BIOMATERIALS

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Preface

One of the most noticeable and beneficial aspects of the recent developments in medical sciences has been the exploitation of technological advances. While it is difficult to single out any one particular branch of biomedical engineering, the tremendous advances have been made in surgery through the use of implanted devices, must certainly number among the more significant. Biomaterials used in these devices, provide needs in such diverse surgical disciplines as ophthalmology, cardiology, neuromuscular surgery, orthopaedics and dentistry. All biomaterials have one thing in common; they must have intimate contact with patient's tissue or body fluid, providing a real physical interface.

Biomaterials of one type or the another have been in clinical use for many years. A reasonable degree of success since 1960s and a rapidly expanding range of materials being made available by advances in basic material science have more recently led to a greater proliferation of biomaterials. A wide spectrum of implanted devices from simple sutures to totally implantable artificial hearts now exists. After an initial period of rapid innovation and experimentation in biomedical engineering when materials were implanted into human body with little prior testing, biomaterial science is now entering in sophisticated technology. The search for new, more reliable devices require a disciplined scientific approach to the subject.

Good biocompatibility is achieved when the material exists within a living body without adversely or significantly affecting it or being affected by it. The biomaterial should have adequate mechanical strength, chemical and physical properties. Thus biomaterials must be compatible with body tissues mechanically, chemically as well as pharmacologically. To research these materials the investigator needs to have a range of techniques for materials production, measurement of strength and surface properties and *in vitro* and *in vivo* techniques for biocompatibility evaluations.

This book is written for those who would like to advance their knowledge of biomaterials. The subject matter of the book is divided into twelve chapters dealing with structure and property relationship of biological and man-made biomaterials. The applications of these materials for various medical devices have been discussed. Recent developments in tissue engineering have also been mentioned.

This manuscript has been organized at Indian Institute of Technology, Bombay as class-notes for an introductory M. Tech. course on biomaterials and I thank M/s Narosa Publishing House, who encouraged me to publish the same.

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Every attempt has been made to make the book short. Any mistakes are mine and I hope the reader will bring them to my notice.

Sujata V. Bhat

Contents

1

Overview of Biomaterials

1.1 INTRODUCTION

The ability to replace or augment damaged organs, or blood vessels or tissues, totally or in part, has improved both the quality and the length of life of many people. The decline in surgical risk during recent decades has encouraged the development of more complex procedures for prosthetic implantation. In addition, a variety of extracorporeal devices, such as the heart, lung and blood dialysis machines are used routinely. The availability and suitability of traditional autogenous, or homogeneous prosthetic elements is severely limited; as a result, intense interest has been focused on the use of synthetic materials which would provide an asymptomatic, long term function within the body or in contact with body fluid.

A biomaterial is defined as any systemically, pharmacologically inert substance or combination of substances utilized for implantation within or incorporation with a living system to supplement or replace functions of living tissues or organs. In order to achieve that purpose, a biomaterial must be in contact with living tissues or body fluids resulting in an interface between living and nonliving substances.

When considering the functions of present biomaterials, one important point, which must be emphasized, is that, usually simple and indeed most often passive functions that are involved. At this stage they are largely mechanical or physical rather than biochemical. For example bone replacements simply serve as mechanical supports and play no part in red cell production. The functional characteristics of implants at the moment are very elementary in terms of normal physiological mechanisms. The electrical function can be taken over by some implants such as pacemakers; neuromuscular stimulator and some primitive chemical functions can be delegated to implants such as dialyzer, oxygenator etc.

The functions of implants fall into one of the following categories: load bearing or transmissions; the control of fluid flow in order to stimulate normal physiological function or situation; passive space filling either for cosmetic reasons or functional reasons; generation of electric stimuli and transmission of light and sound.

An alternate to artificial implants is transplantation of organs such as kidney, heart, etc., but this effort has been hindered due to social, ethical and immunological problems.

The purpose of this book is to review biomaterials and medical devices that are used to replace or augment functions of tissues and organs. The success of these devices is intimately associated with the chemical and mechanical properties of the materials used in device construction. Therefore these properties will be discussed along with biocompatibility and medical applications. Clearly, the economic and medical impact of medical devices is very large and therefore it is not possible to cover all implant applications in details. Only selected examples are discussed.

