Biomaterials

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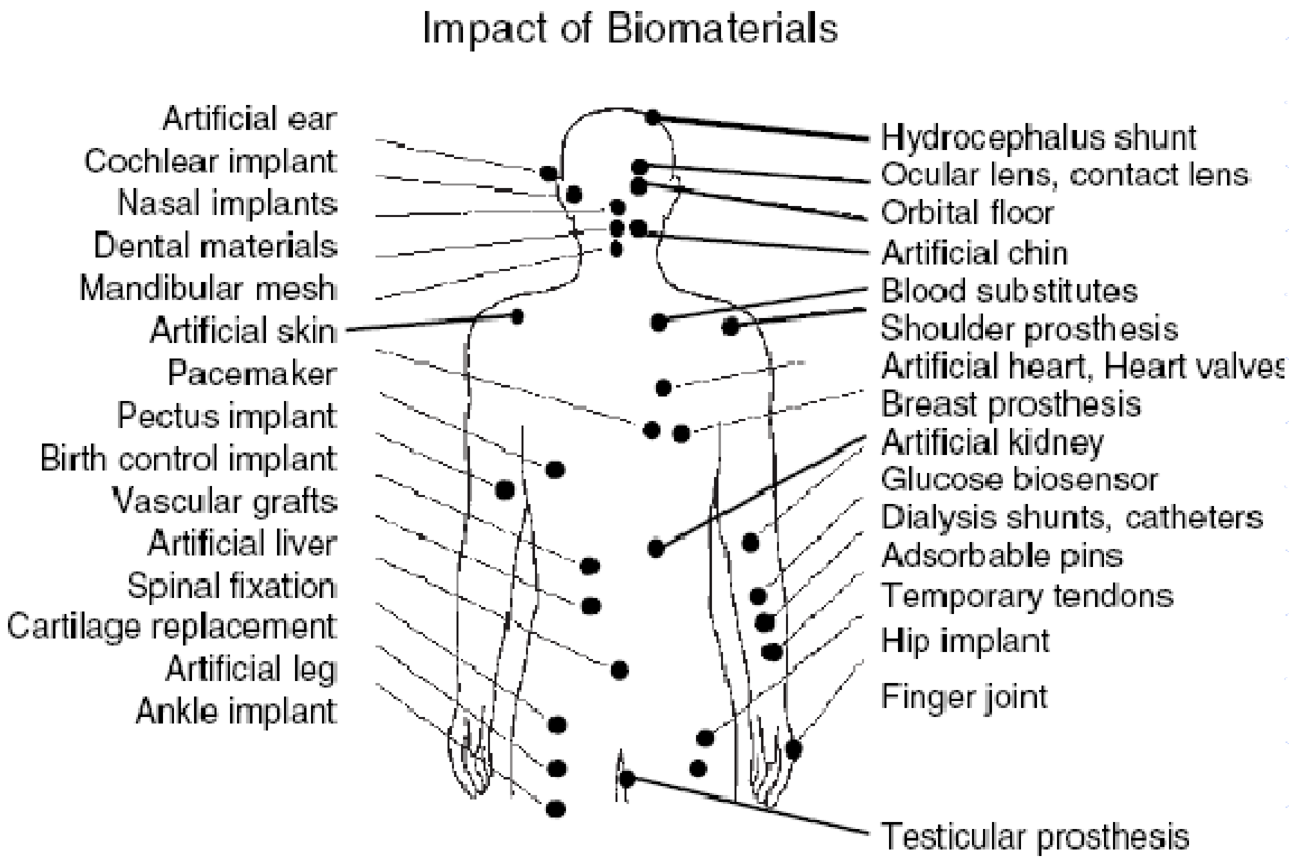
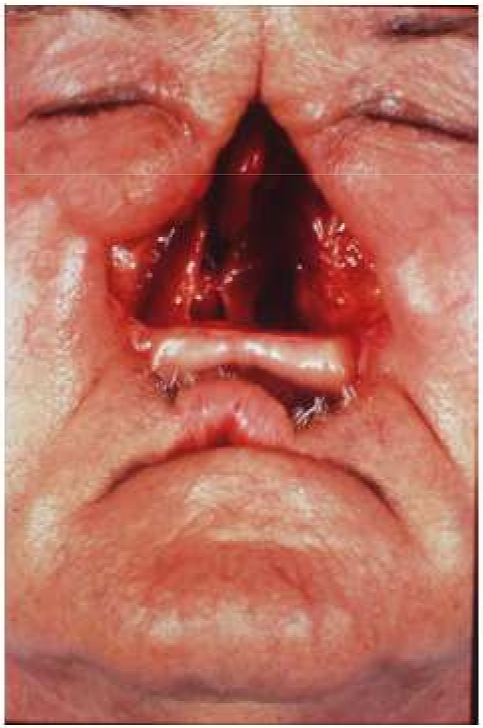
Introduction

