生醫材料導論

Ching-Li Tseng (曾靖孋)

Professor

Graduate Institute of Biomedical Materials &
Tissue Engineering
Taipei Medical University

chingli@tmu.edu.tw

General objectives

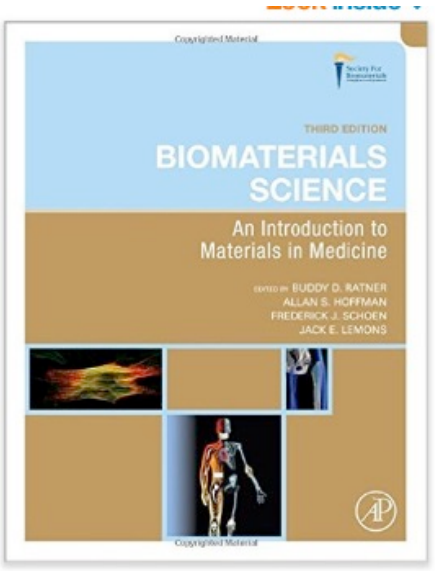
- Introducing variant materials for biomedical application and its theory.
- Learn about the **basic knowledge** in **biomedical materials** for MS1 students.
- To provide students with the **ability to design** and **select suitable biomaterials for implants and prostheses** based on control of biomaterials-tissue interactions.

成績計算

- 出席率 20%
- 期中考 40%
- 團體報告 35%
- 其他 5%

Reference Book

- “Biomaterials: an introduction", Joon B. Park, Roderick. S. Lakers. Springer (2007)
- Introduction “Biomaterials Sciences”, Buddy D. Ranter et al, Academic Press. (2013, 3rd)
- "Advanced biomaterials", Bikramjit Basu, Dhirendra Katti, and Ashok Kumar. John Wiley & Sons (2009).
- " 生物醫學材料",王盈錦,林峰輝,胡孝光,黃玲惠,黃義侑,蔡瑞瑩,闕山璋. 合記圖書出版社. (2007)



ISBN-13: 978-0123746269
ISBN-10: 0123746264

課程內容

序號	週次/日期	授課教師		授課主題	授課大綱	備註
1	週次：1 2022/09/12 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	課程介紹	課程介紹	
2	週次：2 2022/09/19 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的分類介紹–生醫陶瓷	生醫玻璃/氫氧基磷灰石等	
3	週次：3 2022/09/26 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的分類介紹–生醫金屬	生醫金屬–不鏽鋼/鈦合金	
4	週次：4 2022/10/03 星期一 遠距教學週 授課方式：講演 數位學習：遠距教學 遠距教學方式：同步視訊	曾靖嫵 專任	上課時數 2小時	生醫材料的分類介紹–天然高分子	膠原蛋白，玻尿酸，幾丁質/幾丁聚醣	
5	週次：5 2022/10/10 星期一 (國定假日) 國慶日放假					
6	週次：6 2022/10/17 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的分類介紹–合成高分子	合成高分子：聚酯類,聚乳酸，聚氯乙烯等	
7	週次：7 2022/10/24 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	材料生物相容性測試	材料細胞毒性,基因毒性,血液相容性,或致敏性等測試	
8	週次：8 2022/10/31 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	水膠應用	水膠定義/特性; 軟組織應用	
9	週次：9 2022/11/07 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	組織工程	組織工程原理與應用	
10	週次：10 2022/11/14 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	期中考	期中考	

11	週次：11 2022/11/21 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的應用（1）	材料眼科應用與現況反思討論
12	週次：12 2022/11/28 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的應用（2）	骨科材料應用與現況反思討論
13	週次：13 2022/12/05 星期一 授課方式：講演 數位學習：無	曾靖嫵 專任	上課時數 2小時	生醫材料的應用（3）	心血管應用與現況反思討論
14	週次：14 2022/12/12 星期一 遠距教學週 授課方式：講演 數位學習：遠距教學 遠距教學方式：非同步視訊+非同步討論	莊爾元 專任	上課時數 2小時	生醫材料的應用（4）	藥物釋放系統
15	週次：15 2022/12/19 星期一 遠距教學週 授課方式：講演 數位學習：遠距教學 遠距教學方式：同步視訊	楊凱強 專任	上課時數 2小時	支架製備	支架製備
16	週次：16 2022/12/26 星期一 授課方式：分組討論 數位學習：無	曾靖嫵 專任	上課時數 2小時	期末分組報告 1	期末分組報告 1
	週次：17				
17	2023/01/02 星期一 (國定假日) 開國紀念日補假				
18	週次：18 2023/01/09 星期一 期末考試（2字頭教室為統一排考場地，停止使用） 授課方式：分組討論 數位學習：無	曾靖嫵 專任	上課時數 2小時	期末分組報告 3	期末分組報告 3

生醫材料定義

以前

Biomedical materials/ Bio-materials

- A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems. Williams, 1987

  無法自力生活 / 沒有活性 / 和體內有交互作用

  生物材料是用於醫療設備的非活性材料，旨在與生物系統相互作用。
  旨在與生物系統交互以評估、治療、增強或替代身體的任何組織、器官或功能的材料。

- A material intended to interface with biological system to evaluate, treatment, augment or replace any tissue, organ or function of the body*.

  有功能性、沒有毒性

The major difference of biomaterials from other classes of materials is their **ability to remain in a biological environment without damaging the surroundings and without getting damaged in that process.**

生物材料與其他類別材料的主要區別在於它們能夠保持在生物環境中而不會損壞周圍環境並且不會在該過程中受到損壞。

* Williams, D.F. The Williams dictionary of Biomaterials. Liverpool: Liverpool University Press, 1999.

生醫材料定義

現在

- Biomaterials

取代身體的功能

Can be defined as any material used to make devices to replace a part or a function of the body in a safe, reliable, economic, and physiologically acceptable manner.

可以定義為用於製造以安全、可靠、經濟和生理可接受的方式替代身體的一部分或功能的裝置的任何材料。

Hill (1998). Copyright © 1998,Wiley Chap 1, INTRODUCTION

The compelling human side to biomaterials is that millions of **lives are saved**, and the **quality of life** is **improved** for millions more.

生物材料引人注目的人性方面是拯救了數百萬人的生命，並提高了數百萬人的生活質量。

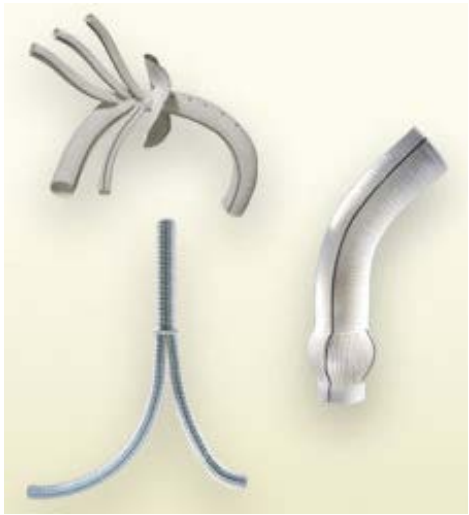
Are the following items biomaterials?

(a) Contact lens

(b) Vascular graft

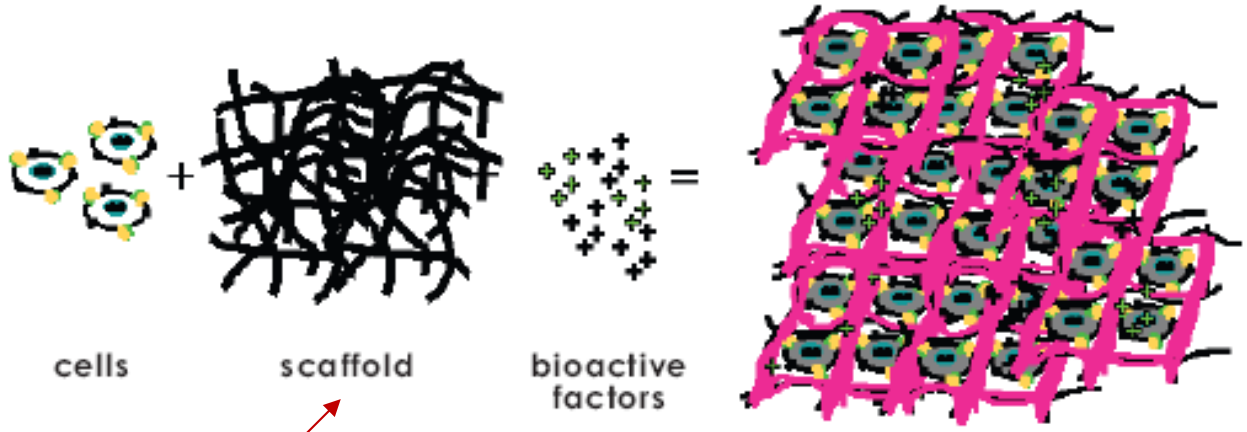
(c) Crutch 拐杖

(d) Steel (不是所有不銹鋼接能放入體內) → 與編號有關



(e) Hip joint

The Tissue Engineering Triad



Biomaterials

目前可做類組織
⇒器官還無法

SCAFFOLDS

gels
foams
fibers
membranes

PROSTHESIS

CELLS

cultivated
adult stem
embryonic stem
autogenous
mobilized
allogeneic
engineered

SIGNALS

Family
TGFβ
FGF
Homeobox
Hedgehog
WNT

醫療器材

Federal Food Drug & Cosmetic (FD &C) section 201(h)

- A device is "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part or accessory which is:

體外試劑也算

  - Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
  - Intender for use in the diagnosis of disease or other conditions, or in the cure, migration, treatment, or prevention of disease, in man or other animals.
  - Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other a animals and which is not dependent upon being metabolized for the achievement of any of is primary intended purposes.

