BIOMATERIALS

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Keywords: materials, biocompatibility, tissue/biomaterial interactions, medical implants, medical device failure

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Summary

This chapter provides an overview of the field of biomaterials and describes many of the materials currently in clinical use. The field of biomaterials covers all materials that interface with a biological system and includes everything from catheters to cardiac assist devices. In this chapter we specifically focus on biomaterials used for implantation as collectively they represent some of the most successful innovations in medicine over the past century. Choosing an effective material for a particular application is not trivial. It requires both detailed knowledge of the properties of the material and a thorough understanding of how the body will respond to its presence. Various metals, ceramics and polymers are successfully used as implanted materials; however, many applications remain imperfect. Biomaterials have been used or are being developed to treat, augment, or replace nearly every tissue in the body. Many inert implants, such as fracture fixation devices and intraocular lenses, are used so commonly that many patients fail to recognise their innovativeness; others efforts, such as those to create artificial hearts, have been less successful. Indeed, not all implanted biomaterials deliver an ideal and/or successful outcome. Infection remains a serious concern when any material is put in the body and many patients with cardiovascular implants have to rely on anti-coagulation drugs for the rest of their lives. Nevertheless, biomaterial implants have been enormously successful and have enhanced the lives of millions of patients. Researchers are working to develop the ‘next generation’ of biomaterials that will deliberately elicit a particular response from the body to achieve a therapeutic goal. Future generations of biomaterials should benefit greatly from innovations currently
taking place in this growing field.

1. Introduction

1.1. History of Biomaterials

We have used materials to repair the body for millennia. Ancient Egyptians used linen threads to close wounds as long as 4000 years ago and Europeans used sutures made from catgut in the Middle Ages. The use of materials to repair the body prior to the era of modern medicine, however, was not limited to sutures. Inca surgeons regularly repaired cranial fractures with gold plates, and ancient Mayans used sea shells to create artificial teeth. It has also been reported that early Europeans fashioned artificial teeth out of iron as far back as 200 AD. Nevertheless, early attempts at using materials in the body were rather hit-and-miss. Only during the last century and a half have physicians and scientists begun to systematically examine interactions between the body and materials.

In the late nineteenth and early twentieth centuries, a number of physicians began to explore the way in which the body reacted to implanted materials. They would, for example, implant a metal in an animal and then observe the tissue response at a later date. The overall consensus from these studies was that the body did not tolerate foreign materials well. These ideas, however, began to change after World War II. Both formal studies and informal observations began to demonstrate that some materials were tolerated in the body. Innovative physicians quickly recognised the potential of using artificial materials to treat a variety of problems, sparking the field of biomaterials as it is known today.

The history of early attempts to implant artificial materials in the body is littered with colourful stories of success and horrifying accounts of failures. In one remarkably successful case, Sir Harold Ridley, a physician who worked with former World War II aviators, noticed that pieces of shattered cockpit canopies that had inadvertently embedded in the eyes of pilots were well tolerated. In making these observations, Ridley made some of the first formal assessments of ‘biocompatibility’. He later went on to create an implantable intraocular lens from the same material the cockpit canopies were made from, a plastic called polymethylmethacrylate. Artificial intraocular lenses, which are used to replace the natural lens of the eye when damaged by cataracts, are used in as many as 7 million people annually and have not fundamentally changed from Dr. Ridley’s original design.

Over the second half of the twentieth century, the field of biomaterials and the use of medical implants exploded as new materials emerged and physicians gained a better understanding of how the body responded to implants. The effects are obvious in medicine today: patients and doctors alike accept and expect functional, long-lasting medical implants to treat almost any malady.

1.2. Materials in Medicine

According to the European Society for Biomaterials, a biomaterial is ‘a material
intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ, or function of the body.’ Biomaterials include materials intended to be implanted in the body for a lifetime, such as total hip replacements, as well as those that interact with the body for short periods of time, such as soft contact lenses. Finding appropriate, safe, and effective materials for use in the body is the work of biomaterial scientists.

