Biomaterials

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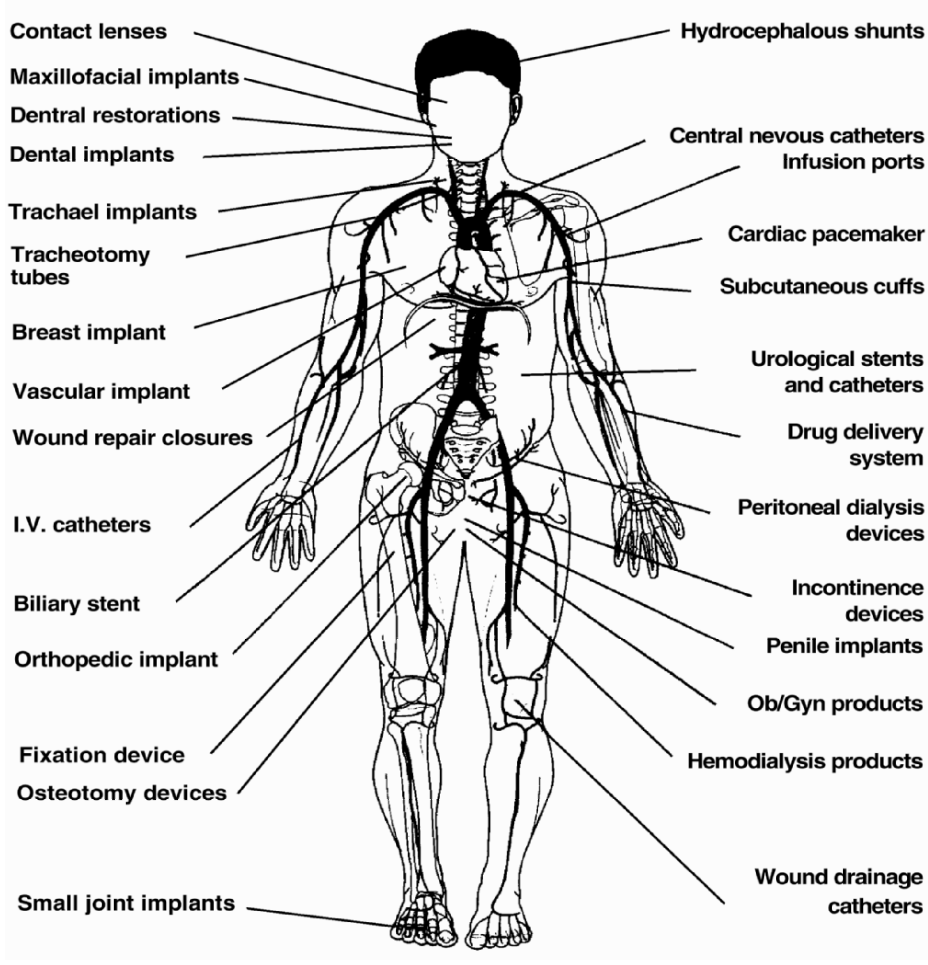
Pages 1 to 16

1

INTRODUCTION



Illustrations of various implants and devices used to replace or enhance the function of diseased or missing tissues and organs. Adapted with permission from Hill (1998). Copyright © 1998, Wiley.

1.1. DEFINITION OF BIOMATERIALS

A *biomaterial* 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. Some people refer to materials of biological origin such as wood and bone as biomaterials, but in this book we refer to such materials as "biological materials." A variety of devices and materials is used in the treatment of disease or injury. Commonplace examples include sutures, tooth fillings, needles, catheters, bone plates, etc. A biomaterial is a synthetic material used to replace part of a living system or to function in intimate contact with living tissue. The Clemson University Advisory Board for Biomaterials has formally defined a biomaterial to be "a systemically and pharmacologically inert substance designed for implantation within or incorporation with living systems." These descriptions add to the many ways of looking at the same concept but expressing it in different ways. By contrast, a *biological material* is a material such as bone, skin, or artery produced by a biological system. Artificial materials that simply are in contact with the skin, such as hearing aids and wearable artificial limbs, are not included in our definition of biomaterials since the skin acts as a barrier with the external world.

Because the ultimate goal of using biomaterials is to improve human health by restoring the function of natural living tissues and organs in the body, it is essential to understand relationships among the properties, functions, and structures of biological materials. Thus, three aspects of study on the subject of biomaterials can be envisioned: biological materials, implant materials, and interaction between the two in the body.