藥→先代謝→代謝產物→與體內反應

隱眼→物理變光

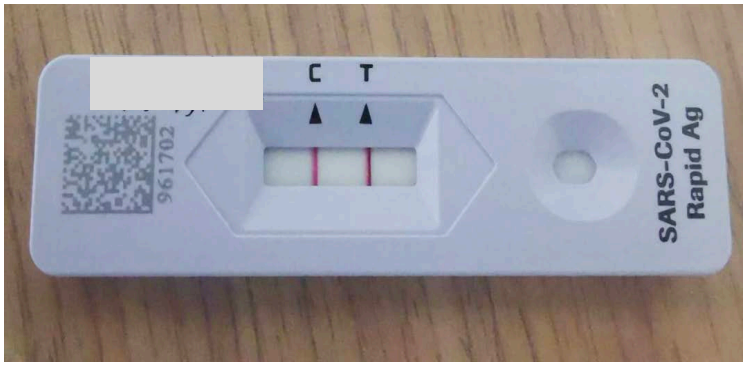
醫療器材

本法所稱醫療器材，係包括診斷、治療、減輕或直接預防人類疾病，或足以影響人體身體結構及機能之儀器、器械、用具及其附件、配件、零件。中央衛生主管機關應視實際需要，訂定醫療器管理辦法。

體外診斷試劑 (in vitro diagnostic device, IVD)

係指蒐集、準備及檢查取自於人體之檢體，作為**診斷疾病**或其他狀況 (包含健康狀態之決定) 而使用之診斷試劑、儀器或系統等醫療器材 。

COVI-19 test



History of Biomaterials

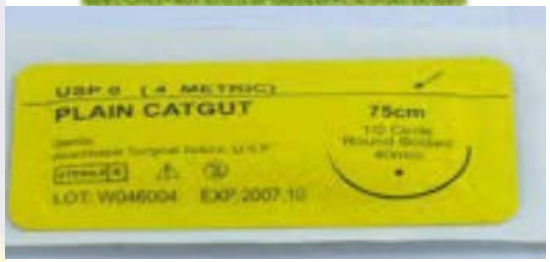
Prehistory of biomaterials

Wood toe in 3000 years old Egyptian mummy

Linen for sutures

Middle ages in Europe

Catgut suture



Prehistory of biomaterials

The Ford mandible

The Ford Mandible

- Dates from the 5th BC.
- It was discovered in a sarcophagus in Sidon.
- The 6th front teeth were about to fall due to a gum disease.
- The Phoenician dentist bound them together with a gold wire in a perfect technique. It is the earliest known example of dentistry.

Prehistory of biomaterials

* Nature (vol 391, 1, 1998)

Mayan people fashioned **nacre teeth** from sea shells in roughly with osseointegration **(Mayan, 600 AD)**

"**Osseointegration** appears viable". The implant was probably set by impaction soon after the tooth loss."

Metal dental implants, 200 A.D.

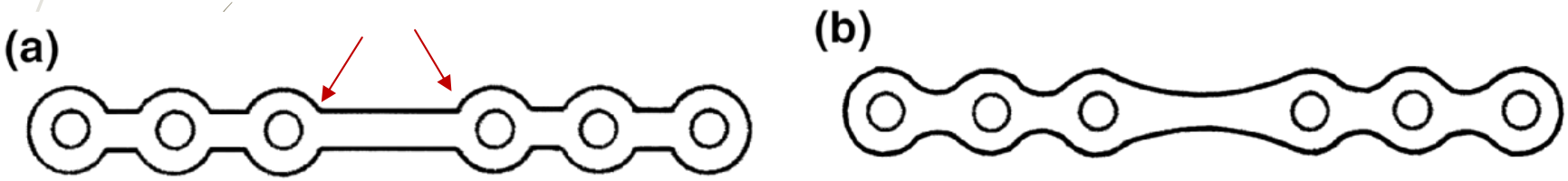
A **wrought iron dental implant** of an upper premolar is from a Gallo-Roman necropolis in France.

Modern History of Biomaterials

1860s **-Aseptic surgical technique** was developed

- Implant various metal devices such as wires and pins constructed of iron, gold, silver, platinum.

Early 1900s using steel



Early design of bone fracture plate: (**a**) Lane, (**b**) Sherman.

1924 **Stellite® (Co–Cr-based alloy)**

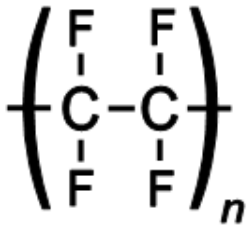
1939 **Tantalum implant**

Modern History of Biomaterials

The development of the biomaterials filed significantly increased after **World War II** with the widespread availability of **synthetic materials** that were originally designed for us in the war.

1939~1945

- **Nylon**
- **Teflon**
- **Silicones**
- **Titanium**
- **Stainless steel**



Polytetrafluoroethen

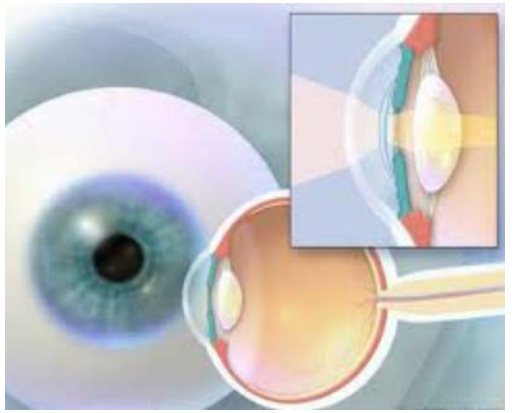
1960- Polyethylene and stainless steel being used for hip implants

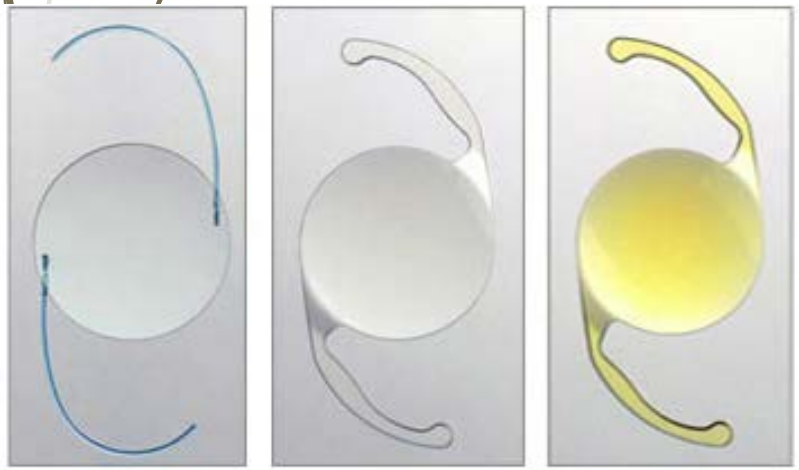
Parachute cloth used for vascular prosthesis

人工水晶體

Intraocular Cataract lenses (IOL)

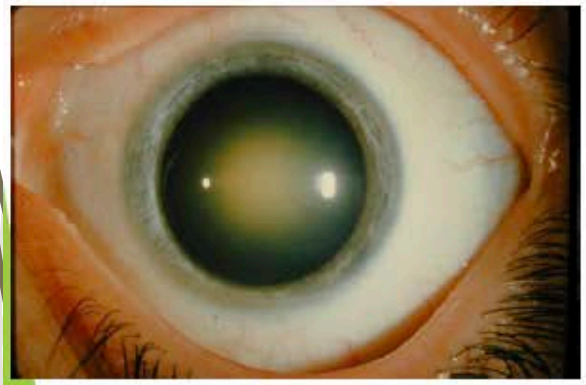
- Sir Harold Ridley, MD (1906-2001) inventor of the plastic intraocular lens (IOL)
- Shards of **polymethyl - methacrylate (PMMA)** unintentionally got lodged into eyes of aviators
- The first implantation in a human of IOL was Nov. 29, 1949