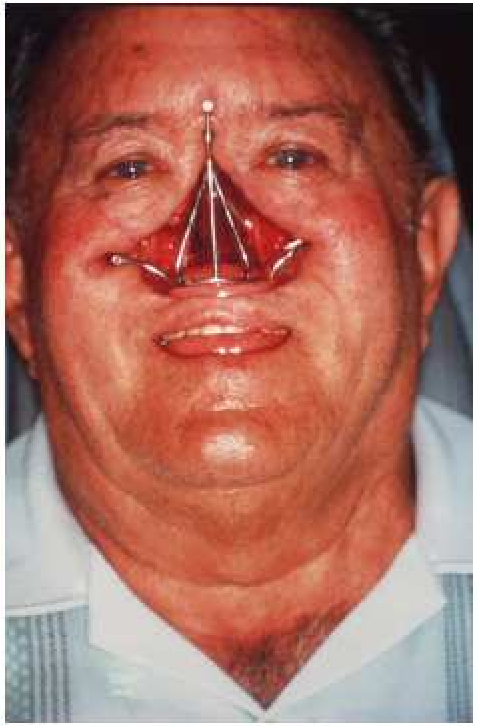
Millions of lives have been saved due to biomaterials and the quality of life for millions more is improved every year due to biomaterials.



Biomaterials have made an enormous impact on the treatment of injury and disease and are used throughout the body.

Clinical applications





A Little History on Biomaterials

- Romans, Chinese used gold in dentistry over 2000.
- Ivory & wood teeth
- Bone plates 1900, joints 1930
- 1960- Polyethylene and stainless steel being used for hip implants

History (cont.)

- Before 1950: Metals and alloys used for dental and orthopedic surgery
- Polyester Tricot used as vascular prosthesis

Note: Materials not designed initially for medical applications
Fatigue tests, Resistance to corrosion, chemical effects tested later

- After WWII: Quality control procedures applied to production of biomaterials to avoid toxic effects

- 1970's: Titanium (low density and toxicity, High resistance to failure and corrosion) replaced Nickel in orthopedic applications

- 1992 : the Total Artificial Heart, that can simulate a natural shape of a pulse pressure is patented

- Today: 3rd generation biomaterials: Smart systems- Systems used for cells regeneration

Evolution

Biomaterials:

First developed to replace organs that no longer function in the proper manner

- Impaired function can be cause by inherited defects, old age, disease, accidents …
- As our understanding of tissues, disease, and trauma improved, the concept of attempting to repair damaged tissues emerged
- More recently, with the advent of stem cell research, medicine believes it will be possible to regenerate damaged or diseased tissues by cell-based tissue engineering approaches

Statistics

Estimates of the numbers of biomedical devices incorporating biomaterials used in the United States in 2002 :

- Total hip joint replacements: 448,000
- Knee joint replacements: 452,000
- Shoulder joint replacements: 24,000
- Dental implants: 854,000
- Coronary stents: 1,204,000
- Coronary catheters: 1,328,000

there are still many unanswered questions regarding the biological response to biomaterials and the optimal role of biomaterials in tissue regeneration that continue to motivate biomaterials research and new product development.

In medicine, a **stent** is a tube that is inserted into a natural conduit of the body to prevent or counteract a disease-induced localized flow constriction

Biomaterials and Healthcare Market – Facts and Figures (US# – global# are typically 2-3 times the US#	
Total US health care expenditures (2000)	$1.400.000.000.000
Total US health research and development (2001)	$82.000.000.000
Number of employees in the medical device industry (2003)	300.000
Registered US medical device manufacturers (2003)	13.000
Total US medical device market (2002)	$77.000.000.000
US market for disposable medical supplies (2003)	$48.600.000.000
US market for biomaterials (2000)	$9.000.000.000
Individual medical device sales:	
Diabetes management products (1999)	$4.000.000.000
Cardiovascular devices (2002)	$6.000.000.000
Orthopaedic-Musculosceletal Surgery (US, 1998)	$4.700.000.000
Wound care US market (1998)	$3.700.000.000
In Vitro diagnostics (1998)	$10.000.000.000
Numbers of Devices (US)	
Intraocular lenses (2003)	2.500.000
Contact lenses (2000)	30.000.000
Vascular grafts	300.000
Heart valves	100.000
Pacemakers	400.000
Blood bags	40.000.000
Breast prosthesis	250.000
Catheters	200.000.000
Heart-lung (oxygenators)	300.000
Coronary stents	1.500.000
Renal dialysis, number of patients (2001)	320.000
Hip prosthesis (2002)	250.000
Knee prosthesis (2002)	250.000
Dental implants (2000)	910.000

Definition I

Williams in 1987 defined a biomaterial as "a nonviable material used in a medical device, intended to interact with biological systems." This definition still holds true today and encompasses the earliest use of biomaterials replacing form (e.g., wooden leg, glass eye) as well as the current use of biomaterials in regenerative medical devices such as a biodegradable scaffold used to deliver cells for tissue engineering.

Definition II

A **biomaterial** is "any substance (other than drugs) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body".

Biocompatibility — The ability of a material to perform with an appropriate host response in a specific application.

Host Response — The response of the host organism (local and systemic) to the implanted material or device.

Definition III

Definition of a Biomaterial

Biomaterial (def.) = A biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure.