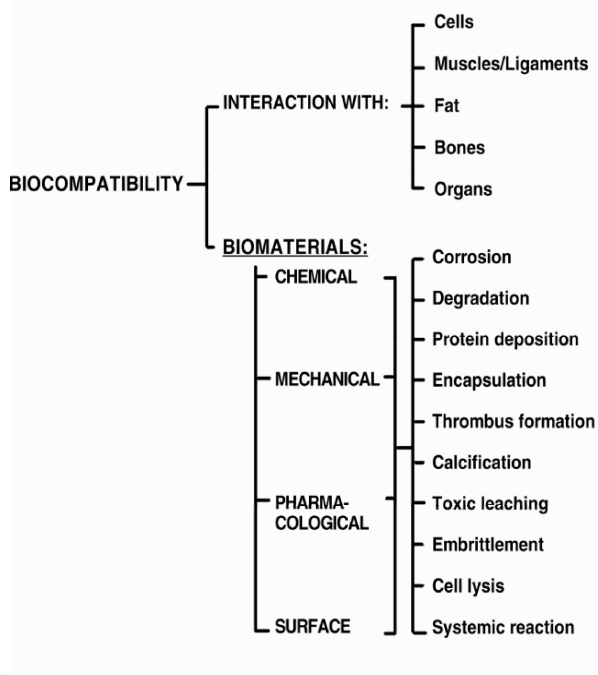


Figure 1-1. Schematic illustration of biocompatibility. Modified with permission from Hill (1998). Copyright © 1998, Wiley.

The success of a biomaterial or an implant is highly dependent on three major factors: the properties and biocompatibility of the implant (Figure 1-1), the health condition of the recipient, and the competency of the surgeon who implants and monitors its progress. It is easy to understand the requirements for an implant by examining the characteristics that a bone plate must satisfy for stabilizing a fractured femur after an accident. These are:

1. Acceptance of the plate to the tissue surface, i.e., biocompatibility (this is a broad term and includes points 2 and 3)
2. Pharmacological acceptability (nontoxic, nonallergenic, nonimmunogenic, noncarcinogenic, etc.)
3. Chemically inert and stable (no time-dependent degradation)
4. Adequate mechanical strength
5. Adequate fatigue life
6. Sound engineering design
7. Proper weight and density
8. Relatively inexpensive, reproducible, and easy to fabricate and process for large-scale production

Development of an understanding of the properties of materials that can meet these requirements is one of the goals of this book. The list in Table 1-1 illustrates some of the advantages, disadvantages, and applications of four groups of synthetic (manmade) materials used for implantation. Reconstituted (natural) materials such as collagen have been used for replacements (e.g., arterial wall, heart valve, and skin).

Table 1-1. Class of Materials Used in the Body

Materials	Advantages	Disadvantages	Examples
Polymers (nylon, silicone rubber, polyester, polytetrafuoroethylene, etc)	Resilient Easy to fabricate	Not strong Deforms with time May degrade	Sutures, blood vessels other soft tissues, sutures, hip socket, ear, nose
Metals (Ti and its alloys, Co–Cr alloys, Au, Ag stainless steels, etc.)	Strong, tough ductile	May corrode Dense Difficult to make	Joint replacements, dental root implants, pacer and suture wires, bone plates and screws
Ceramics (alumina zirconia, calcium phosphates including hydroxyapatite, carbon)	Very bio-compatible	Brittle Not resilient Weak in tension	Dental and orthopedic implants
Composites (carbon–carbon, wire- or fiber- reinforced bone cement)	Strong, tailor-made	Difficult to make	Bone cement, Dental resin

The materials to be used in vivo have to be approved by the FDA (United States Food and Drug Administration). If a proposed material is substantially equivalent to one used before the FDA legislation of 1976, then the FDA may approve its use on a Premarket Approval (PMA) basis. This process, justified by experience with a similar material, reduces the time and expense for the use of the proposed material. Otherwise, the material has to go through a series of "biocompatibility" tests**.** In general biocompatibility requirements include:

1. Acute systemic toxicity
2. Cytotoxicity
3. Hemolysis
4. Intravenous toxicity
5. Mutagenicity
6. Oral toxicity
7. Pyrogenicity
8. Sensitization

The guidelines on biocompatibility assessment are given in Table 1-2. The data and documentation requirements for all tests demonstrate the importance of good recordkeeping. It is also important to keep all documents created in the production of materials and devices to be used in vivo within the boundaries of Good Manufacturing Practices (GMP), requiring completely isolated clean rooms for production of implants and devices. The final products are usually sterilized after packaging. The packaged item is normally mass sterilized by γ-radiation or ETO (ethylene oxide gas).