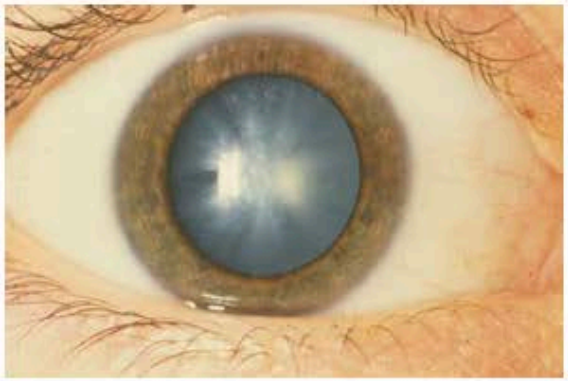


人工水晶體

白內障 (Cataract)



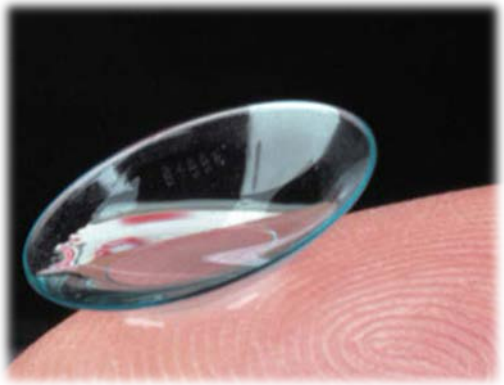
Nuclear Cataract



Cortical Cataract

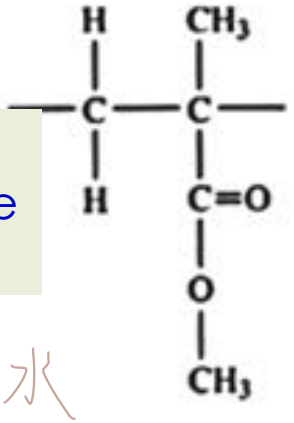
Posterior subcapsular Cataract

隱形眼鏡

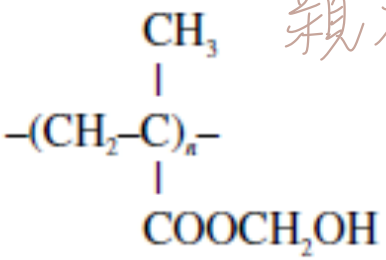


Contact lens

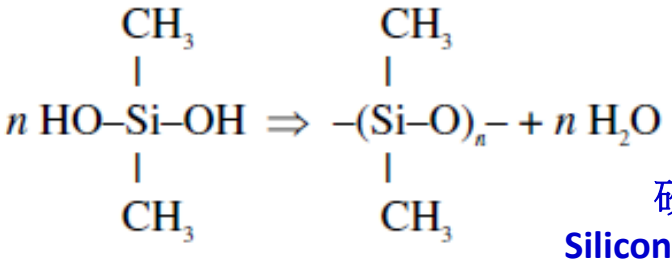
聚甲基丙烯酸甲酯
polymethyl –methacrylate
(PMMA)



親水



甲基丙烯酸羟乙酯
poly(hydroxyethyl-methacrylate)
poly-HEMA



矽膠
Silicone rubber

透氧率與隱形眼鏡厚度之關係

透氧率↑ ∝ 厚度"薄"

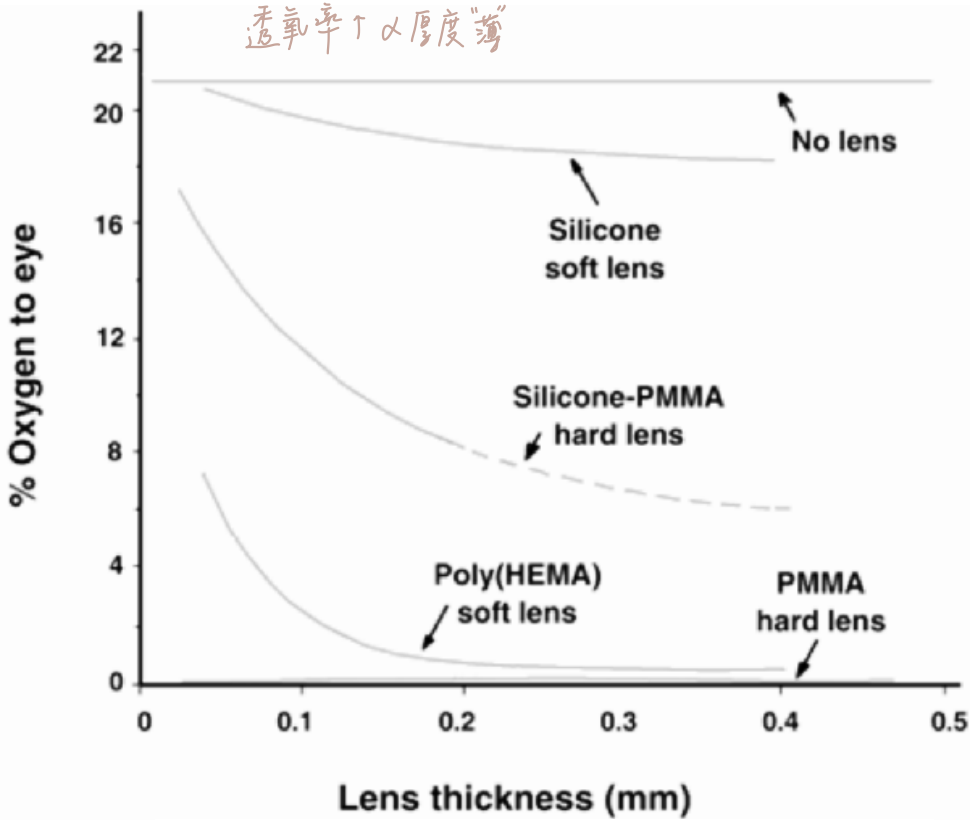


Figure 7-8. Ultimate tensile strength versus time for polymethylmethacrylate in saline solution at 37ºC.

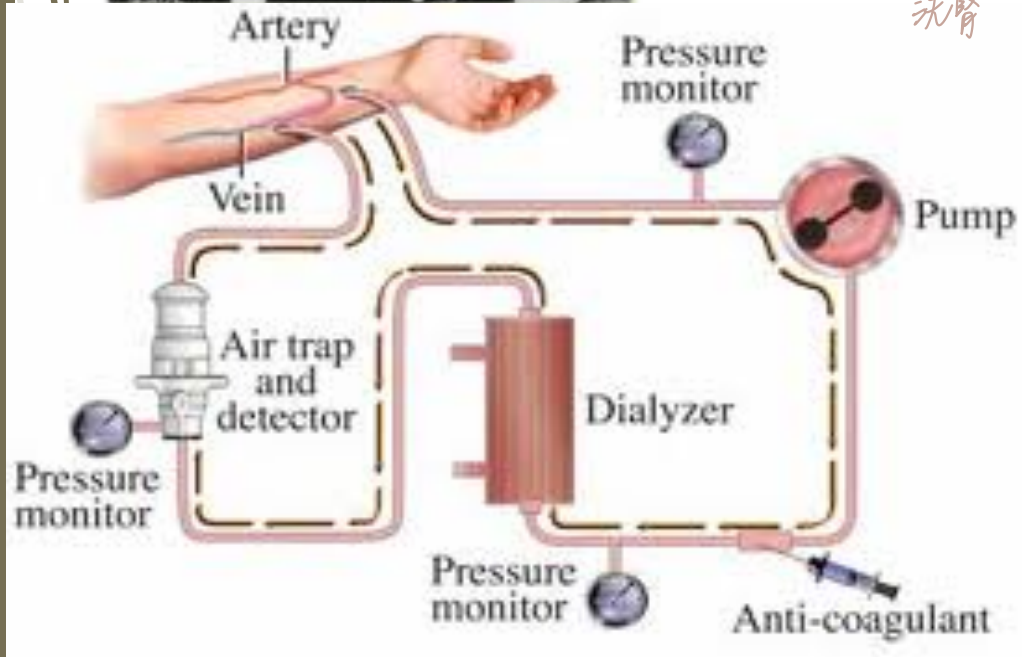
Washing machine - artificial kidney

1910 John Hopkins University (John Jacob Abel)
remove toxins from rabbit blood

1943 Willim J. Kolff
built a drum dialyzer system
- 100 liter tank, wood slats,
- 130 feet cellulose sausage casing tubing