1.2 HISTORICAL DEVELOPMENTS

Thus history of biomaterials dates back, to antiquity. Many of the initial thrusts were attempts by man to correct deformities, since, in the years before anesthesia and asepsis, surgical procedures were limited to the body surface.

Among the earliest operations performed were those by Hindu surgeons for restoration of missing parts. Sushruta, in about 600BC, repaired an injured nose with a patch of living flesh taken off the region of the cheek. This technique for nose reconstruction migrated from East to West. Around 1430, the Brancas, a family of Sicilian Laymen, perfected the method now referred to as the Italian method for nose construction by using skin flap taken from the arm. In the nineteenth century, Von Graefe and Dieffenbach recorded several techniques for reconstruction of missing parts. In the twentieth century, Gillies in England, Davis, Ivy and Kazanjian in the United States and Filator in Russia were stimulated by World War I tragedies to pioneer newer methods of wound closure and tissue transfer.

The earliest written record of an application of metal in surgical procedures is from the year 1565. However, until J. Lister's aseptic surgical technique was developed in the 1860s, various metal devices such as wires and pins which were constructed of iron, gold, silver, platinum etc. and tissue trasplantations were not largely successful mainly due to infection after implantation. The modern implant developments, which centered on repairing long bones and joints, began at the end of the nineteenth century. Lane in England (1893-1912) designed a fracture plate using steel. A brief summary of the historical developments of biomaterials is described in Table 1.1.

With the beginning of plastic industry in the 1930s, the use of polymers in a variety of reconstructive applications was witnessed. Yet, for the most part, it was the aftermath of heavy casualties of World War II that sparked off the search for the much-needed implants and extracorporeal devices. Due to the difficulties of surgical techniques and material problems, cardiovascular implants were not attempted until the 1950s. A major advancement was made by Voorhees, Jaretzta and Blackmore (1952) when they used a cloth prostheses 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 clothes blood compatible pseudo or neointima was formed by the tissue ingrowth.

Heart valve implantation was possible only after the development of open-heart surgery in the mid 1950s and development of commercial heart valve by Star and Edwards in 1960. Among extracorporeal devices, the first dialysis on human being using rotary drum dialyzer was reported by Kolff and Berk in 1944 which was further modified for routine use by Schriber in1960.

1.3 CONSTRUCTION MATERIALS

It is not surprising that the different conditions of use have led to an equally varied range of accepted biomaterials. Tissue replacement with synthetics is achieved by selecting the material that has physical properties most similar to those of natural tissue. Tables 1.2 and 1.3 illustrate the surgical applications of groups of materials namely metal, alloys, ceramics, polymers and composites, and comparison of mechanical properties of biological materials and biomaterials respectively. Rigid metal alloys, ceramics, fiber reinforced composites and high molecular weight polymers are used to replace bone and dentin. In contrast, soft and pliable elastomers are employed for soft tissue reconstruction. There are electrically conducting metals for electrodes, optically transparent plastics for intraocular prostheses and radioopaque materials to act as markers.

Within metals, three main alloys, namely titanium-aluminium, stainless steel and cobalt-chromium alloys are used universally for most of the high load bearing applications in skeletal system. Conducting metals like platinum and platinum-iridium alloys are used for electrical stimulation of the heart,

Table 1.1 Major historical developments of biomaterials*

Year	*Author*	*Activity*
600BC	Sushruta Samhita	Nose reconstruction.
Late 18th-19th century		Various metal devices to fix fractures; wires and pins made of Fe, Au, Ag and Pt
1860-1870	J. Lister	Aseptic surgical techniques developed
1893-1912	W.A. Lane	Steel screws and plates for fracture fixation
1912	W.D. Sherman	Vanadium steel plate, first alloy developed exclusively for medical use; less stress concentration and corrosion
1926	E.W. Hey-Groves	Used carpenter's screw for femoral neck fracture fixation
1926	M.Z. Large	18-8sMo (2-4% Mo) stainless steel for greater corrosion resistance than 18-8 stainless steel
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® (developed in 1929; 19 w/o Cr-9 w/o Ni stainless steel)
1938	P. Wiles	First total hip replacement
1940s	M. J. Dorzee, A. Franceschetti	Acrylics for corneal replacement
1944	W.J. Kolff	Hemodialyser
1946	J. Judet and R. Judet	First biomechanically designed hip prosthesis. First plastics used in joint replacement
1952	A.B. Voorhees, A. Jaretzta, A.H. Blackmore	First blood vessel replacement made of cloth
1953	A. Kantrowitz	Intraortic balloon pumping
1958	J. Charnley	First use of acrylic bone cement in total hip replacements
1958	S. Furman, G. Robinson	First successful direct stimulation of heart
1960	A. Starr, M. l. Edwards	Heart valve
1980s	W.J. Kolff et al.,	Artificial heart

*Adapted from Park (1984) and Spotnitz (1987)

other muscles and nervous tissues. Nitinol, an alloy of nickel and titanium finds applications in orthodontics.