Table 1-2. Guidance on Biocompatibility Assessment

A. Data required to assess suitability
   1. Material characterization. Identify the chemical structure of a material and any potential toxicological hazards. Residue levels. Degradation products. Cumulative effects of each process.
   2. Information on prior use. Documented proof of prior use, which would indicate the material(s) suitability.
   3. Toxicological data. Results of known biological tests that would aid in assessing potential reaction (adverse or not) during clinical use.

B. Supporting documents
   1. Details of application: shape, size, form, plus time in contact and use.
   2. Chemical breakdown of all materials involved in the product.
   3. A review of all toxicity data on those materials in direct contact with the body tissues.
   4. Prior use and details of effects.
   5. Toxicity tests [FDA* or ISO (International Standard Organization guides)]
   6. Final assessment of all information including toxicological significance.

*FDA internet address: http://www.fda.gov/cdrh/index.html.
CDRH (Center for Devices and Radiological Health of the FDA) administers medical devices.

Table 1-3 shows a series of criteria to be employed in developing new bone cement. The original bone cement was used by Dr. J. Charnley in total hip replacement fixation on the advice of Dr. D. Smith (a dentist) in the early 1960s. Cold curing acrylic was used in dentistry for many years, but this was the first time it was employed for such an application in orthopedics. Although this qualifies for PMA status under the FDA regulations, one still has to provide clinical data, proof of substantially the same or better performance than the previous bone cement, and chemical and physical performance in vitro and in vivo if one is trying to market a new or similar bone cement in the United States. More examples from the history of the development of biomaterials are given below in §1.3.

The surgical uses of implant materials are given in Table 1-4. One can classify biomaterials into permanent and transient, depending on the time intended to be in the body. Sometimes a temporary implant becomes permanent if one does not remove it, such as a bone plate after a fractured bone is completely healed.

Table 1-3. Criteria for Judgment and Registration of Bone Cements (McDermott, 1997) in the United States, as Specified by the Food and Drug Administration

Property	Parameter/test method	Standard/method (alternatives)
Chemical composition	Raw materials	NMR (if in the liquid phase), FTIR, HPLC/MS
	Added components	Ash
	Purity	ICP/MS, GC/FTIR/MS, titration
Molecular weight (MW)	Relative viscosity MW	Viscosimetry
		GPC (polystyrene standard)
Physical properties	Morphology	Light microscopy; SEM
	Porosity	Scanning acoustical microscopy, x-ray
	Aging due to water uptake	ISO 5833 (bending strength)
Handling properties	Doughing time	ISO 5833, ASTM F451
	Setting time	ISO 5833, ASTM F451
	Intrusion/viscosity	ISO 5833, ASTM F451
Polymerization	Maximum temperature	ISO 5833, ASTM F451
	Shrinkage	Density balance, pycnometer (ASTM D2566)
Degree of polymerization	Content of residual monomer	GC, HPLC/GPC, FTIR
	Release of residual monomer	CC, HPLC/GPC
Stability	Monomer stability (enforced)	ISO 5833, ASTM F451
	BPO content	Titration, FTIR
	Doughing/setting time	ISO 5833, ASTM F451
Modulus of elasticity	Four-point bending	ISO 5833
Compression modulus	Compression	ISO 5833
Tensile modulus	Tensile strength	ASTM D638
Fatigue	Tensile/compression fatigue; tensile/tensile fatigue	ASTM D638
	Four-point bending	Method of Dr. Soltesz, ASTM E399
Fracture toughness	Compact tension/notched bending strength	ASTM E399
Fatigue-crack propagation	Compact tension	ASTM E647
Static strength	ISO 5833	
Flexural strength	Four-point bending	ISO 5833
Compressive strength	Uniaxial compression	150 5833, ASTM F451
Tensile strength	Uniaxial tension	ASTM D638
Shear strength	Cement-cement shear; cement-implant shear	ASTM D732
Viscoelasticity	DMA/compressive creep	DMA/ASTM D2990
Shelf life		Mechanical properties of the hardened cement

See §7.3.4.2 of this text for many of the terms used in this table. Reprinted with permission from Kühn (2000). Copyright © 2000, Springer.

Another important area of study is that of the mechanics and dynamics of tissues and the resultant interactions between them. Generally, this study, known as *biomechanics,* is incorporated into the design and insertion of implants, as shown in Figure 1-2. More sophisticated analysis can be made using computer methods, such as FEM and FEA (finite-element modeling/analysis). These approaches help to design a better prosthesis or even custom make them for individual application.