1960 **Kidney dialysis machines** (originally using a natural polymer derivative, cellulose)

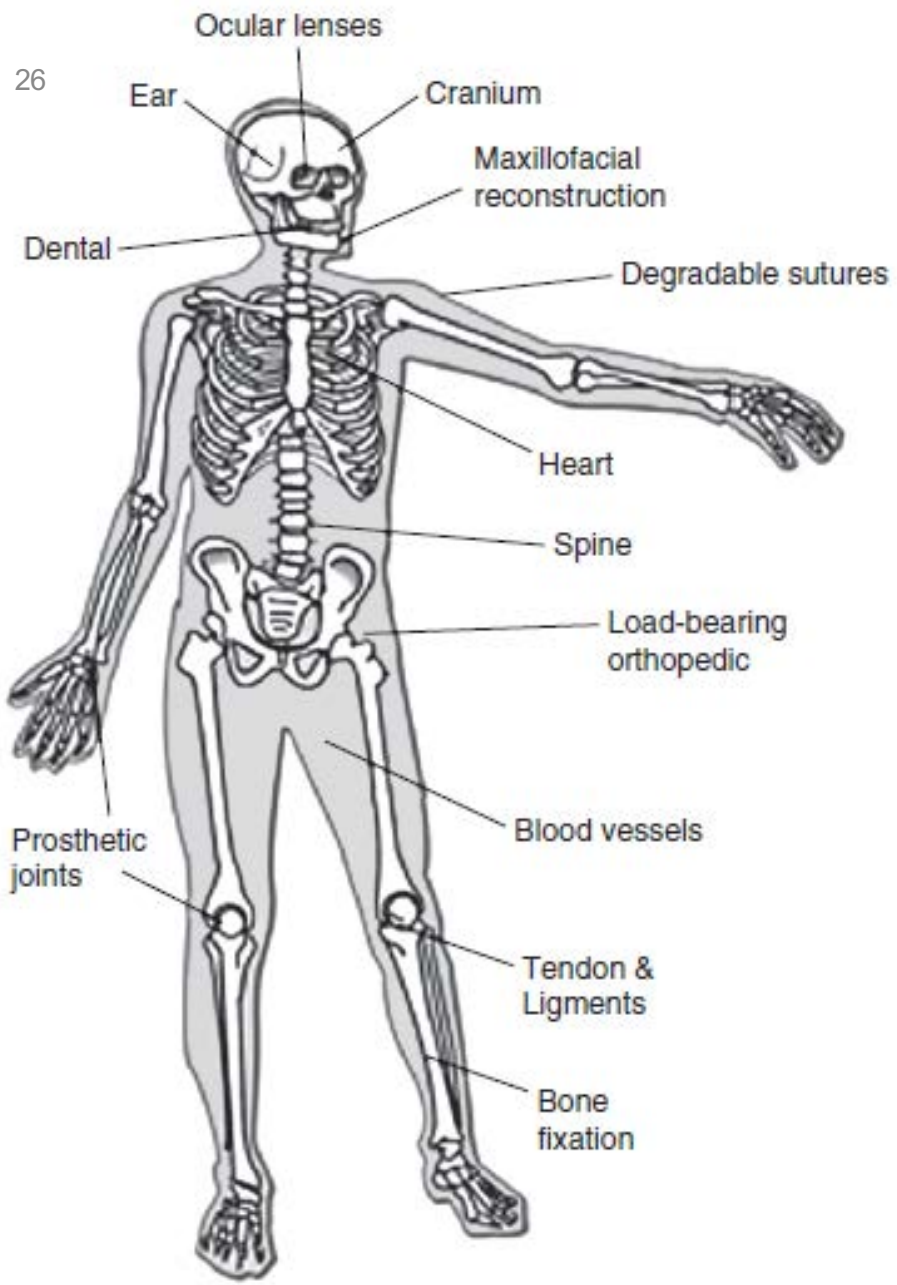
洗腎



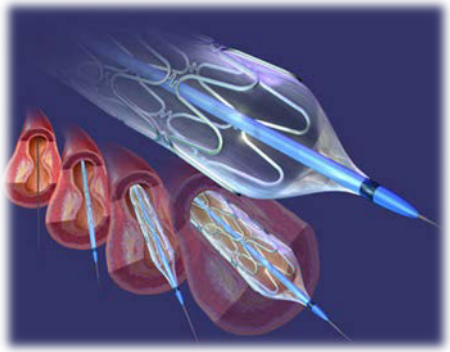
Dr. Belding Scribner

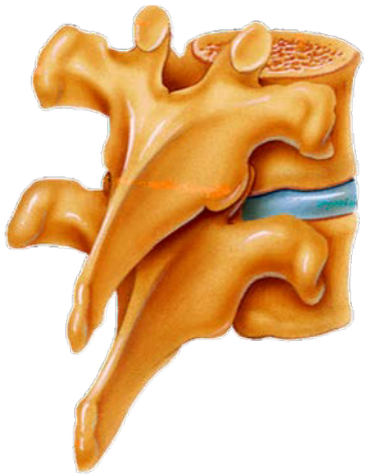
A shunt implanted between an artery and vein (Teflon tube, Dacron) chronic dialysis.

人工廔管(洗腎一直摩擦血管引太傷3會磨損)



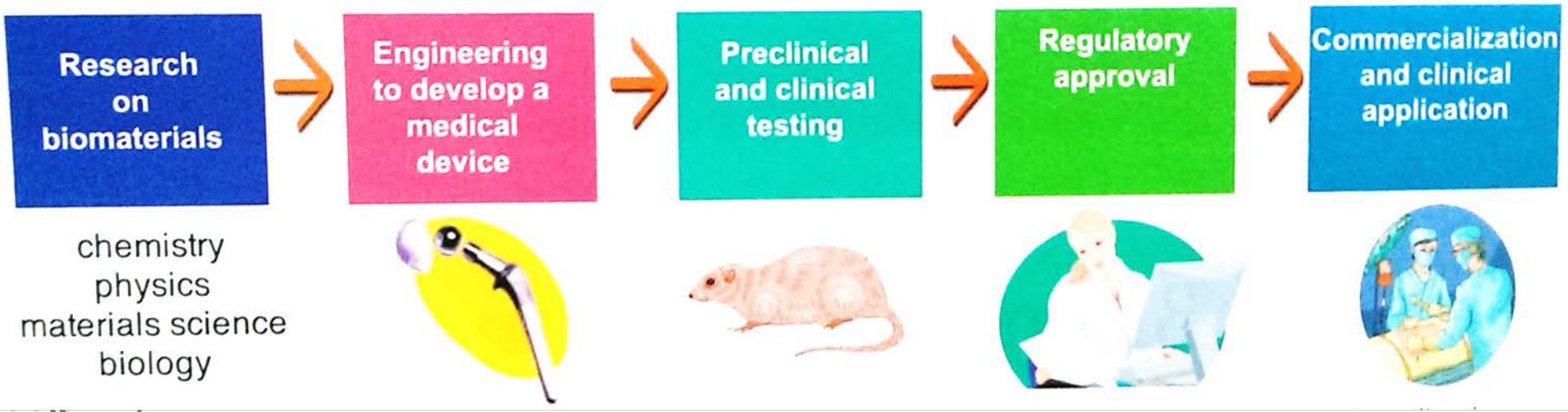
USA	Expenditure (USD)
Health care	14 billion
Biomaterials	9 billion





J Black, in chapter: Biocompatibility: Definition and Issues, Biological Performance of Materials: Fundamentals of Biocompatibility, CRC Press, US, 2006