D.F Williams, Medical Device Technology, october 2009

Definition IV

Biomaterials: definition

- Materials that constitute parts of medical implants, extracorporeal devices, and disposables that have been utilized in medicine, surgery, dentistry, and veterinary medicine as well as in every aspect of patient health care (Dee et al.)

Biocompatible material features

1) Absence of carcinogenicity (the ability or tendency to produce cancer)
2) Absence of immunogenicity (absence of a recognition of an external factor which could create rejection)
3) Absence of teratogenicity (ability to cause birth defects)
4) Absence of toxicity

Keywords

- Metallic/glass/Polymeric/Ceramic/Composite
- Fracture/fatigue/creep/corrosion/degradation
- Tissue response/healing/biocompatibility/host response/carcinogenicity
- Hard/soft tissue implants
- Vascular/Breast/Urological/Art. Organ
- Mucosal contacting …

Wright Medical Technology- Interesting Idea !

The REPIPHYSIS® works by inserting an expandable implant made from titanium in an aerospace polymer into the child’s healthy bone, after which standard recovery and rehabilitation are expected. However, instead of undergoing repeated surgeries to extend the bone, the REPIPHYSIS® uses an electromagnetic field to slowly lengthen the implant internally.

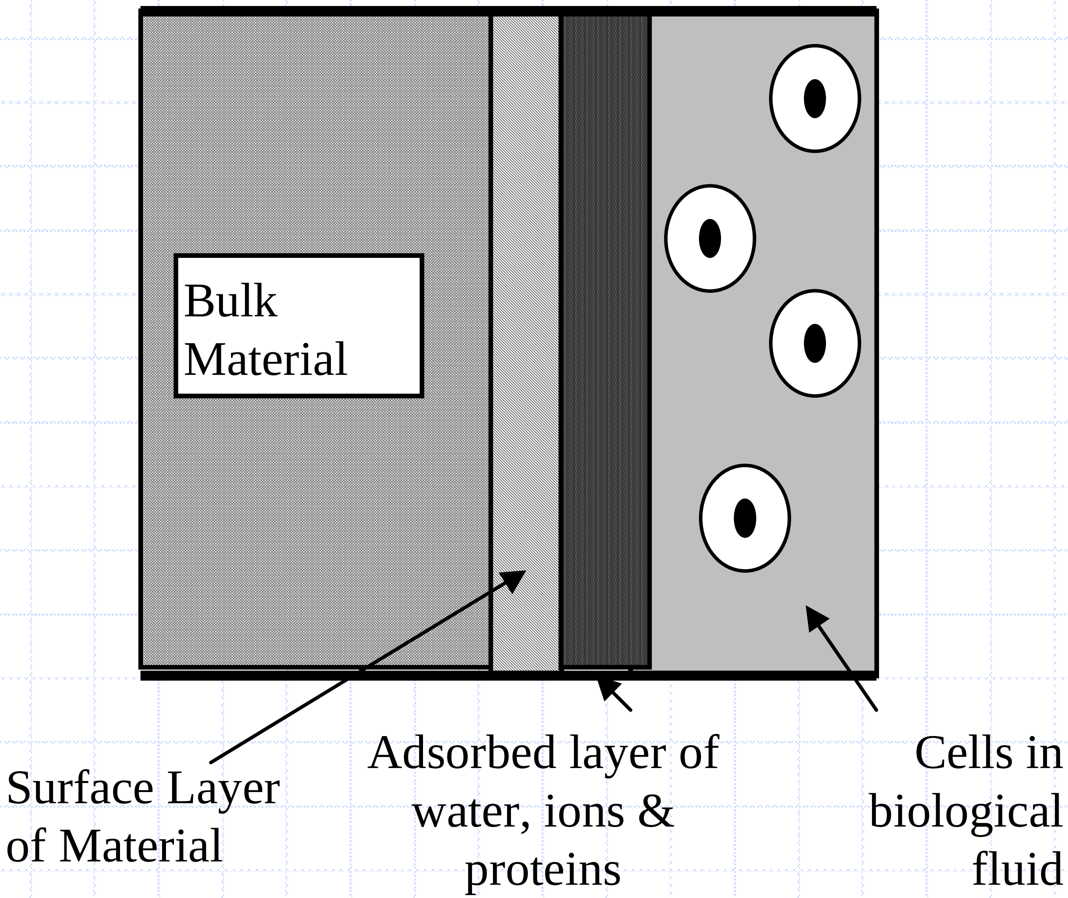
Material Selection Parameters

- Mechanical
- Thermal/Electrical Conductivity
- Diffusion
- Water Absorption
- Biostability
- Biocompatibility

Test Conditions:

	Value	Location
pH	6.8	Intracellular
	7.0	Interstitial
	7.15-7.35	Blood
pO_2	2-40	Interstitial (mm Hg)
	40	Venous
	100	Arterial
Temperature	37	Normal Core
	28	Normal Skin
Mechanical Stress	4×10^{7} N m^{-2}	Muscle (peak stress)
	4×10^{8} N m^{-2}	Tendon (peak stress)
Stress Cycles (per year)	3×10^{5}	Peristalsis
	5×10^{6} - 4×10^{7}	Heart muscle contraction