Table 1-4. Surgical Uses of Biomaterials

Permanent implants
Muscular skeletal system — joints in upper (shoulder, elbow, wrist, finger) and lower (hip, knee, ankle, toe) extremities, permanently attached artificial limb
Cardiovascular system — heart (valve, wall, pacemaker, entire heart), arteries, veins
Respiratory system — larynx, trachea, and bronchus, chest wall, diaphragm, lungs, thoracic plombage
Digestive system — tooth fillings, esophagus, bile ducts, liver
Genitourinary system — kidney, ureter, urethra, bladder
Nervous system — dura, hydrocephalus shunt
Special senses — corneal and lens prosthesis, ear cochlear implant, carotid pacemaker
Other soft tissues — hernia repair sutures and mesh, tendons, visceral adhesion
Cosmetic implants — maxillofacial (nose, ear, maxilla, mandible, teeth), breast, eye, testes, penis, etc.
Transient implants
Extracorporeal assumption of organ function — heart, lung, kidney, liver, decompressive-drainage of hollow viscera-spaces, gastrointestinal (biliary),genitourinary, thoracic, peritoneal lavage, cardiac catheterization
External dressings and partial implants — temporary artificial skin, immersion fluids
Aids to diagnosis — catheters, probes
Orthopedic fixation devices — general (screws, hip pins, traction), bone plates (long bone, spinal, osteotomy), intertrochanteric (hip nail, nail-plate combination, threaded or unthreaded wires and pins), intramedullary (rods and pins), staples, sutures and surgical adhesives

Nanotechnology is a rapidly evolving field that involves material structures on a size scale typically 100 nm or less. New areas of biomaterials applications may develop using nanoscale materials or devices. For example, drug delivery methods have made use of a microsphere encapsulation technique. Nanotechnology may help in the design of drugs with more precise dosage, oriented to specific targets or with timed interactions. Nanotechnology may also help to reduce the size of diagnostic sensors and probes.

Transplantation of organs can restore some functions that cannot be carried out by artificial materials, or that are better done by a natural organ. For example, in the case of kidney failure many patients can expect to derive benefit from transplantation because an artificial kidney has many disadvantages, including high cost, immobility of the device, maintenance of the dialyzer, and illness due to imperfect filtration. The functions of the liver cannot be assumed by any artificial device or material. Liver transplants have extended the lives of people with liver failure. Organ transplants are widely performed, but their success has been hindered due to social, ethical, and immunological problems.

Since artificial materials are limited in the functions they can perform, and transplants are limited by the availability of organs and problems of immune compatibility, there is current interest in the regeneration or regrowth of diseased or damaged tissue. *Tissue engineering* refers to the growth of a new tissue using living cells guided by the structure of a substrate made of synthetic material. This substrate is called a *scaffold*. The scaffold materials are important since they must be compatible with the cells and guide their growth. Most scaffold materials are biodegradable or resorbable as the cells grow. Most scaffolds are made from natural or synthetic polymers, but for hard tissues such as bone and teeth ceramics such as calcium phosphate compounds can be utilized. The tissue is grown in vitro and implanted in vivo. There have been some clinical successes in repair of injuries to large areas of skin, or small defects in cartilage. The topic of tissue engineering, an area of current research activity, is discussed in Chapter 16.

It is imperative that we should know the fundamentals of materials before we can utilize them properly and efficiently. Meanwhile, we also have to know some fundamental properties