The path from the basic science to clinical application



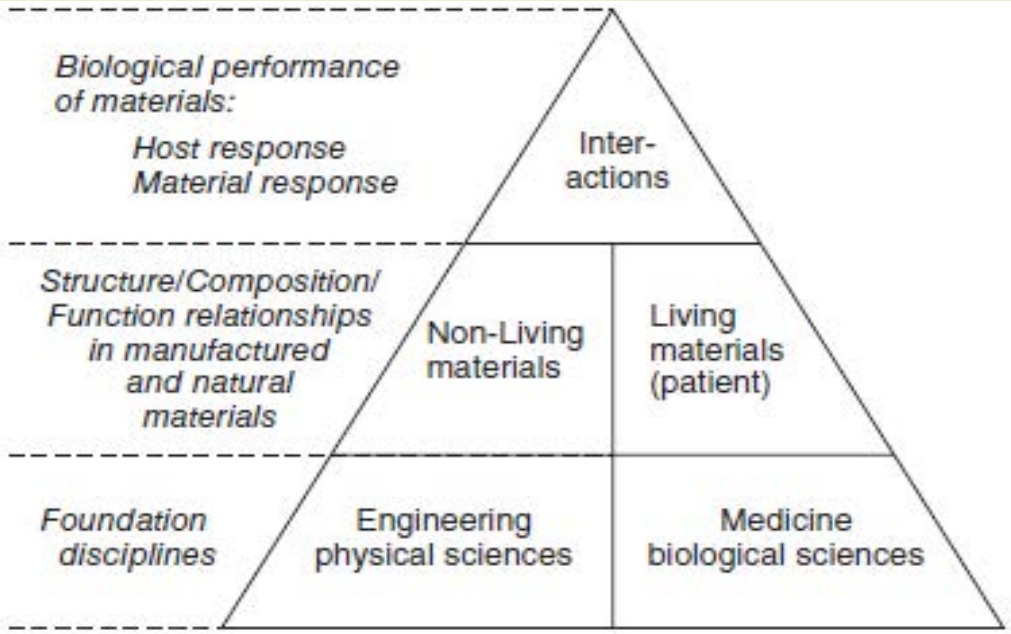
研究 研發 動物實驗 臨床試驗 法規認證 上市

Biomaterials science

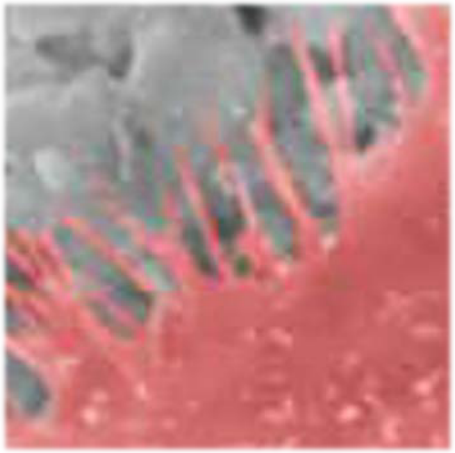
The study of biomaterials and their interactions with the biological environment.

Materials Science - mechanical properties,
- surface modification of implants.

Biological topics – immunology,
- toxicity
- wound healing processes



Biomaterials science



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

在特定的應用下，在體內可有適當的宿主反應

- Biochemically compatibile, non-toxic, non-irritable, non- allergenic and non–carcinogenic
- Biomechanically compatible with surrounding tissues.
- A bioadhesive contact must be established between the materials and living tissues.

Consider material properties and biological reaction to ensure that the chosen material is appropriate for the given application.

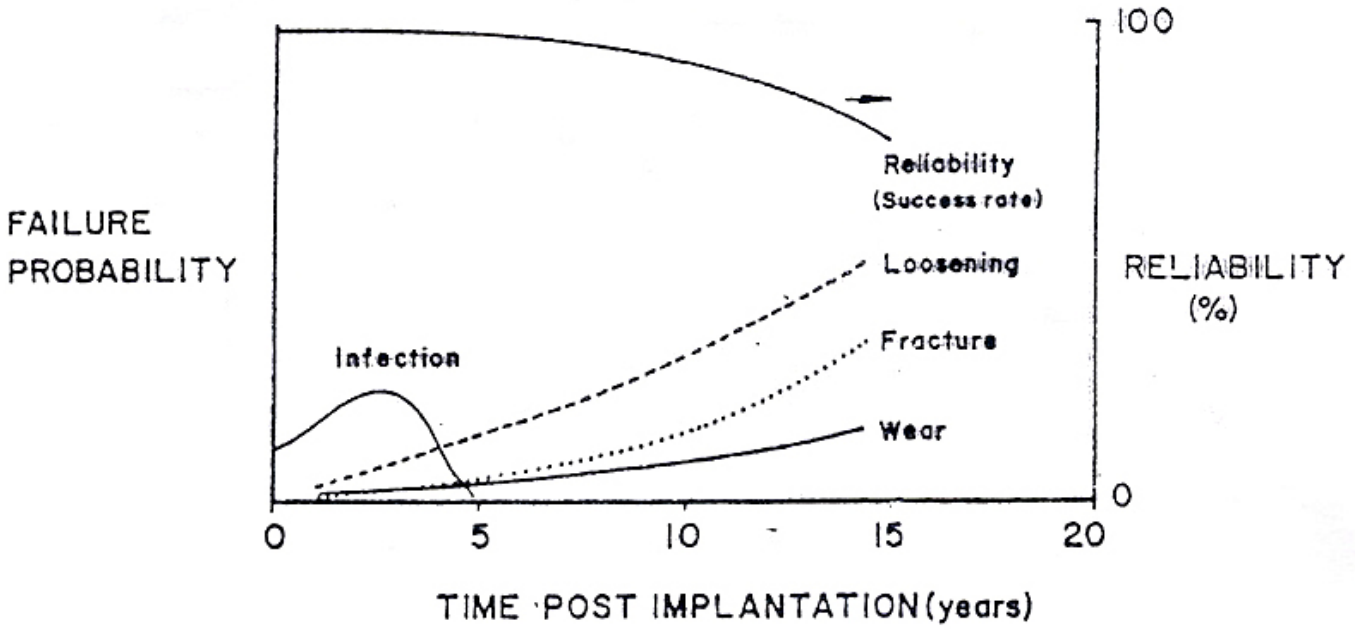
* Williams, D.F. The Williams dictionary of Biomaterials. Liverpool: Liverpool University Press, 1999.

Failure modes also depend on the type of implant and its location and function in the body

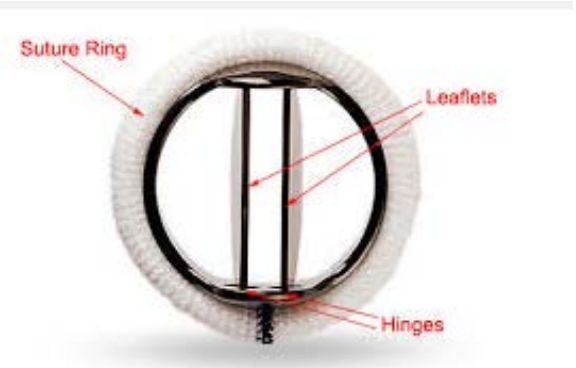
A total joint replacement

→ **infection** is most likely soon after surgery

→ **loosening** and **implant fracture** become progressively important



Biomaterials in Organs



Organ	Examples
Heart	Cardiac pacemaker, artificial heart valve
Lung	Oxygenator machine
Eye	Contact lens, eye lens replacement
Ear	Artificial stapes, cosmetic reconstruction of outer ear
Bone	Bone plate
Kidney	Kidney dialysis machine
Bladder	Catheter

Biomaterials in Body Systems

System	Examples
Skeletal	Bone plate, total joint replacement
Muscular	Sutures
Digestive	Sutures
Circulatory	Artificial heart vales, blood vessels
Respiratory	Oxygenator machine
Integumentary	Sutures, burn dressings, artificial skin
Urinary	Catheters, kidney dialysis machine
Nervous	Hydrocephalus drain, cardiac pacemaker
Endocrine	Microencapsulated pancreatic islet cells
Reproductive	Augmentation mammoplasty, other cosmetic replacements

Host Response

宿主反應

The formation of a structural and biological bond between the material and host tissues.

惰性 → 有功能但不會起反應的

耐受性 → 是生物相容性的材料

- **Bioinert / biotolerant:**

  are biocompatible materials, **but cannot induce any interfacial biological bond** between implants and tissues (bone).

  但植入物不會與生物結合

- **Bioactive:**

  表面與植入物相附、並形成生物、化學鍵

  are a group of biocompatible materials that can **attach directly with body tissues** and **form chemical and biological bonds** during early stages of the post implantation period.

- **Bioresorbable:**

  會被吸收、在體內完全被新組織取代

  新生組織

  are the type of biocompatible materials that are **gradually resorbed before they finally disappear** and are totally replaced by new tissues *in vivo*.