Alumina is an extremely stable and inert ceramic material, which is used, in orthopedic joint replacements. The chemical inertness and high abrasive resistance provide improvements over the hitherto widely used metals. Bioglass is employed to improve surface properties of alumina and metal alloys. The degradable ceramics, which are almost invariably based on calcium phosphates, find

Table 1.2 Examples of materials used in implants

Materials	*Advantages*	*Disadvantages*	*Common applications*
Polymers Polyolefins, Polyesters, Polyamides, Polyurethane, Polyacetals, Polyether Silicone rubber.	Low density Easy to fabricate	Low mechanical strength; Additives, oligomers may cause tissue reactions	Cardiovascular, maxillofacial, soft skeletal tissue such as tendon, ligament, space filling devices, dental implants, bone cement, lens, intraocular and middle ear prostheses, sutures, tissue adhesives, percutaneous devices, drainage tubes, shunts, drug delivery systems
Metals Stainless steel, Cobalt-chromium, Titanium alloys.	High impact strength, High resistance to wear, ductile, absorption of high strain energy	Low biocompatibility, corrosion in physiological environment, mismatch for mechanical properties with soft connective tissues	Orthopedic load bearing and fixation devices, dental implants.
Pt, Pt-Ir alloy	High conductivity	Low mechanical strength, high cost	Neuromuscular stimulation
Ceramics Alumina, Zirconia	Good biocompatibility, Inert, corrosion resistance, high tensile strength,	Undesirable surface properties, special techniques are needed for material fabrication,	Hip and Knee prostheses, dental implants, improving biocompatibility.
Calcium phosphates	Biodegradable	Degradation not controllable	Temporary support, assist regeneration of natural tissues.

applications in hard tissue regeneration. In cardiovascular applications, inert carbons are used to improve blood compatibility. They also find dental applications.

Polymers have physical properties that most closely resemble those of soft tissues and therefore this class of materials is used extensively to replace the functions of soft tissues including skin, tendons, cartilage, vessel walls, lens, breast and bladder. A number of synthetic polymers find applications as biomaterials. They include polyolefins, polyamides, polyesters, polyurethanes, polyacrylates, polysulfones, polyethers and silicone rubbers. Some of these materials are also used as sutures, tissue adhesives, shunts, catheters, and space fillers.

Biodegradable polymers such as natural and synthetic polyesters, polyamides are employed as biodegradable sutures or as bone plates which provide temporary scaffolding or support respectively, while natural tissue regeneration takes place.

Various drug delivery systems are developed on biodegradable properties of polymers. Reconstituted collagen polymers have been extensively used for replacements of arterial wall, heart valves and skin. Membranes made from natural and synthetic polymers find applications in extracorporeal devices such as dialysers and oxygenators.

Table 1.3 Mechanical properties of some biological materials and biomaterials*

Material	*Ultimate strength (MPa)*	*Modulus (MPa)*	*Ref.*
Soft tissue			
Arterial wall	0.5-1.72	1.0	Silver 1987
Hyaline cartilage	1.3-18	0.4-19	
Skin	2.5-16	6-40	
Tendon/ligament	30-300	65-2500	
Hard tissue (bone)			
Cortical	30-211	16-20 (GPa)	Cowin 1989
Cancellous	51-193	4.6-15 (GPa)	
Polymers			
Synthetic rubber	10-12	4	Black 1988
Carbon Glassy	25-100	1.6-2.6 (GPa)	
Crystalline	22-40	0.015 (GPa)	
Metal alloys			
Steel	480-655	193 (GPa)	Black 1988
Cobalt-chromium	655-1400	195 (GPa)	
Platinum	152-485	147 (GPa)	
Titanium	550-860	100-105 (GPa)	
Ceramics			
Alumina	90-390 (Gpa)	160-1400 (GPa)	Heimke 1986
Hydroxyapatite	600	19 (GPa)	
Composites			
Fibers	0.09-4.5 (GPa)	62-577 (GPa)	Black 1988
Matrices	41-106	0.3-3.1	

*Adapted with permission from Silver (1994)

Composite materials consist of two or more types of phases usually include stiff fibers embedded in a ductile matrix yielding a material with properties that are between those of each phase. For example carbon fibers are embedded in Teflon matrix to obtain a material called Proplast® having more desirable properties than either of constituents.