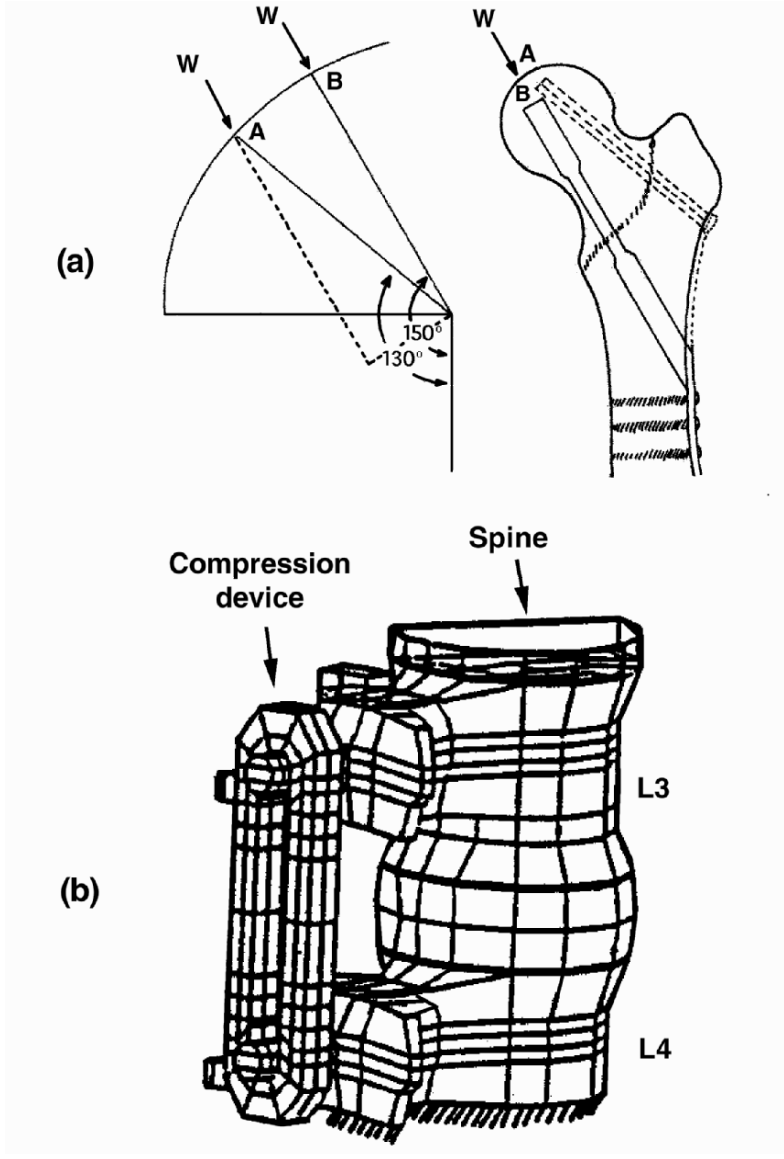


Figure 1-2. (**a**) Biomechanical analysis of femoral neck fracture fixation. Note that if the implant is positioned at 130º, rather than 150º, there will be a force component that will generate a bending moment at the nail-plate junction. The 150º implant is harder to insert and therefore not preferred by surgeons. Reprinted with permission from Massie (1964). Copyright © 1964, Charles C. Thomas. (**b**) Finite-element model (FEM) of spinal disc fusion. Reprinted with permission from Goel et al. (1991). Copyright © 1991, American Association of Neurological Surgeons.

and functions of tissues and organs. The interactions between tissues and organs with man-made materials have to be more fully elucidated. Fundamentals-based scientific knowledge can be a great help in exploring many avenues of biomaterials research and development.

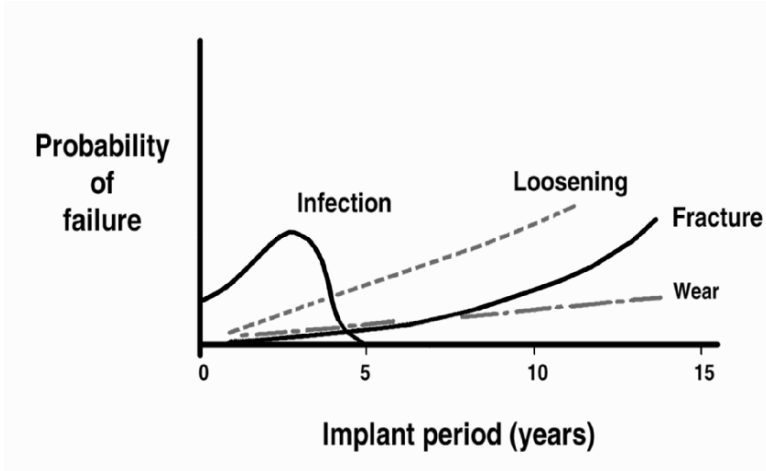


Figure 1-3. A schematic illustration of probability of failure versus implant period for hip joint replacements. Reprinted with permission from Dumbleton (1977). Copyright © 1977, Taylor & Francis.

1.2. PERFORMANCE OF BIOMATERIALS

The performance of an implant after insertion can be considered in terms of reliability. For example, there are four major factors contributing to the failure of hip joint replacements. These are fracture, wear, infection, and loosening of implants, as shown in Figure 1-3. If the probability of failure of a given system is assumed to be f, then the reliability, r, can be expressed as

$$r = 1 - f, \tag{1-1}$$

Total reliability r_t can be expressed in terms of the reliabilities of each contributing factor for failure:

$$r_t = r_1, r_2, ..., r_n, \tag{1-2}$$

where $r_1 = 1 - f_1$, $r_2 = 1 - f_2$, and so on.