Requirement of Biomaterials

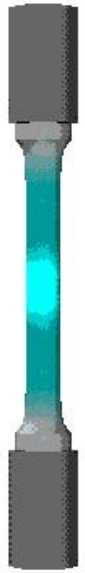
The **successful** biomaterial is highly dependent on three major factors:

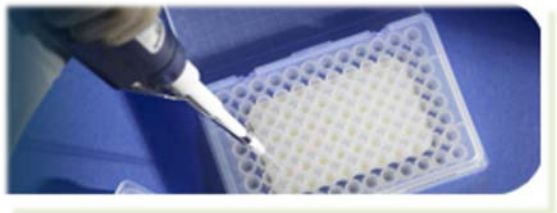
- ✓ **Properties and biocompatibility of the implant**
- ✓ **Health condition of recipient/patient**
- ✓ **Competence of the surgeon**

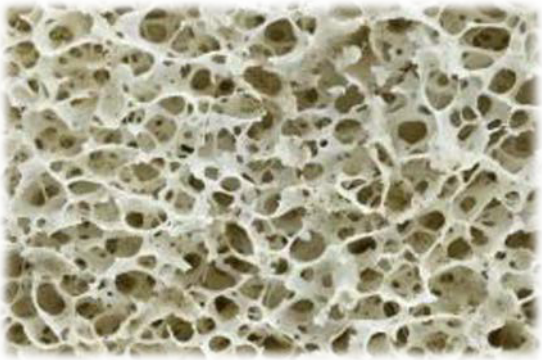
  - Acceptance to the tissue
  - Nontoxic and non-carcinogenic
  - Chemically inert and stable (time-dependent degradation)
  - Adequate mechanical strength
  - Adequate fatigue life
  - Engineering design
  - Proper weight and density
  - Relatively inexpensive, reproducible, and easy to fabricate

Material Selection Parameters

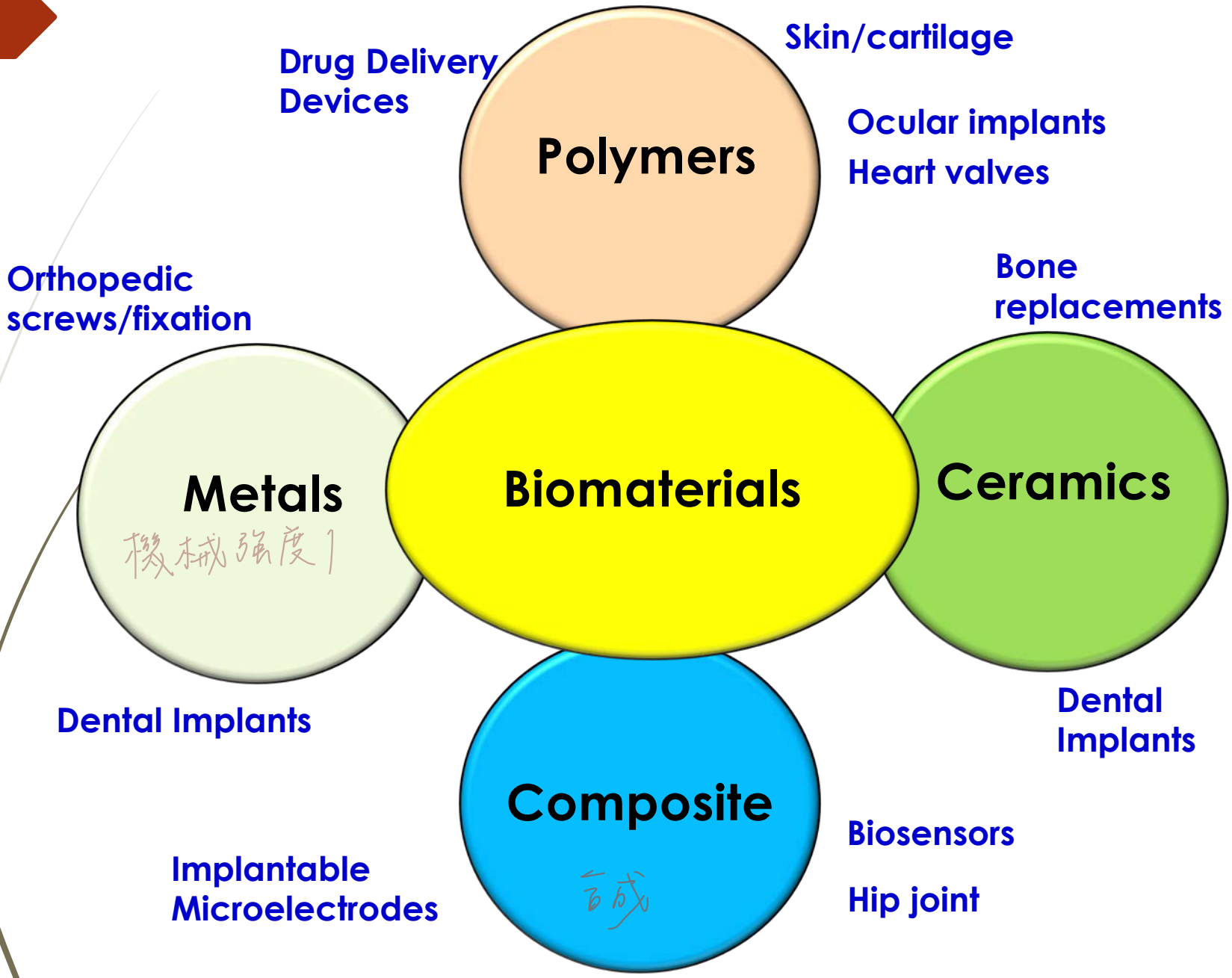
- Mechanical
- Thermal/Electrical Conductivity
- Diffusion
- Water Absorption
- Bio-stability
- Biocompatibility







Material property



Metal

- **316L Stainless Steel, . Co-Cr-Mo Alloy**
- **Ti_6Al_4V (Ti-alloy)**
- **Amalgam (Ag/Sn/Cu/Zn/Hg)**
- **Metal coated with porous bioactive ceramics**

TABLE 1.2

Metals Commonly Used in Biomedical Applications

Metal	Applications
Cobalt-chromium alloys	Artificial heart valves, dental prostheses, orthopedic fixation plates, artificial joint components, vascular stents
Gold and platinum	Dental fillings, electrodes for cochlear implants
Silver-tin-copper alloys	Dental amalgams
Stainless steel	Dental prostheses, orthopedic fixation plates, vascular stents
Titanium alloys	Artificial heart valves, dental implants, artificial joint components, orthopedic screws, pacemaker cases, vascular stents

Bioceramics

- **Bioinert Ceramics:**

  Al_2O_3, ZrO_2, SiC, Si_3N_4…

- **Bioactive Ceramics:**

  Surface Active → HAP and Bioglass

  Resorbable → TCP

  Dissolvable → Calcium phosphate with Ca/P < 1

1983 Klein and 1989 Le Geros

Degradation rate of Hydroxyapatite (HAP) was relatively slow and Tricalcium phosphate (TCP) was supposed too fast. It was thought that the combination of TCP/HAP composite would provide a better environment for bone substitute.

1986-1996 Moore and Chapman

Biphasic calcium phosphate
80HAP/20TCP, 70HAP/30TCP…

Polymeric Biomaterials

Nature components

Collagen

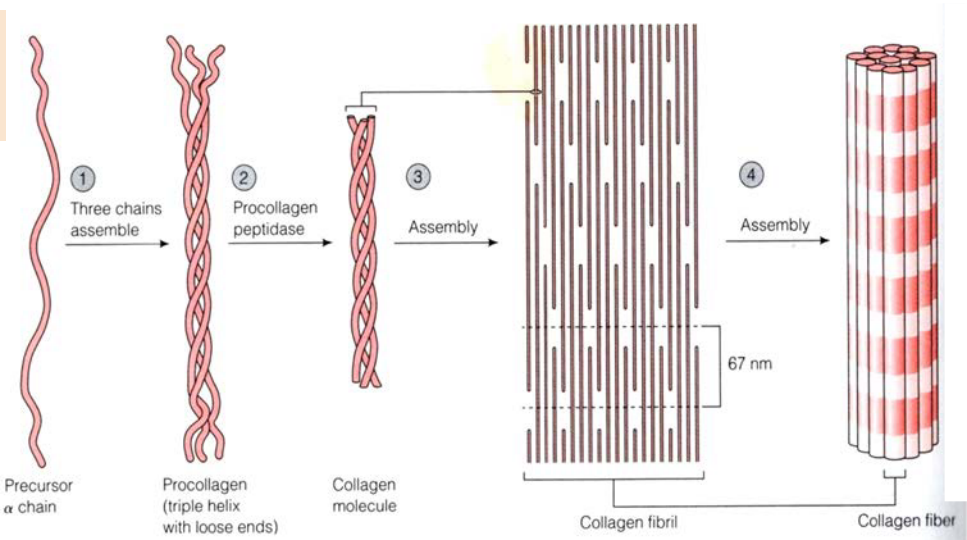


Figure 11-3 Collagen Assembly. ① Collagen precursor chains are assembled in the ER lumen to form triple-helical procollagen molecules. ② After secretion from the cell, procollagen is converted to collagen in a peptide-cleaving reaction catalyzed by the enzyme procollagen peptidase. ③ The molecules of collagen molecules, also called tropocollagen, then bind to each other and self-assemble into collagen fibrils. ④ The fibrils assemble laterally into collagen fibers. In striated collagen, the 67-nm repeat distance is created by packing together rows of collagen molecules in which each row is displaced by one-fourth the length of a single molecule.