The concepts of growth and change lead to the proposal of tissue engineering as a new discipline. Tissue engineering is defined as the application of the principles of engineering and biology towards a fundamental understanding of the structure-function relationship of tissues and the development of biological substitute to restore, maintain or improve tissue functions. Tissue engineering has already proven valuable in developing materials that block unwanted reactions between transplanted cells and host tissues, in making polymer-cell composites for patching injured tissues to help them heal without scarring, in expanding therapeutic cells in culture and in growing relatively simple tissues in the laboratory. Already this young field is having impact in medicine. The laboratory-grown skin is being tested to replace grafts for treating burn patients and those with skin ulcers. Bone marrow cells removed before chemotherapy are being multiplied in culture to speed recovery when they are reinjected. Cultured liver cells are used to detoxify blood from patients with liver failure to keep them alive until a donor organ becomes available (Hubbell and Langer, 1995). Other examples include artificial blood vessels covered with the patient's own endothelial cells; skin substitutes made of keratinocytes, immuno-isolated pancreatic cells for control of sugar metabolism etc. (Palsson and Hubbell, 1995).

An important trend in biomaterial research and development is the synthesis of new polymers that combine capabilities of biological recognition (biomimetic) with special physicochemical properties of the synthetic polymer system. Another important trend in such 'molecular bioengineering' is to develop, perhaps via computer aided molecular design, new artificial biomimetic systems by exact placement of functional groups on rigid polymer backbones, cross-linked structures or macromolecular assemblies.

A wide variety of ways, through which biomolecules and cells can be combined with polymeric biomaterials, provides tremendously exciting opportunities for the biomaterial scientists and engineers. (Hoffman, 1992).

1.4 IMPACT OF BIOMATERIALS

Biomaterials have changed dramatically during the past three decades. In the early days, relatively few engineering materials such as stainless steel, chromium steel etc. were used to make artificial parts of relatively simple design. Today the field of biomaterials has evolved to such an extent that more than fifty different materials are used in various types of complex prosthetic devices. This development of biomaterials used in medical devices has occurred in response to the growing number of patients afflicted with traumatic and non-traumatic conditions.

Trauma is a Greek word for wound, meaning an injury to a living body caused by application of external force or violence. Next to heart disease and cancer, trauma is the third largest killer in the developed countries. For people between the ages of 15 and 50 it is the number one killer (Fung, 1990). As population grows older there is an increased need for medical devices to replace damaged or worn tissues. Besides, other conditions, which necessitate the use of biomaterials, include congenital or developmental defects, genetic or acquired diseases and the desire to create unnatural situation as in fertility control.

The wound and burn dressings are perhaps the most widely used biomaterials. In severe burn injuries it is critical to remove dead tissues from the wounds and apply appropriate burn and wound dressings. The formation of bedsores or skin loss due to ulceration in patients who experience prolonged bed rest, also require similar wound dressings.

As the average age of our population increases, more and more people suffer from arthritis leading to joint disorders which need correction. Total knee or hip replacements are achieved using implants that are composites of metal, polymer and ceramic. Steady growth in the number of joint replacements is expected over the next decade.

Implants, which are regularly used in ophthalmology, include lens implants, viscoelastic solutions for eye surgery, corneal transplants and protective corneal shields. Facial implants are also becoming widely used by surgeons for reconstructive as well as for purely cosmetic reasons.

Oral implants fall mainly in two general categories. The first is artificial teeth or dentures and dental appliances that support and anchor artificial teeth. The second category of implants is totally implanted in oral cavity. They include devices for repairing damaged or diseased mandibles, supports for rebuilding the alveolar ridge and packings for stimulating the growth of bone to correct lesions associated with periodontal disease. In addition, conventional amalgams and resins are used as fillings and metal alloys as crown materials.

Vascular grafts made of synthetic polymers are routinely used to replace the aorta, in patients with pathologic conditions. The replacement of diseased heart valves and bypassing blocked coronary