Equation (1-2) implies that even though an implant has a perfect reliability of one (i.e., $r = 1$), if an infection occurs every time it is implanted then the total reliability of the operation is zero. Actually, the reliability of joint replacement procedures has greatly improved since they were first introduced.

The study of the relationships between the structure and physical properties of biological materials is as important as that of biomaterials, but traditionally this subject has not been treated fully in biologically oriented disciplines. This is due to the fact that in these disciplines

workers are concerned with the biochemical aspects of function rather than the physical properties of "materials." In many cases one can study biological materials while ignoring the fact that they contain and are made from living cells. For example, in teeth the function is largely mechanical, so that one can focus on the mechanical properties of the natural materials. In other cases the functionality of the tissues or organs is so dynamic that it is meaningless to replace them with biomaterials, e.g., the spinal cord or brain.

1.3. BRIEF HISTORICAL BACKGROUND

Historically speaking, until Dr. J. Lister's aseptic surgical technique was developed in the 1860s, attempts to implant various metal devices such as wires and pins constructed of iron, gold, silver, platinum, etc. were largely unsuccessful due to infection after implantation. The aseptic technique in surgery has greatly reduced the incidence of infection. Many recent developments in implants have centered around repairing long bones and joints. Lane of England designed a fracture plate in the early 1900s using steel, as shown in Figure 1-4a. Sherman of Pittsburgh modified the Lane plate to reduce the stress concentration by eliminating sharp corners (Figure 1-4b). He used vanadium alloy steel for its toughness and ductility. Subsequently, Stellite® (Co–Cr-based alloy) was found to be the most inert material for implantation by Zierold in 1924. Soon 18-8 (18 w/o Cr, 8 w/o Ni) and 18-8sMo (2–4 w/o Mo) stainless steels were introduced for their corrosion resistance, with 18-8sMo being especially resistant to corrosion in saline solution. Later, another alloy (19 w/o Cr, 9 w/o Ni) named Vitallium® was introduced into medical practice. A noble metal, tantalum, was introduced in 1939, but its poor mechanical properties and difficulties in processing it from the ore made it unpopular in orthopedics, yet it found wide use in neurological and plastic surgery. During the post-Lister period, the various designs and materials could not be related specifically to the success or failure of an implant, and it became customary to remove any metal implant as soon as possible after its initial function was served.

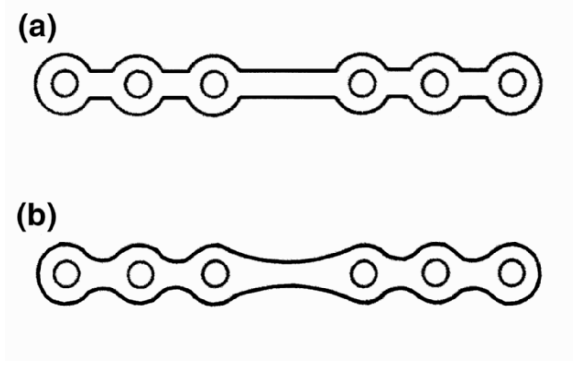


Figure 1-4. Early design of bone fracture plate: (**a**) Lane, (**b**) Sherman.

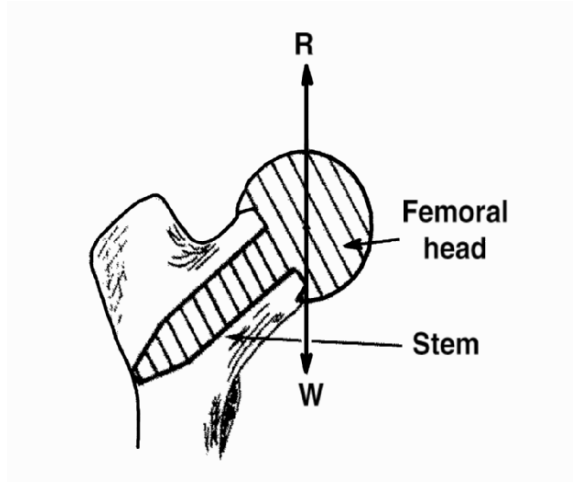


Figure 1-5. The Judet prosthesis for hip surface arthroplasty. Reprinted with permission from Williams and Roaf (1973). Copyright © 1973, W.B. Saunders.