Table 11-2 Types of Collagen and Their Occurrence and Structure

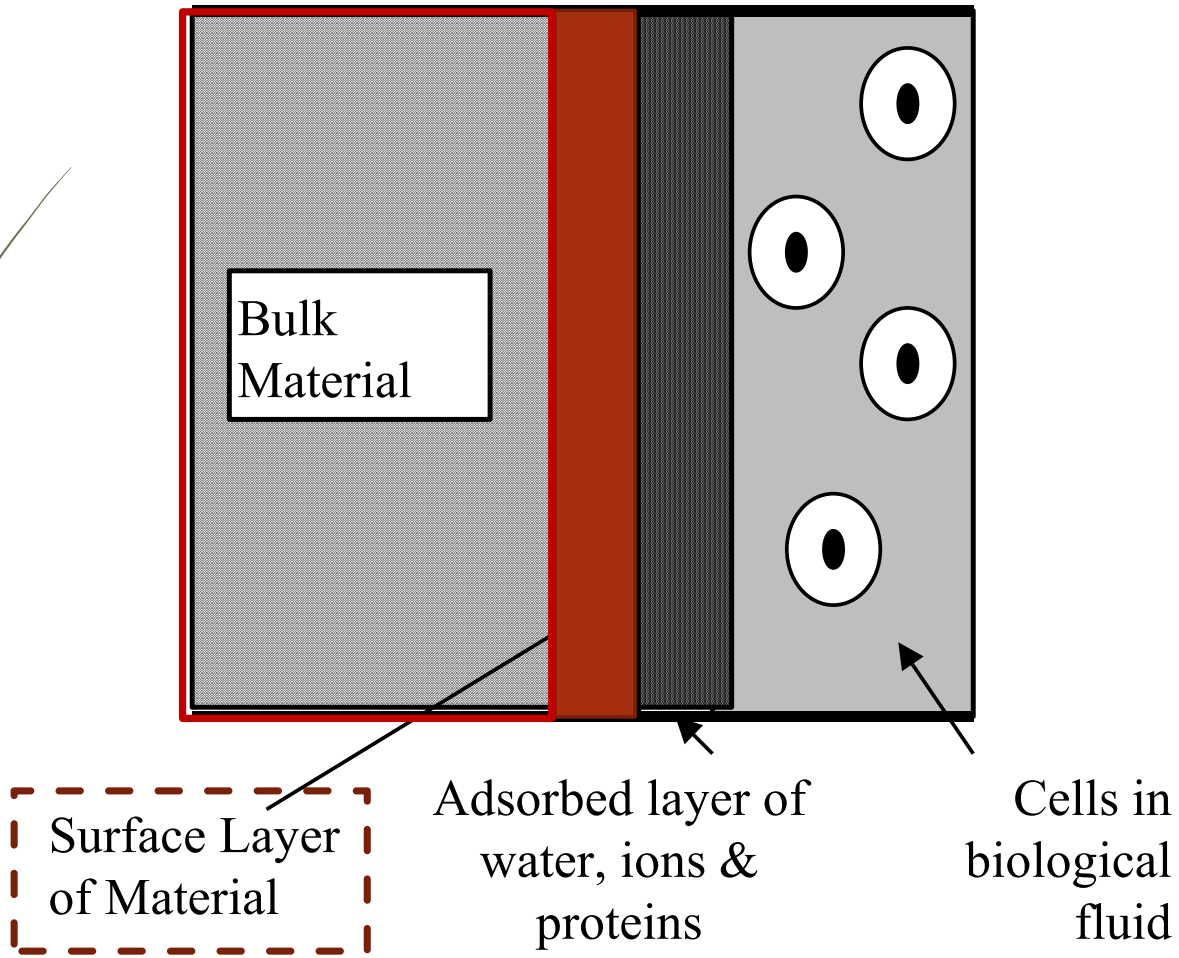
Type	*Occurrence*	*Structure**
I	Skin, bones, tendons, ligaments; cornea of eye	Striated fibrils
II	Cartilage, intervertebral discs; vitreous humor of eye	Striated fibrils
III	Skin, tendons; blood vessel walls; uterine walls	Striated fibrils
IV	Basal lamina	Fine, unstriated fibrils
V	Cornea of eye; interstitial tissues	Striated fibrils
VI	Nerves and blood vessels	Fine fibrils
VII–XV	Occurrence varies with type; most are minor components of cartilage or tendons	Fine fibrils

Fibrils of types I, II, III, and V have striated patterns that can be readily seen with an electron microscope, whereas type IV collagen is not striated. Types VI–IX have molecular structures that are consistent with striation, but no such patterns have yet been seen. Types X–XV have molecular structures that make striations unlikely.

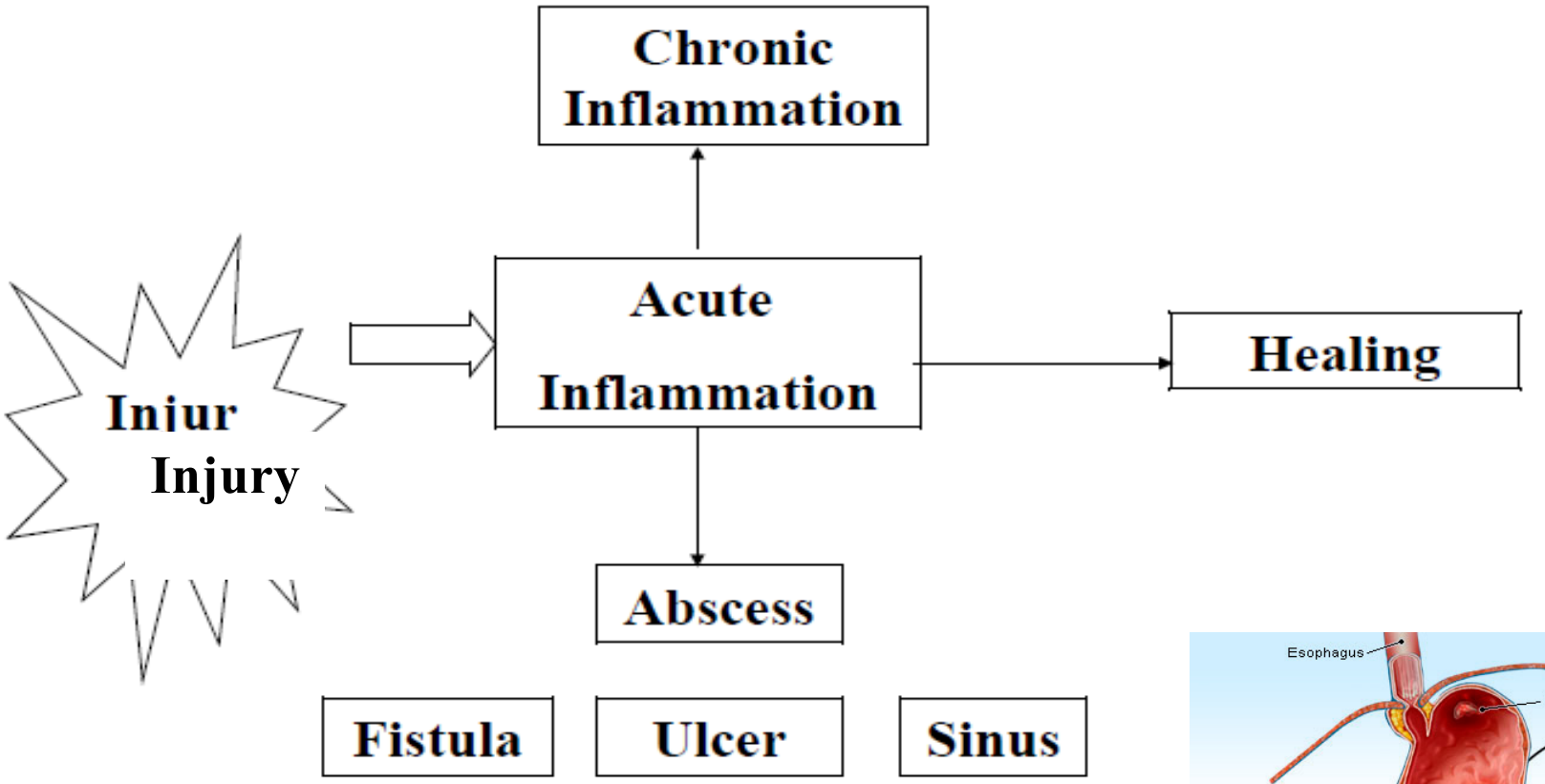
Composites materials

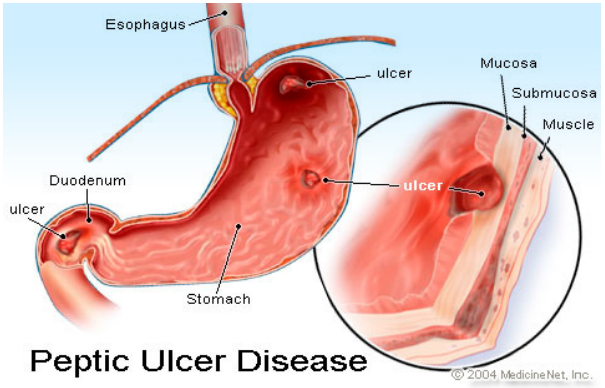
Hip joint replacement (Medical device)

Biocompatibility is primarily a surface phenomenon.