When choosing a material to interact with the body, the first important criterion to examine is that of biocompatibility. Biocompatibility is defined as ‘the ability of a material to perform with an appropriate host response in a specific situation’. This modern definition is somewhat different than the obvious statement one might expect: a biomaterial should be non-toxic. That is, it is now accepted that for a material to be functional, it should be more than non-toxic or inert in the body, it should instead engage in an appropriate response with the body so that it can fulfill its purpose. The concept of biocompatibility being dependent on the ability of the implant to fulfill its purpose rather than being an inherent property of a particular material cannot be understated. As this chapter will detail, while some materials can be completely appropriate and ‘biocompatible’ in some situations, they can also be utterly dysfunctional in others. Although most biomaterials used in patients today are functional because they elicit a minimal response, the field is expanding to incorporate materials that attempt to actively interact with the body to achieve a better outcome.

2. Types of Materials

2.1. Metals

Throughout our history, metals have played a fundamental role in enabling technological development. Nowhere is this more apparent than in the development of medical implants. During the 1960s, improved understanding of metallurgy combined with the development of superior surgical techniques, resulted in the implantation of the first total hip implant made from a stainless steel stem. Since this pioneering work, metallic implants have become a multi-billion dollar industry with millions of procedures performed to date.

Why is it that metals have been so successful as implants? The answer to this question lies in the chemical structure of metals and the way in which they bond. Metals can be thought of as positively charged ion cores surrounded by a ‘sea’ or ‘cloud’ of loosely bound electrons. Because the electrons are loosely bound, they can move freely, rendering metals thermal and electrical conductors. Additionally, the positive ion cores closely pack in regular cubic or hexagonal crystalline structures. The closely packed organised arrangements determine the metal’s mechanical properties, or how the metal responds to an applied force. Strong bonding to neighbouring atoms lends the metal strength while the ability of planes of atoms to slide past one another grants the metal its ductility – the ability to deform without breaking.

Metals have various applications throughout the body as implants. Electrically conductive metals such as platinum, for example, have proved effective as electrodes in implantable cardiac pacemakers and defibrillators. The majority of metallic implants,
however, are used in orthopaedic applications to stabilise fractures or replace defective joints. Metals are chosen for these applications because they tend to have high tensile strengths and good fatigue resistance compared to ceramics and polymers. In practice this means that a metallic implant will require a high load to cause deformation and will resist failure caused by repeated loadings. Perhaps most importantly in biological applications, metals are not prone to brittle fracture. That is, metals will deform before failing and not suddenly break and injure a patient.

While metals in general exhibit properties that make them attractive for load-bearing applications, choosing a particular metal for a given application is not trivial. Metals have different mechanical properties which make some advantageous compared with others for certain situations, and even metals with identical compositions can behave differently depending on how they are processed. However, perhaps most importantly for biological applications, the reaction of the metal with the physiological environment needs to be considered. The physiological environment is a 37 °C aqueous solution containing dissolved gases, electrolytes, proteins, and cells. In fact, it is not unlike warm sea water, and as such will corrode many metals. Because corrosion can both cause potentially harmful metal ions to be released into the body and may compromise the mechanical integrity of the implant, corrosion resistance is imperative when choosing a metal. In addition to corrosion, toxicity also needs to be considered. Aluminium, for example, has excellent mechanical properties, but has been associated with toxicity if excessive amounts of it accumulate in the body. The final consideration for choosing a metal for a medical implant is cost. Some metals cost much more than others as a raw material, and processing and machining costs can vary considerably depending on application.

While metals have been used for centuries in various applications, it is worthwhile to remember that most metals are not used in their elemental form, but rather alloyed or mixed with other metals. Brass, for example, is an alloy of zinc and copper, and the medically relevant metal stainless steel is an alloy consisting mostly of iron and chromium. The other two most commonly used metals in medical applications are commercially pure titanium and titanium alloys and cobalt-chromium alloys.