Biocompatibility is primarily a surface phenomenon …



Test Animals

- Rabbits – ear, skin
- Guinea Pigs – skin, esp C@
- Mice – genotoxicity
- Horseshoe Crab
- Pig – implant
- Bacteria
- People – long term

An Interdisciplinary Field

Bioengineers

Material Scientists

Immunologists

Chemists

Biologists

Surgeons

…

Journals

- Biomaterials World News
- Materials Today
- Nature
- Journal of Biomedical Materials Research
- Cells and Materials
- Journal of Biomaterials Science
- Artificial Organs
- ASAIO Transactions
- Tissue Engineering
- Annals of Biomedical Engineering
- Medical Device Link
- … see: http://www.biomat.net/biomatnet.asp?group=1_5

Clinical applications

Applications for Medical Devices

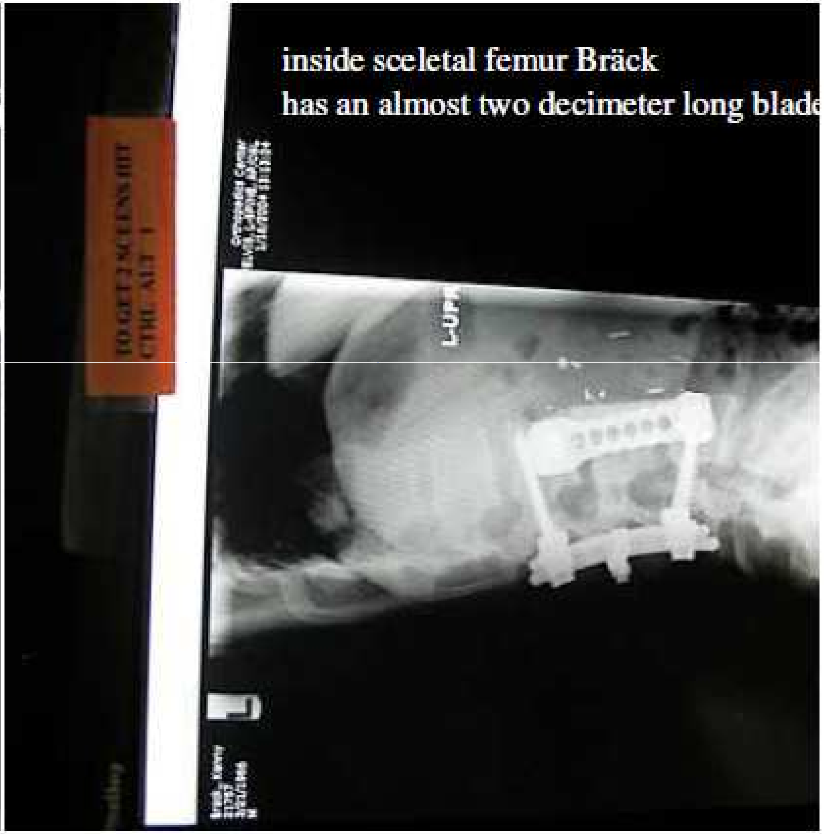
1)Total implanted device

2)Partially implanted device

3)Totally externals device

Some examples

Kenny Bräck– 34 screws of titanium, cobolt and stainless steel



Kenny Bräck– 34 screws of titanium, cobolt and stainless steel

Uses of Biomaterials

- Replace diseased part – dialysis
- Assist in healing – sutures
- Improve function – contacts
- Correct function – spinal rods
- Correct cosmetic – nose, ear
- Aid dx – probe
- Aid tx – catheter
- Replace dead - skin

Some Commonly Used Biomaterials

Material	Applications
Silicone rubber	Catheters, tubing
Dacron	Vascular grafts
Cellulose	Dialysis membranes
Poly(methyl methacrylate)	Intraocular lenses, bone cement
Polyurethanes	Catheters, pacemaker leads
Hydogels	Opthalmological devices, Drug Delivery
Stainless steel	Orthopedic devices, stents
Titanium	Orthopedic and dental devices
Alumina	Orthopedic and dental devices
Hydroxyapatite	Orthopedic and dental devices
Collagen (reprocessed)	Opthalmologic applications, wound dressings

Categories of implantable materials	Composition	Use
Polymers carbon	Gore-Tex(PTFE expanded)	Thoracic and abdomen rebuilding Filling Defect of the soft tissue Cranio-facial reconstruction
	Poly-propylene (Marlex, Prolene)	Thoracic and abdominal wall reconstruction Surgical Suture
	Poly-ethylene (Medpore)	Filling Defect of the soft tissue
	Poly-ethylene tereftalato (Dacron,Mersilene)	Surgical Suture Vascular prosthesis
	Poliuretano	Coating of breast implants
	Polyesters aliphatic (ac. Poly-latic, poly-glycolic ecc.)	Surgical Suture Absorbable mini plates and screws
	Metilmetacrilato (MMA)	Thoracic and abdomen rebuilding Cranio-facial reconstruction