Inflammation end points





Mechanical compatibility

- Optimizing **load transfer** between the **implant** and **natural tissues.**
- Proper mechanical properties and duration to retain required functions during the expected serving period in the body.

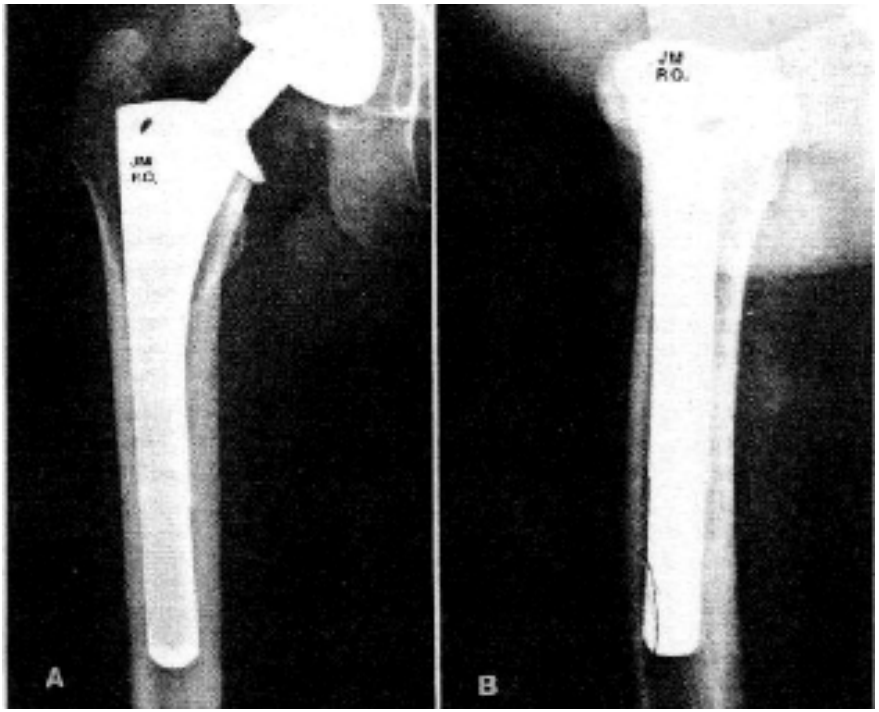
Stress Shielding Effect

Bone: 7-30 GPa

Ti and alloys: 88 GPa

Bone loss (resorption)

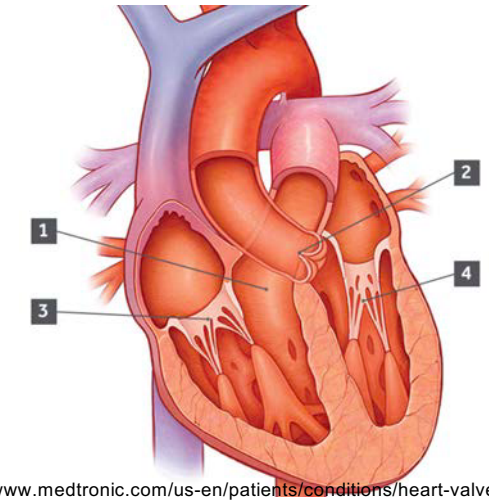
Bone or implant fracture



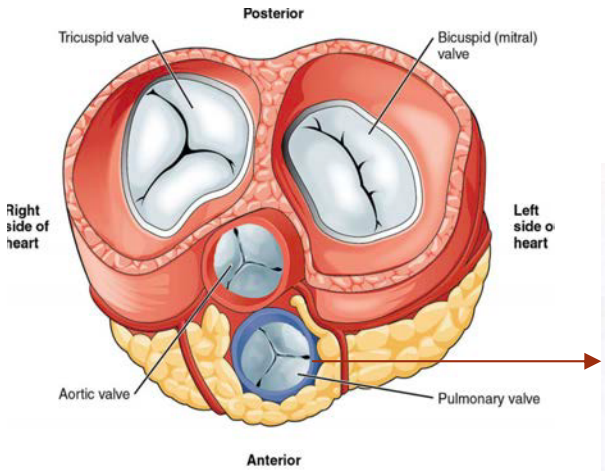
Classic Examples

Substitute Heart valves:

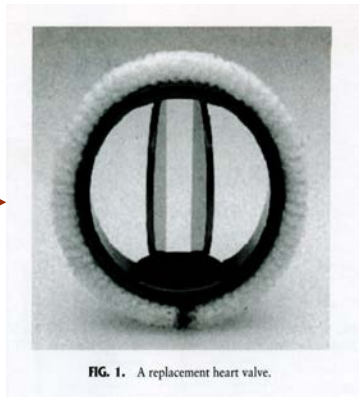
- **Heart valve** prostheses are fabricated from **carbons, metals, elastomers, fabrics** and ***natural (e.g. pig) valves*** and other tissues chemically pretreated to reduce their immunologic reactivity and enhance durability.
- Problem: degeneration of tissue, mechanical failure, **postoperative infection**, and ***induction of blood clot***.



http://www.medtronic.com/us-en/patients/conditions/heart-valve-disease/about-the-heart.html



http://teachmeanatomy.info/thorax/organs/heart/heart-valves/



Evolution of Heart valve

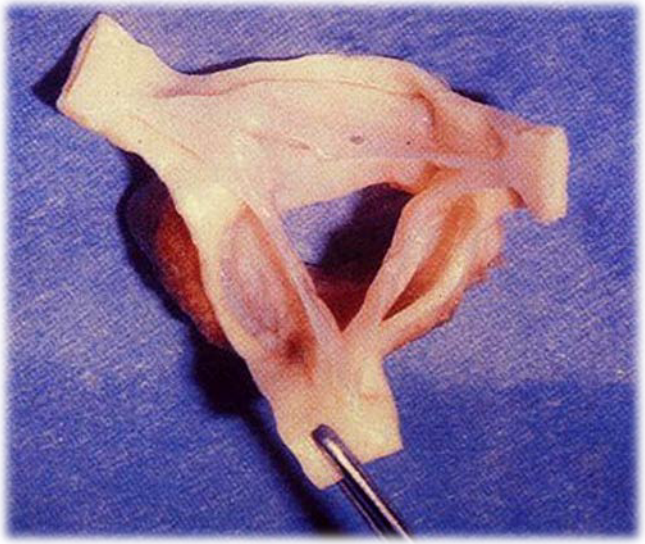
Structural

Bioinertness

Soft Tissue Replacements

Bioactivity

Functional Tissue Engineering Constructs



Regenerative functional tissue

First Generation Implants

- "ad hoc" implants (specific)
- Specified by physicians using common and borrowed materials
- Most successes were accidental rather than by design

- 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

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)

- Titanium alloy dental and orthopedic implants
- Cobalt-chromium-molybdenum orthopedic implants
- UHMW polyethylene bearing surfaces for total joint replacements
- Heart valves and pacemakers

Third generation implants

- Bioengineered implants using bioengineered materials
- Few examples on the market
- Some modified and new polymeric devices many under development

- **Tissue engineered implant**s designed to regrow rather than replace tissues
- Integra Life Sciences - artificial skin
- Genzyme - cartilage cell procedure
- Some resorbable bone repair cements
- Genetically engineered "biological" components (Genetics Institute and Creative Biomolecules BMPs)

Summary

- ✓ Basic definition of biomaterials
- ✓ Example of biomaterials application
- ✓ Characteristics of Biomaterials Science
  - Multidisciplinary
  - Many diverse materials
  - Development of biomaterials/medical devices
  - Magnitude of the field
  - Success and failure

Reference

- Biomaterials - The Interection of Biology and Materials Science. J. S. Temenoff & A.G. Mikos (2008) Pearson Prentice Hall.
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