2.1.1. 316L Stainless Steel

316L is the designation given to the most commonly used stainless steel in biomedical applications. The 316 designation specifies that the alloy contains mostly iron, about 17% chromium, 10% nickel and small amounts of other metals. The addition of 17% chromium plays a vital role in making the metal corrosion resistant. Chromium forms a ceramic oxide layer on the surface of the metal, protecting the vulnerable metal underneath, in a process called ‘passivation’. Another important part of the designation 316L is the ‘L’, which signifies ‘low carbon’. The presence of even slightly more than 0.03% carbon impurities allows for the formation of carbides, or carbon-containing alloys. Carbides such as Cr23C6, for example, can deplete the areas surrounding them of chromium, thereby compromising the metal’s ability to form a passive, corrosion-resistant layer.

Although stainless steels are designed to be corrosion resistant, they are not the most
corrosion resistant alloys available for medical implants. Over time, stainless steel will corrode, especially at joints and crevices, so it is often only used for implants intending to stay in the body short term (less than 1 year). Its low cost and ease of manufacturing and machining, however, still make it a very popular choice for the appropriate application, such as non-permanent fracture fixation devices.

2.1.2. Commercially Pure Titanium and Titanium Alloys

Titanium is an excellent choice for medical implant applications because, similarly to stainless steel, it forms a stable oxide (TiO₂) layer on its surface. This layer passivates the metal and provides it with protection against corrosion. Titanium and its alloys are also often lauded for their mechanical properties: they are very strong, but also lightweight. Titanium is approximately half as dense as stainless steel, but has nearly the same yield strength. That is, identically sized pieces of titanium and stainless steel will withstand the same force before breaking, despite the fact that the titanium weighs half as much. Furthermore, although the two have similar yield strengths, titanium’s elastic modulus is only about half that of stainless steel. That is, while it will fail at a similar load, it is less stiff and so will deform more under the same applied load. While this might seem to be a disadvantage for titanium, it is actually often cited as an advantage for medical applications. The most common mode of failure for most joint prostheses is aseptic loosening, or failure because the implant becomes unstable in the joint for reasons other than infection. Although the road to aseptic loosening involves far more factors than implant stiffness, it is understood that when an implant is far stiffer than the native tissue (as in the case of metals which are about an order of magnitude stiffer than bone), the implant will bear the majority of the load in a process called stress shielding. While again this seems like an ideal situation, in reality, bone needs mechanical loading to maintain its structure and remodel effectively. When that loading is removed by the presence of a stiff implant, the bone resorbs, contributing to loosening of the implant and ultimately its failure. Therefore, titanium’s lower modulus may contribute to better long-term outcomes.

Titanium is used in implants in two forms. The first is as an alloy combining titanium with approximately 6% aluminium and 4% vanadium and appropriately designated Ti-6Al-4V ELI. The ELI indicates ‘extra low interstitial’ and specifies that the alloy has a very low content of impurities such as iron and oxygen. The ELI designation actually makes the metal more ductile, but slightly less strong; however, it also enhances the alloy’s fracture toughness and makes it more resistant to fatigue fracture. It should be noted that vanadium and aluminium are toxic when released into the body. The corrosion resistance afforded by the titanium oxide layer on the surface of Ti-6Al-4V, however, prevents the release of Al and V ions into the body avoiding issues of toxicity.

The second form of titanium used in implants is commercially pure (cp) titanium. As its name indicates, cp titanium is composed of almost entirely (approximately 99%) titanium with just small amounts of interstitial elements such as oxygen, carbon, and nitrogen. Cp titanium forms a single phase making it more ductile than Ti-6Al-4V, and with approximately only half its strength. These properties make cp titanium useful in applications where formability is important, such as fracture fixation. Ti-6Al-4V, on the other hand, is more often used in applications requiring high strength such as hip and
knee replacements.

