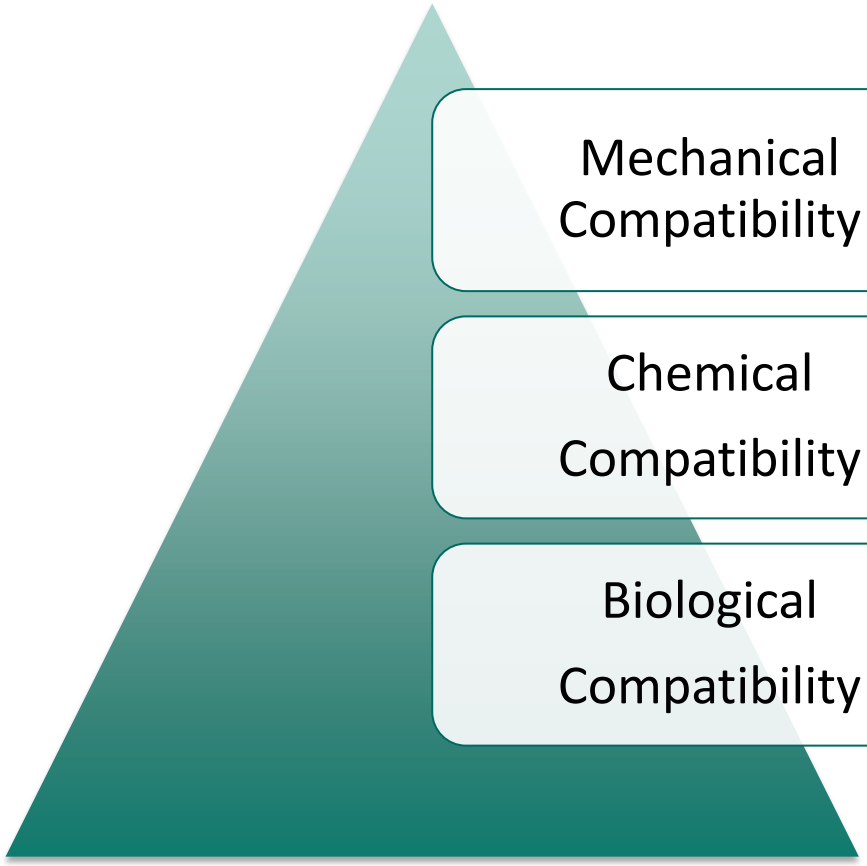
Hydrophobic polymers lacking hydrolysable bonds are the most biostable.





(Biomaterials Science, 2004)