Fracture repair of the femoral neck was not initiated until 1926, when Hey-Groves used carpenter's screws. Later, Smith-Petersen (1931) designed the first nail with protruding fins to prevent rotation of the femoral head. He used stainless steel but soon changed to Vitallium®. Thornton (1937) attached a metal plate to the distal end of the Smith-Petersen nail and secured it with screws for better support. Smith-Petersen later (1939) used an artificial cup over the femoral head in order to create new surfaces to substitute for the diseased joints. He used glass, Pyrex®, Bakelite®, and Vitallium®. The latter was found more biologically compatible, and 30–40% of patients gained usable joints. Similar mold arthroplastic surgeries were performed successfully by the Judet brothers of France, who used the first biomechanical designed prosthesis made of an acrylic (methylmethacrylate) polymer (Figure 1-5). The same type of acrylic polymer was also used for corneal replacement in the 1940s and 1950s due to its excellent properties of transparency and biocompatibility.

Due to the difficulty of surgical techniques and to material problems, cardiovascular implants were not attempted until the 1950s. Blood vessel implants were attempted with rigid tubes made of polyethylene, acrylic polymer, gold, silver, and aluminum, but these soon filled with clot. The major advancement in vascular implants was made by Voorhees, Jaretzta, and Blackmore (1952), when they used a cloth prosthesis made of Vinyon®N copolymer (polyvinyl chloride and polyacrylonitrile) and later experimented with nylon, Orlon®, Dacron®, Teflon®, and Ivalon®. Through the pores of the various cloths a pseudo- or neointima was formed by tissue ingrowth. This new lining was more compatible with blood than a solid synthetic surface, and it prevented further blood coagulation. Heart valve implantation was made possible only after the development of open-heart surgery in the mid-1950s. Starr and Edwards (1960) made the first commercially available heart valve, consisting of a silicone rubber ball poppet in a metal strut (Figure 1-6). Concomitantly, artificial heart and heart assist devices have been developed. Table 1-5 gives a brief summary of historical developments relating to implants.

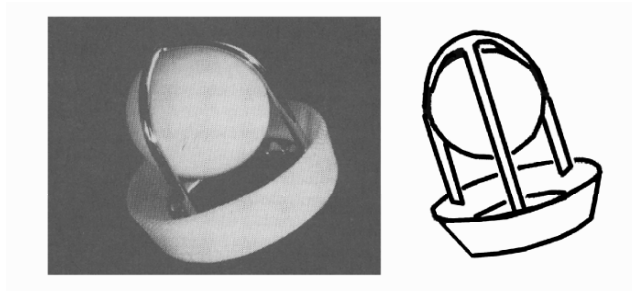


Figure 1-6. An early model of the Starr-Edwards heart valve made of a silicone rubber ball and metal cage. Reprinted with permission from the Edwards Laboratories.

Table 1-5. Notable Developments Relating to Implants

Year	Investigator	Development
Late 18th–19th century		Various metal devices to fix fractures; wires and pins from Fe, Au, Ag, and Pt
1860–1870	J. Lister	Aseptic surgical techniques
1886	H. Hansmann	Ni-plated steel fracture plate
1893–1912	W.A. Lane	Steel screws and plates for fracture fixation
1909	A. Lambotte	Brass, Al, Ag, and Cu plate
1912	Sherman	Vanadium steel plate, first alloy developed exclusively for medical use
1924	A.A. Zierold	Stellite® (CoCrMo alloy), a better material than Cu, Zn, steels, Mg, Fe, Ag, Au, and Al alloy
1926	M.Z. Lange	18-8sMo (2–4% Mo) stainless steel for greater corrosion resistance than 18-8 stainless steel
1926	E.W. Hey-Groves	Used carpenter's screw for femoral neck fracture
1931	M.N. Smith-Petersen	Designed first femoral neck fracture fixation nail made originally from stainless steel, later changed to Vitallium®
1936	C.S. Venable, W.G. Stuck	Vitallium; 19 w/o Cr-9 w/o Ni stainless steel
1938	P. Wiles	First total hip replacement
1946	J. and R. Judet	First biomechanically designed hip prosthesis; first plastics used in joint replacement
1940s	M.J. Dorzee, A. Franceschetti	Acrylics for corneal replacement
1947	J. Cotton	Ti and its alloys
1952	A.B, Voorhees, A. Jaretzta, A.H. Blackmore	First blood vessel replacement made of cloth
1958	S. Furman, G. Robinson	First successful direct stimulation of heart
1958	J. Charnley	First use of acrylic bone cement in total hip replacements
1960	A. Starr, M.L. Edwards	Heart valve
1970s	W.J. Kolff	Experimental total heart replacement
1990s		Refined implants allowing bony ingrowth
1990s		Controversy over silicone mammary implants
2000s		Tissue engineering
2000s		Nanoscale materials

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PROBLEMS

1-1. a. Determine the probability of failure of a hip joint arthroplasty after 15 and 30 years, assuming the following (t is in years).

b. Which factor is the most important for the longevity of the arthroplasty?