Some Applications of Synthetic Materials and Natural in Medicine	
Applications	**Types of Materials**
Skeletal system	
Joint replacements (hip, knee)	Titanium, Ti-Al-V alloy, stainless steel, polyethylene
Bone plate for fracture fixation	Stainless steel, cobalt-chromium alloy
Bone cement	Poly (methyl acrylate)
Bony defect repair	Hydroxyapatite (HA)
Artificial tendon and ligament	Teflon, Dacron
Dental implant for tooth fixation	Titanium, Ti-Al-V alloy, stainless steel, alumina, CaP, polyethylene
Cardiovascular system	
Blood vessel prosthesis	Dacron, Teflon, polyurethane
Heart valve	Reprocessed tissue, stainless steel, carbon materials
Catheter	Silicone rubber, Teflon, polyurethane
Organs	
Artificial heart	Polyurethane
Skin repair template	Silicone – collagen composite
Artificial kidney (hemodialyzer)	Cellulose (modified), polyacrylonitrile
Heart–lung machine	Silicone rubber
Senses	
Cochlear replacement	Platinum eletrodes, titanium
Intraocular lens	Poly (methyl acrylate), silicone rubber, hydrogels (variety of)
Contact lens	Silicone-acrylate, hydrogels
Corneal bandage	Collagen, hydrogels

Categories of implantable materials	Composition	Use
Not carbon Polymers	Silicon	Breast implants Prosthetics for increased facial characteristics
Ceramics	Hydroxyapatite	Small cellular defects reconstruction
	Phosphate tricalcium	Small bone defect reconstruction
Metals	Titanium, stainless steels and cobalt and magnesium alloys	Mini plates and screws Orthopedic prosthesis Surgical tools

What's a biodegradable implant?

Once implanted, should maintain its mechanical properties until it is no longer needed and then be absorbed and excreted by the body, leaving no trace

Biodegradable implants are designed to overcome the disadvantages of permanent metal-based devices

Problems caused by permanent implants

- Physical irritations
- Chronic inflammatory local reactions
- Thrombogenicity and long term endothelial dysfunction (for cardiovascular applications)
- Inability to adapt to growth
- Not allowed or disadvantageous after surgery
- Stress shielding, corrosion, accumulation of metal in tissues (for internal fixation applications)
- Repeat surgery necessary

Advantages of biodegradable implants

- More physiological repair
- Possibility of tissue growth
- Less invasive repair
- Temporary support during tissue recovery
- Gradual dissolution or absorption by the body afterwards.

Note: these implants may act a new biomedical tool satisfying requirement of compatibility and integration.

Problems/test for w Biomaterials

- Acute toxicity (cytotoxicity) arsenic
- Sub chronic/chronic Pb
- Sensitization Ni, Cu
- Genotoxicity
- Carcinogenicity
- Reproductive &/or developmental Pb
- Neurotoxicity
- Immunotoxicity
- Pyrogen, endotoxins

FDA & ISO 10993

- FDA mandates tests based on length of contact (24 Hr, 1-30 Days, >30 days)
- See table for details
- ISO 10993 – required for European Union Certification
- See FDA Device Categories & examples

First Generation Implants

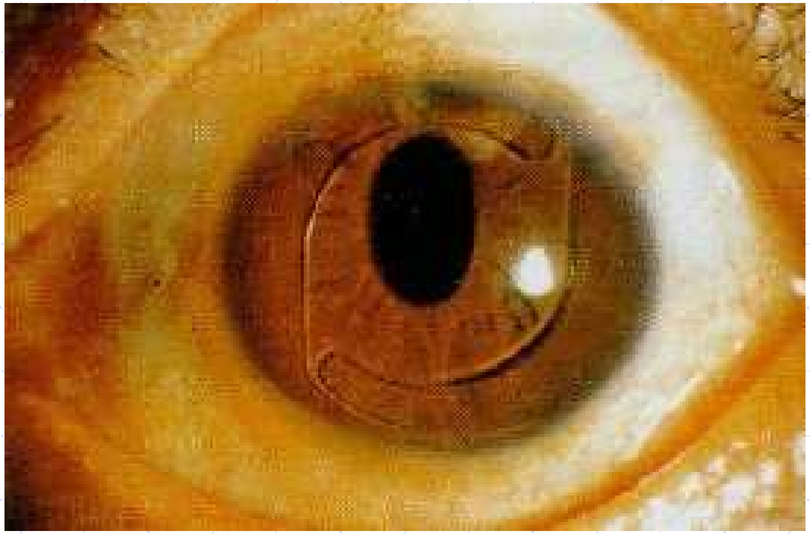
- "ad hoc" implants
- specified by physicians using common and borrowed materials
- most successes were accidental rather than by design