Requirements for Biomaterials



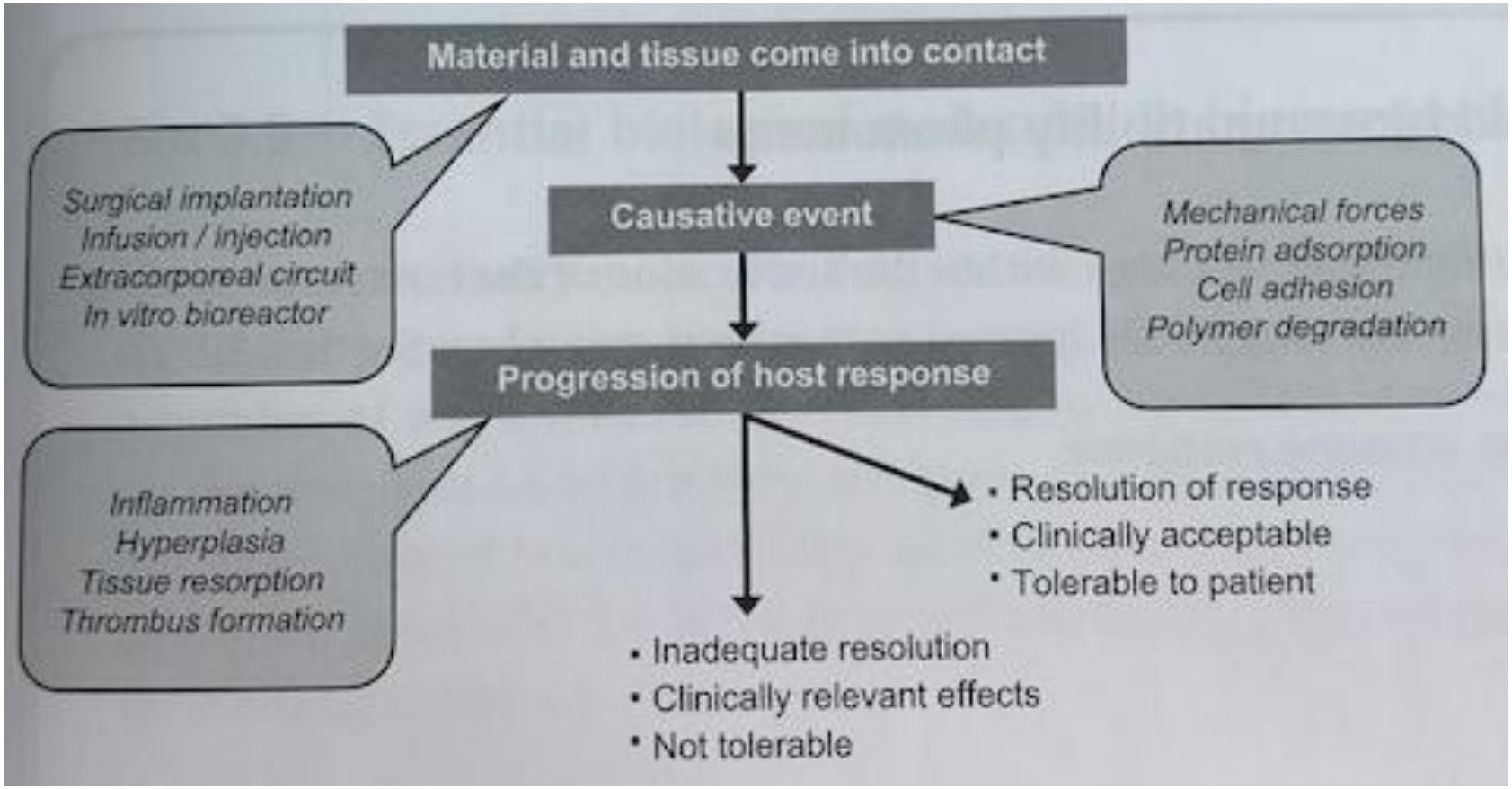
modulus of elasticity, tensile strength, compressive and shear strength, ductility, hardness, toughness, flexibility

surface tension/ surface energy, degradability, corrosion, surface roughness

adhesion of cells, immunogenicity cytotoxicity, inflammation

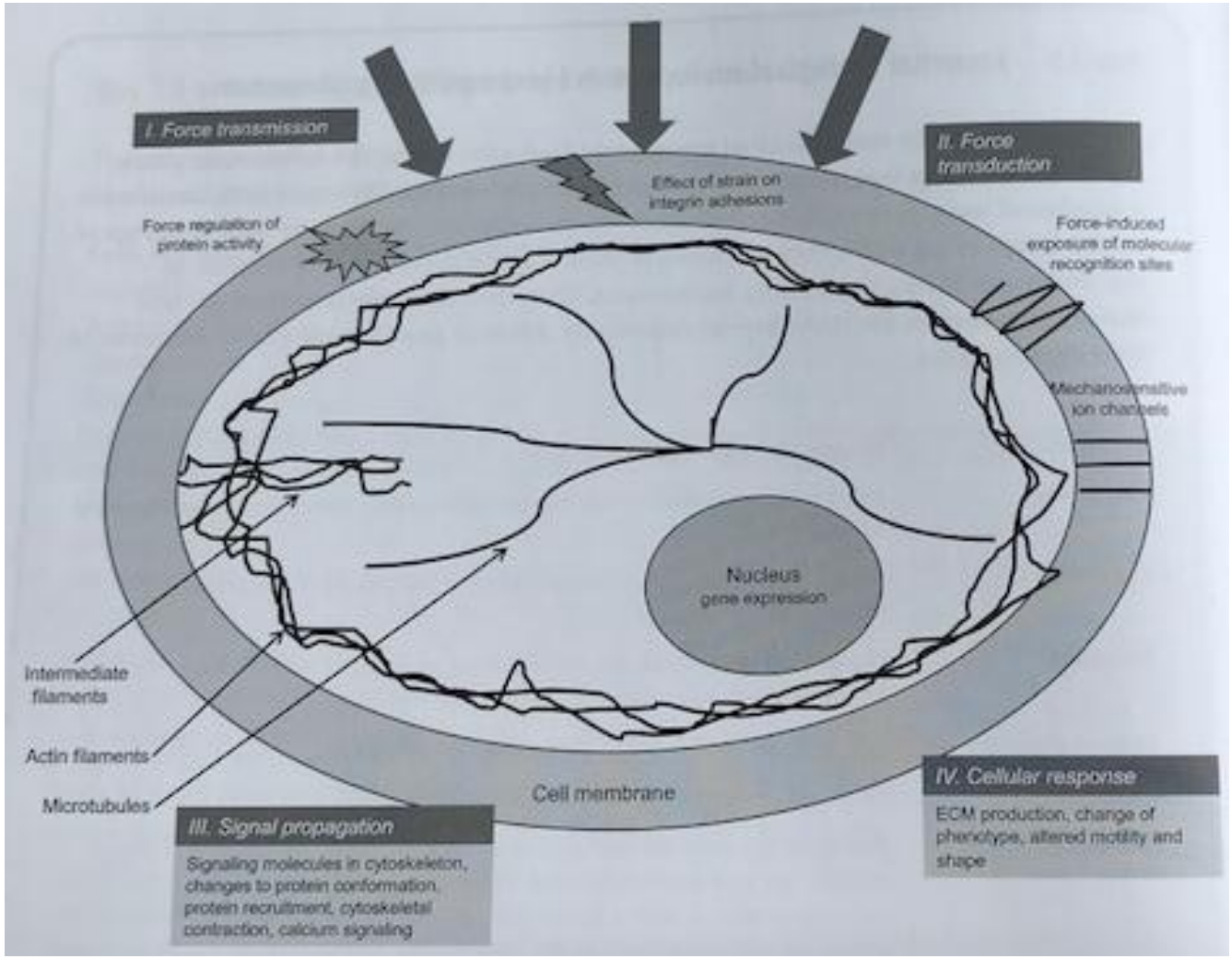
Biocompatibility „refers to te ability of a material to perform with an appropriate host response in a specific application“