Infection	$f_i = 0.05e^{-t}$
Loosening	$f_{lo} = 0.01e^{+0.15t}$
Fracture	$f_{fr} = 0.01e^{+0.01t}$
Wear	$f_w = 0.01e^{+0.1t}$
Surgical error	$f_{su} = 0.001$
Pain	$f_{pn} = 0.005$

1-2. Plot the individual failure versus time on a graph similar to that in Figure 1-1. Use any graphics software rather than spreadsheet software to achieve a high-quality graph. Also, plot the total success (r_t) versus time on the same graph.

1-3. How would the failure modes shown in Figure 1-1 differ if an obsolete material such as vanadium steel were used to make the hip joint implant (femoral stem)?

1-4. Discuss the feasibility and implications of replacing an entire arm.

1-5. Discuss the ethical problems associated with using fetal brain tissue for transplantation purposes to treat Parkinson's disease; or fetal bone marrow to treat leukemia.

1-6. Discuss the advantages and disadvantages of kidney transplantation as compared to the use of a dialysis machine.

1-7. Discuss the pros and cons of medical device litigation such as that associated with silicone breast implants in the United States. Be brief.

SYMBOLS/DEFINITIONS

Latin Letters

f: Probability of failure
r: Reliability or probability of success

Terms

Biomaterial: A synthetic material used to replace part of a living system or to function in intimate contact with living tissue. Also read the various definitions given by other authors in the text.

Biomechanics: The study of the mechanical laws relating to the movement or structure of living organisms.

Biological material: A material produced by a living organism.

Biocompatibility: Acceptance of an artificial implant by the surrounding tissues and by the body as a whole. The biomaterial must not be degraded by the body environment, and its presence must not harm tissues, organs, or systems. If the biomaterial is designed to be degraded, then the products of degradation should not harm the tissues and organs.

CDRH (Center for Devices and Radiological Health): Branch of the FDA that administers medical devices-related regulations.

Cytotoxicity: Toxic to living cells.

ETO (ethylene oxide gas, $(CH_2)_2O$): A flammable toxic gas used as a sterilization agent.

FDA (Food and Drug Administration): Government agency regulating testing, production, and marketing of food and drugs including medical devices within the United States.

FEM or FEA (finite-element modeling/analysis): Stress and strain analysis of a structural body using computer software. The object is divided into small elements that are amenable to analysis. Boundary conditions are applied and the distribution of stresses and strains calculated.

Gamma (γ)**-radiation**: The emission of energy as short electromagnetic waves that cause ionization. The radioactive isotope ^{60}Co is an effective source of the radiation. To be effective for sterilization, about 10^6 Gy (J/kg) is needed.

GMP (Good Manufacturing Practices): Medical devices are made in a clean room condition to prevent any contamination. Such practices are required by the FDA for manufacture of implants.

Hemolysis: Lysis (dissolution) of erythrocytes in blood with the release of hemoglobin.

ISO (International Standard Organization): ISO9000 is a set of standards related to medical devices necessary to maintain an efficient and quality system. A standard focuses on controlling organizations rather than specific requirements for final products. ASTM 13.01 focuses on specific products in the United States.

Microsphere: A microscopic hollow sphere, especially of a protein or synthetic polymer.

Mutagenicity: The capacity of a chemical or physical agent to cause permanent genetic alterations.

Nanotechnology: The branch of technology that deals with dimensions and tolerances of less than 100 nanometers — for example, manipulation of individual atoms and molecules.

PMA (Premarket Approval): Some medical devices can be approved by the FDA without extensive tests required by FDA through MDE (medical device exemptions) 510K (http://www.accessdata.fda.gov).

Pyrogenic: Caused or produced by combustion or the application of heat-inducing fever.

Sensitization: Making (an organism) abnormally sensitive to a foreign substance, such as a metal.

Systemic: Denoting the part of the circulatory system concerned with transportation of oxygen to and carbon dioxide from the body in general.

Tissue engineering: Generation of new tissue using living cells, optimally the patient's own cells, as building blocks, coupled with biodegradable materials as a scaffold.

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3. American Society for Artificial Internal Organs, Annual

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