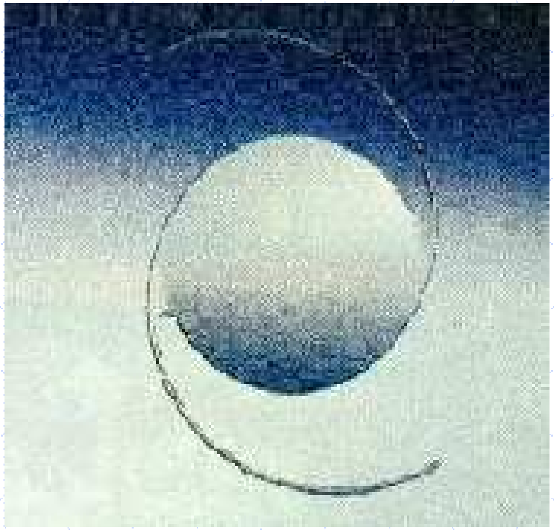
Examples — First Generation Implants

- gold fillings, wooden teeth, PMMA dental prosthesis
- steel, gold, ivory, etc., bone plates
- glass eyes and other body parts
- dacron and parachute cloth vascular implants

Intraocular Lens

3 basic materials - PMMA, acrylic, silicone





Vascular Grafts

Second generation implants

- engineered implants using common and borrowed materials
- developed through collaborations of physicians and engineers
- built on first generation experiences
- used advances in materials science (from other fields)

Examples — Second generation implants

- titanium alloy dental and orthopaedic implants
- cobalt-chromium-molybdinum orthopaedic implants
- UHMW polyethylene bearing surfaces for total joint replacements
- heart valves and pacemakers

Artificial Hip Joints

http://www.totaljoints.info/Hip.jpg

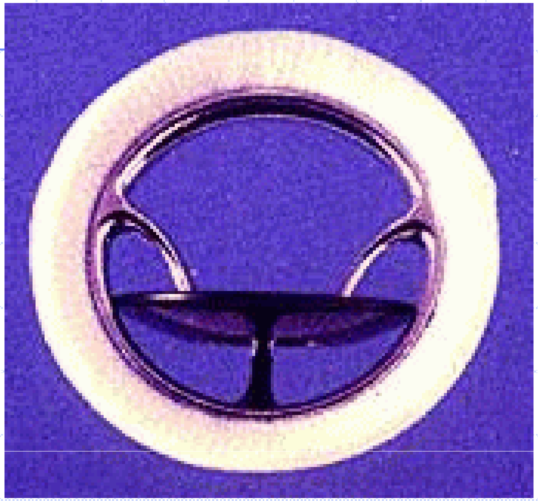
Third generation implants

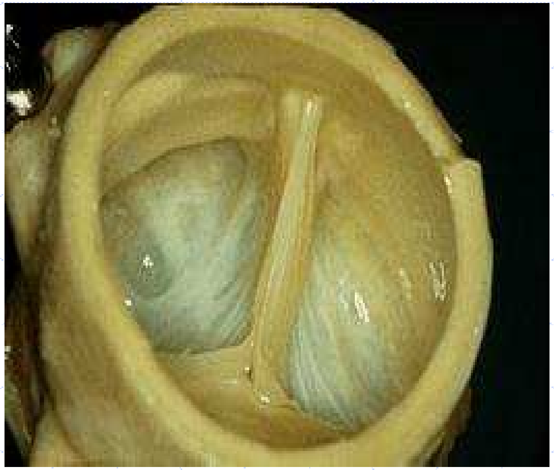
- bioengineered implants using bioengineered materials
- few examples on the market
- some modified and new polymeric devices
- many under development

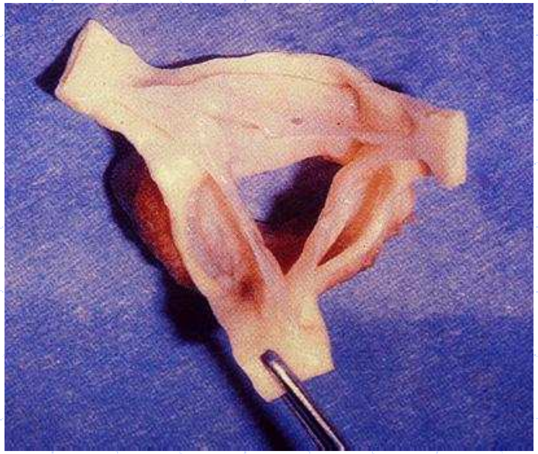
Example - Third generation implants

•tissue engineered implants designed to regrow rather than replace tissues
•Integra LifeSciences artificial skin
•Genzyme cartilage cell procedure
•some resorbable bone repair cements
•genetically engineered "biological" components