These descriptions of titanium’s superiority as an implant material compared to stainless steel begin to beg the question why stainless steel is used at all. The answer comes down to economics. As a mined metal, titanium is more expensive than iron and other components of stainless steel. Furthermore, the precise and clean manufacturing requirements for titanium, especially to achieve the ‘ELI’ required for medical implants, makes creating an implant very expensive. In short, choosing a material comes down to application. If stainless steel can be used, such as in short-term fracture fixation, then it remains the material of choice. For lifetime service where corrosion resistance and strength are both important, the more expensive cp titanium and its alloys are favoured.

2.1.3. Cobalt-Chromium Alloys

The final commonly used class of metals for medical implants are the cobalt-chromium (Co-Cr) alloys. The alloys consist of approximately 58-70% cobalt, 26-30% chromium and small amounts of other important alloying metals. The most common alloy for medical implants utilises the addition of 6% molybdenum to form a Co-Cr-Mo alloy, but tungsten, nickel, iron, and titanium are also regularly used. The cobalt within Co-Cr alloys forms an alpha phase while the chromium allows the metal to develop a passive oxide layer (Cr2O3) similarly to stainless steel. As with stainless steels, the passivation of the surface renders Co-Cr alloys corrosion resistant and thus suitable for long-term implantation in the body. Co-Cr alloys, however, are most attractive for their mechanical properties, and are therefore used in high-loading applications such as total joint replacement in the hip and knee. Co-Cr alloys have both high strength and excellent fatigue resistance, but they tend not to be as ductile as other metals. They are also very attractive because they are hard and more resistant to wear than titanium implants, especially as a bearing surface in conjunction with the polymer ultra high molecular weight polyethylene. As wear particle-associated aseptic loosening has been implicated as the most common cause of implant failure, the possibility of diminishing the likelihood of this complication makes Co-Cr alloys very attractive. Co-Cr alloys remain, however, both difficult and expensive to machine and fabricate to the exacting standards required for medical implants, even with the addition of alloying elements intended to aid in manufacturing.

2.2. Ceramics

The second class of materials used as biomaterials that we will cover are ceramics. As with metals, humans have enjoyed a long history with ceramics beginning with the development of early pottery over ten thousand years ago. This relationship has expanded to the point that ceramics are nearly ubiquitous in modern society and are utilised in everything from jet engines to high-tech fuel cells and even joint prostheses. Ceramics are inorganic, non-metallic compounds formed between metallic and non-metallic elements. The non-metallic description refers to the bonds that form in ceramics and not their constituent elements. That is, while ceramics are often formed from metallic elements, their bonding is strictly non-metallic. Instead, they are usually crystalline in structure (with the exception of glasses which are amorphous or lack organized structure) and are held together by ionic or covalent bonds.
The strong ionic and covalent bonds in ceramics lend them their characteristic mechanical properties. Whereas in metals, the loosely associated electrons allow planes of atoms to slide past one another lending the material its ductility, the bonds in ceramics are very strong, and when they break either a crack forms or the material breaks catastrophically. In other words, ceramics tend to be strong, but very brittle. The brittleness of ceramics tends to preclude their medical use in most load bearing applications. Actual fracture strengths of ceramics tend to be one to two orders of magnitude lower than their theoretical strengths calculated by considering interatomic forces. This is understood to be due to the mode of fracture of most ceramics. Unless a ceramic is manufactured perfectly, it will contain flaws and cracks. These then act as sites of stress concentrations and initiate failure.

Despite their poor tensile properties, ceramics have other properties that make them very useful in many medical applications. Firstly, ceramics tend to be very biocompatible. Bioinert ceramics tend not to be susceptible to corrosion because their strong bonds are very difficult to break and thus it is very difficult for them to release atoms into solution. The tendency of ceramics to be very resistant to corrosion has already been discussed with regard to metals. Many metals including stainless steels, titanium alloys, and cobalt-chromium alloys are passivated by producing a ceramic layer at their surface which protects the underlying metal from corrosion. Ceramics, however, are not completely resistant to corrosion. A ceramic placed in body fluid will actually lose strength over time. This is thought to be the result of the preferential dissolution of impurities, which lead to crack formation and/or propagation, ultimately diminishing the material’s strength.