Biocompatibility Paradigm



(Williams, 2014)

Mechanotransduction



- force transmission
- force transduction
- signal propagation
- cellular response

Implantable devices:
Mismatch of the materials elastic modulus and flexural rigidity with those of the tissue results in differential stresses and strains, e.g. stress shielding by a high modulus metal implant will result in resorption of bone.
Osteocytes act as mechanosening cells.

Compressive forces generate shear stress, stimulating oteoblasts

(Williams, 2014)

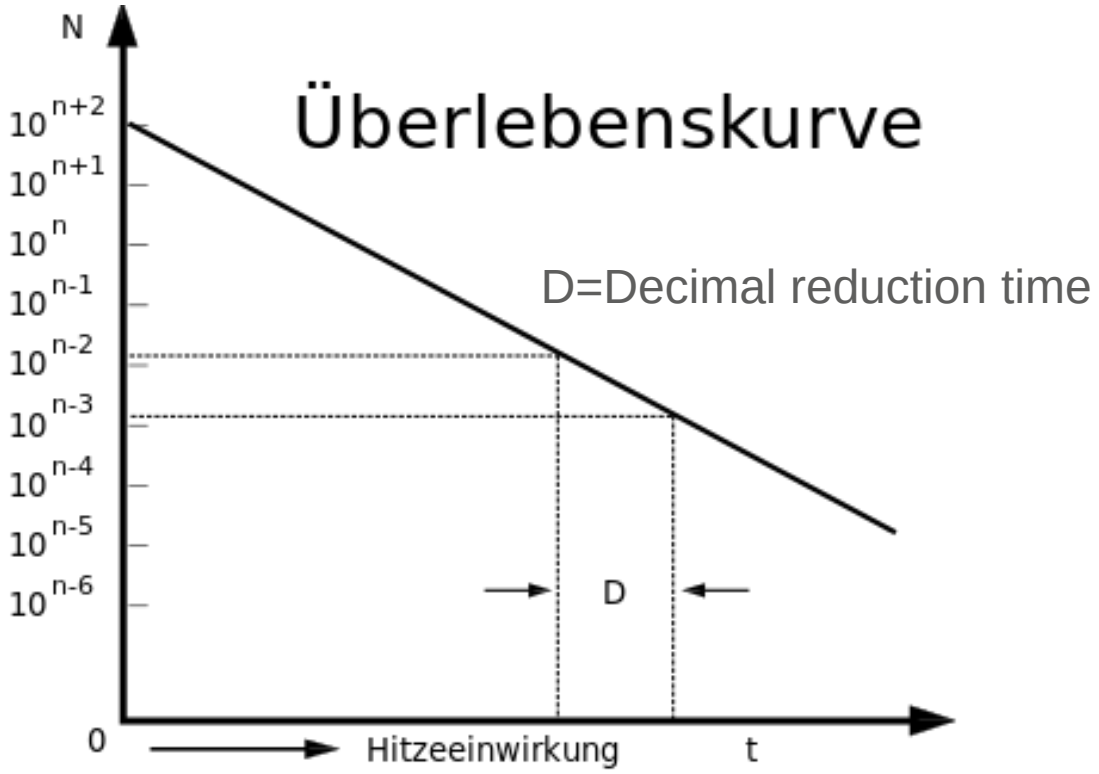
Sterility and Sterilization of Materials