Substitute Heart Valves







Evolution of Biomaterials

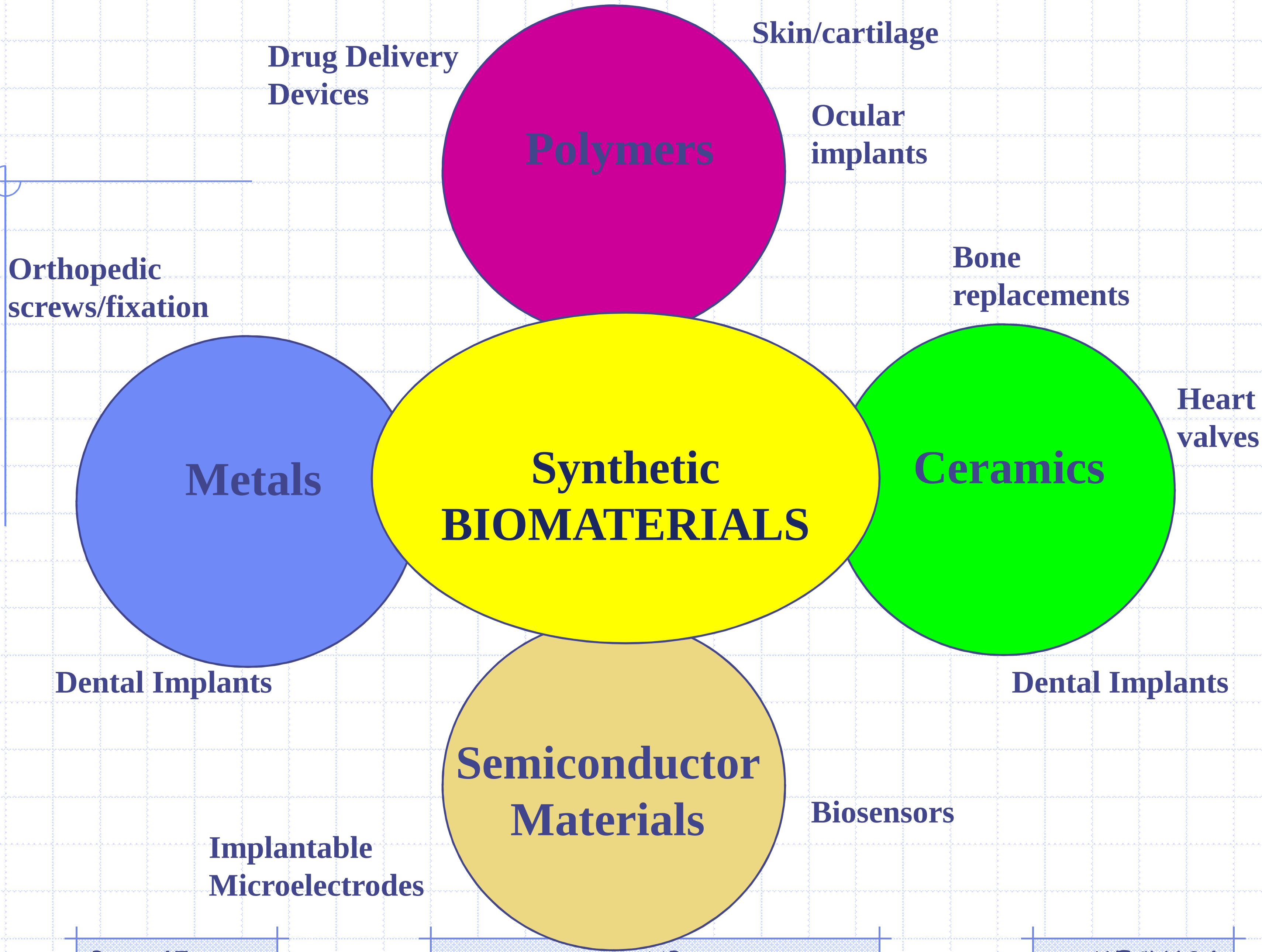
Structural

Soft Tissue Replacements

Functional Tissue Engineering Constructs

Advances in Biomaterials Technology

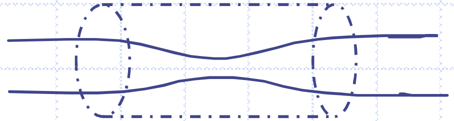
- Cell matrices for 3-D growth and tissue reconstruction
- Biosensors, Biomimetic , and smart devices
- Controlled Drug Delivery/ Targeted delivery
- Biohybrid organs and Cell immunoisolation
  - New biomaterials - bioactive, biodegradable, inorganic
  - New processing techniques


Drug Delivery Devices
Polymers
Skin/cartilage
Ocular implants
Orthopedic screws/fixation
Bone replacements
Metals
Synthetic BIOMATERIALS
Ceramics
Heart valves
Dental Implants
Dental Implants
Semiconductor Materials
Biosensors
Implantable Microelectrodes

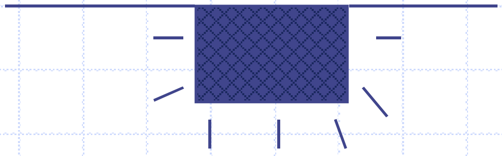
Biomaterials for Tissue Replacements

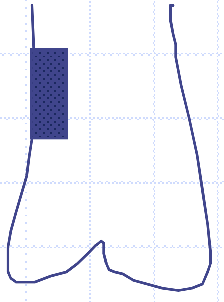
- Bioresorbable vascular graft

- Biodegradable nerve guidance channel



- Skin Grafts





- Bone Replacements

Biomaterials - An Emerging Industry

- Next generation of medical implants and therapeutic modalities
- Interface of biotechnology and traditional engineering
- Significant industrial growth in the next 15 years -- potential of a multi-billion dollar industry