Although there is no strict classification system for medically important ceramics, they can generally be classified into three groups: bioinert, bioactive, and biodegradable. The bioinert ceramics are the most commonly used and have the longest history in medical applications. Bioinert ceramics include alumina, zirconia, and pyrolytic carbon. Alumina and zirconia are oxide ceramics, while pyrolytic carbon is a turbostratic carbon ceramic. Bioactive and biodegradable ceramics, which are designed to erode over time in the body, are fairly new in medicine. Their potential as materials in a wide variety of regenerative medicine applications makes them a very popular topic of research.

Bibliography

Black, J., Biological Performance of Materials. 3rd ed. 1999, New York, USA: Marcel Dekker, Inc. [A comprehensive look at the issues surrounding biocompatibility and factors that influence implant success.]


Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine, 2nd ed. 2004, Elsevier Academic Press: San Diego, CA, USA. [A comprehensive book that examines the field of biomaterials and touches on nearly every use of biomaterials in the body. Much of this chapter draws from the expertise related by the authors of this book.]


Biographical Sketches

Eileen Gentleman is a post-doctoral research associate in the Department of Materials at Imperial College London. Her work includes exploring the effects of novel degradable bioactive glass-based cements on bone cells and bone tissue engineering with a focus on bio mineralisation. She earned her PhD in Biomedical Engineering from Tulane University (New Orleans, USA) in 2005 where her research focused on using collagen-based biomaterials for engineering soft tissues. She also served as a Christine Mirzayan Science and Technology Graduate Policy Fellow at the National Academy of Engineering in Washington, DC where she examined methods for assessing technological literacy. In 2008 she was co-winner of the June Wilson Award recognising her contributions to the field of biomaterials. Her research interests include orthopaedic tissue engineering, biomineralisation, stem cell biology, and cell-biomaterial interactions.

Michael D. Ball is a post-doctoral researcher in biomaterials in the Department of Materials at Imperial College London. His work includes studying the influence of surface properties on the growth and adhesion of cells and investigating cell-surface interactions. His current research interests focus on examining the effects of surface chemistry and topography on cell and protein interactions with cardiovascular and orthopaedic biomaterials. He earned his PhD in Biomaterials from Nottingham University in 1999, with research focusing on osteoblast responses to hydroxyapatite.

Molly M. Stevens is currently Professor of Biomedical Materials and Regenerative Medicine and the Research Director for Biomedical Material Sciences in the Institute of Biomedical Engineering at Imperial College London. She joined Imperial in 2004 after a Postdoctoral training in the field of tissue engineering with Professor Robert Langer in the Chemical Engineering Department at the Massachusetts Institute of Technology (MIT). Prior to this she graduated from Bath University with a first class honours degree in Pharmaceutical Sciences and was then awarded a PhD in biophysical investigations of specific biomolecular interactions and single biomolecule mechanics from the Laboratory of Biophysics and Surface Analysis at the University of Nottingham (2000). In 2007 she was awarded the prestigious Conference Science Medal from the Royal Pharmaceutical Society and in 2005 the Philip Leverhulme Prize for Engineering. She has also recently been recognised by the TR100, a compilation of the top...
innovators, under the age of 35, who are transforming technology - and the world with their work. Her previous awards include the Ronald Belcher Memorial Lecture Award from the Royal Society of Chemistry (2000) and both the Janssen Prize and the UpJohn Prize for academic excellence and research. Research in regenerative medicine within her group includes the directed differentiation of stem cells, the design of novel bioactive scaffolds and new approaches towards tissue regeneration. She has developed novel approaches to tissue engineering that are likely to prove very powerful in the engineering of large quantities of human mature bone for autologous transplantation as well as other vital organs such as liver and pancreas, which have proven elusive with other approaches. In the field of nanotechnology the group has current research efforts in exploiting specific biomolecular recognition and self-assembly mechanisms to create new dynamic nano-materials, biosensors and drug delivery systems.