Sterile: free of living microorganisms, including spores and other active biological agents (prions, viruses)

Manufacturing: sterile process or terminal sterilization

Sterilization (10^{-6})
Disinfection (10^{-5})

- Heat
- Filtration
- Radiation
- Chemicals



[Bin im Garten]

Heat

moist heat sterilization (autoclaving)
121°C, 20 min or 134°C, 18 min

dry heat sterilization
160-180°C, 30-120 min

!

Potential effects:
Degradation of heat sensitive components
Disruption of physical structure
Agglomeration

[Systec]

Sterile Filtration

passage through sterile filters (0.2 µm) into a sterile container
for heat labile substances and suspensions

Compatibility of filter materials with solvents
and contained substances

Potential effects:
Stripping off adsorbed substances
Loss of materials/substances by retention/adsorption

Not suitable for highly viscous solutions

[Millipore]

Gamma Irradiation

Ionizing radiation emitted by radioisotopes, e.g. Cobalt-60

Electromagnetic radiation

Potential effects:
Formation of reactive free radicals/ cascades of free radical reactions
Formation of peroxides
Crosslinking or chain scission

Chemical Sterilization

Ethylene oxide (C_2H_4O), epoxide

toxic compound

(mutagen: changing the genetic material, DNA

clastogen: induces breakage of chromosomes)

Potential effects:
Alkylation of compounds
toxic residues

Classification of Medical Products by Type of Contact)

In contact with body surfaces
- Intact skin (e.g. electrodes, external prostheses, bandages)
- Mucous membranes (e.g. contact lenses, dental prostheses)
- Harmed or damaged skin (e.g. wound dressing)

From the outside in contact with the inner body
- vasculature, indirect (e.g. transfusion devices, tubing)
- Tissue, bones, dentin (e.g. dental cement, fillings)
- Circulating blood (e.g. intravascular catheter, dialysers)

Implantable
- tissue, bone (e.g. nails, plates, prostheses, pacemakers)
- Blood (e.g. heart valves, stents)

Types of Contact Duration and Biompatibility

- Short-term (up to 24 h)
- Prolonged (24 h – 30 days)
- Permanent (> 30 days)

- Systemic Toxicity (by release of constituents into the body)
  acute (within 24 h), subacute (up to 28 days)
  subchronic (10 % of the life span), chronic effects (> 10% of the life span)

- Skin, eye or mucous membrane irritation (e.g. inflammation)
- Hemolysis (lysis of red blood cells)
- Thrombogenicity (potential for clot formation)
- Sensitization (including an immune response)
- Genotoxicity (DNA destruction, mutation, chromosomal aberration)
- Cancerogenity (tumorigenic potential)
- Reproductive toxicity (e.g. embryonic development)

Strategy for Biological Evaluation of Medical Devices

- ❑ type of application/contact
- ❑ duration of body contact
- ❑ appropriateness of testing procedures (*in vitro*, *in vivo*)
- ❑ choice of model organism or cell-type
- ❑ Read-out

Questions

- ❑ Define biomaterials, what are main application fields, give examples, what are the main material classes?
- ❑ Describe properties of ceramics, metals, and polymers important for their usage as biomaterials
- ❑ What is wear? What is the biological result of wear?
- ❑ What is corrosion? How can it be prevented or reduced? What are results of corrosion in relation to prosthetic devices?
- ❑ How do polymers degrade in the body?
- ❑ Which techniques are used to sterilise biomaterials?
- ❑ Which parameters have to be considered in order to evaluate the biocompatibility of biomaterials?

Literature

Books:

- Ratner et al. (2004) Biomaterials Science
- Williams (2014) Essential Biomaterials Science
- Epple (2003) Biomaterialien und Biomineralisation
- Puleo and Bizios (2009) Biological Interactions on Materials Surfaces

Articles:

- Wörz et al., J. Mater. Chem. (2012) 22, 19547
- Nahta and Esteva, Cancer Letters (2006) 232: 123

Next Lecture: May 24, 2019

Liquid Repellent Surfaces

Dr. Rene Hensel

Functional Microstructures

no lecture: May 31, 2019