Biomaterials Companies

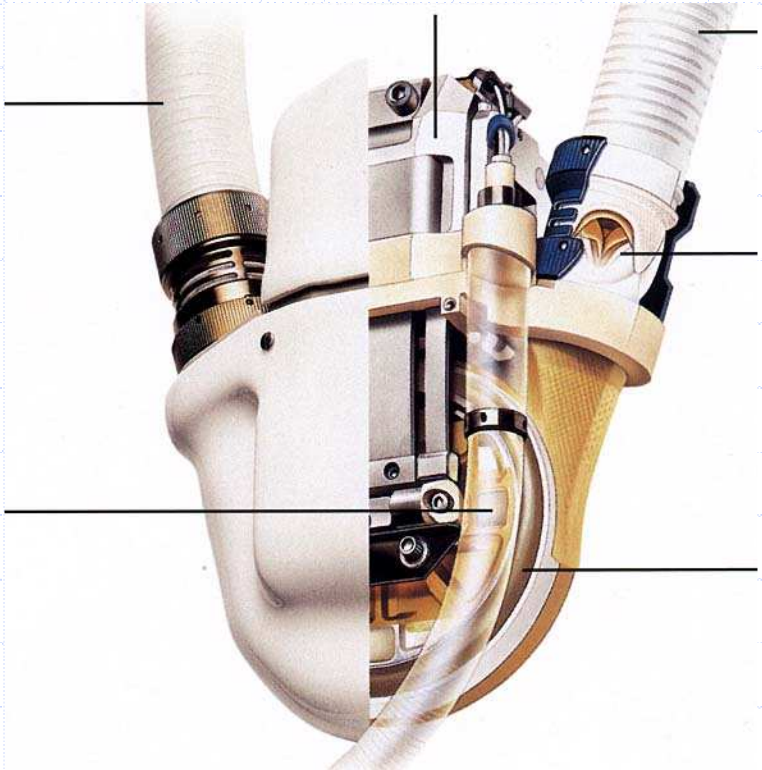
- **BioForma Research & Consulting, Inc**., fibrinolytic systems, protein-material interactions
- **Baxter International** develops technologies related to the blood and circulatory system.
- **Biocompatibles Ltd.** develops commercial applications for technology in the field of biocompatibility.
- **Carmeda** makes a biologically active surface that interacts with and supports the bodys own control mechanisms
- **Collagen Aesthetics Inc.** bovine and human placental sourced collagens, recombinant collagens, and PEG-polymers
- **Endura-Tec Systems Corp**. bio-mechanical endurance testing ofstents, grafts, and cardiovascular materials
- **Howmedica** develops and manufactures products in orthopaedics.
- **MATECH Biomedical Technologies**, development of biomaterials by chemical polymerization methods.
- **Medtronic, Inc**. is a medical technology company specializing in implantable and invasive therapies.
- **Molecular Geodesics Inc**., biomimetic materials for biomedical, industrial, and military applications
- **Polymer Technology Group** is involved in the synthesis, characterization, and manufacture of new polymer products.
- **SurModics**, offers PhotoLink(R) surface modification technology that can be used to immobilize biomolecules
- **W.L. Gore Medical Products Division**, PTFE microstructures configured to exclude or accept tissue ingrowth.
- **Zimmer**, design, manufacture and distribution of orthopaedic implants and related equipment and supplies.

What are some of the Challenges?

- To more closely replicate complex tissue architecture and arrangement *in vitro*
- To better understand extracellular and intracellular modulators of cell function
- To develop novel materials and processing techniques that are compatible with biological interfaces
- To find better strategies for immune acceptance

Disciplines involved in biomaterials science and the path from a need to a manufactured medical device	
Action	**Facilitator**
Identify a Need treat a condition replace an organ cosmetic	• Physician/Dentist • Researcher • Inventor
Device Design	• Physician, Engineer
Materials Synthesis	• Ceramicist, Metallurgist, Polymer Chemist
Materials Testing mechanical properties toxicology biorection to the material protein interactions, cell interactions, tissue reaction	• Bioengineer • Mechanical engineer • Biochemist • Veterinarian
Fabrication	• Engineer, machinist
Sterilization and Packaging	• Bioengineer, industrial designer
Device Testing toxicology In Vitro biointeractions animal testing	• Bioengineer • Physician/dentist
Regulatory pre-market approval limited clinical study clinical trials long-term follow-up	• Regulatory specialist • Regulatory agency • Congress
Clinical Use	• Physician, dentist, optometrist
Explant Analysis explant registry pathological examination testing to understand failure	• Pathologist • Bioengineer

Application: LVAD



Some Key Questions in Biomaterials

- Can patient retain her/his body part (hip, tooth, eye lens, heart, etc)?
- If replacement necessary, how do patient obtain an optimal recovery?
- Artificial material or autologous tissue? Replacement organ?
- If artificial material, which?
- Functionality? Prosthesis design?
- Cyclic mechanical loading?
- Durability of prostheses? Patient age.
- Biocompatibility? Integration.
- Blood compatibility?
- Immune reactions?
- Chemical tolerability?
- Cell toxicity and cell differentiation?
- Ethics (animals, humans, company funding/maximal earning, publishing,..)