

MME 4506

Biomaterials

A Brief History of Biomaterials
and Introduction

History of Biomaterials

Biomaterials have been widely used in medicine, dentistry and biotechnology for about 50 years.

Before the understanding of biocompatibility there were crude biomaterials throughout history with poor to mixed results.

The introduction of nonbiological materials into the human body is estimated to occur around 7000 BC at Kennewick, Washington, USA. The remainings of a man buried in Kennewick contained a spear point embedded in the hip bone. It had apparently healed inside his body and let him wander through the region. So the foreign material implant was tolerated as a biomaterial.

Mayan people are known to devise teeth implants from sea shell nacre around 600 A.D. and apparently achieved bone integration. Similarly an iron dental implant in a corpse dated 200 A.D. was found in Europe with proper bone integration



Sutures were relatively common manufactured biomaterials for thousands of years.

In the early history large wounds were closed by cautery or sutures.

Linen, catgut were the natural materials used as sutures by Egyptians and Middle Easterns.

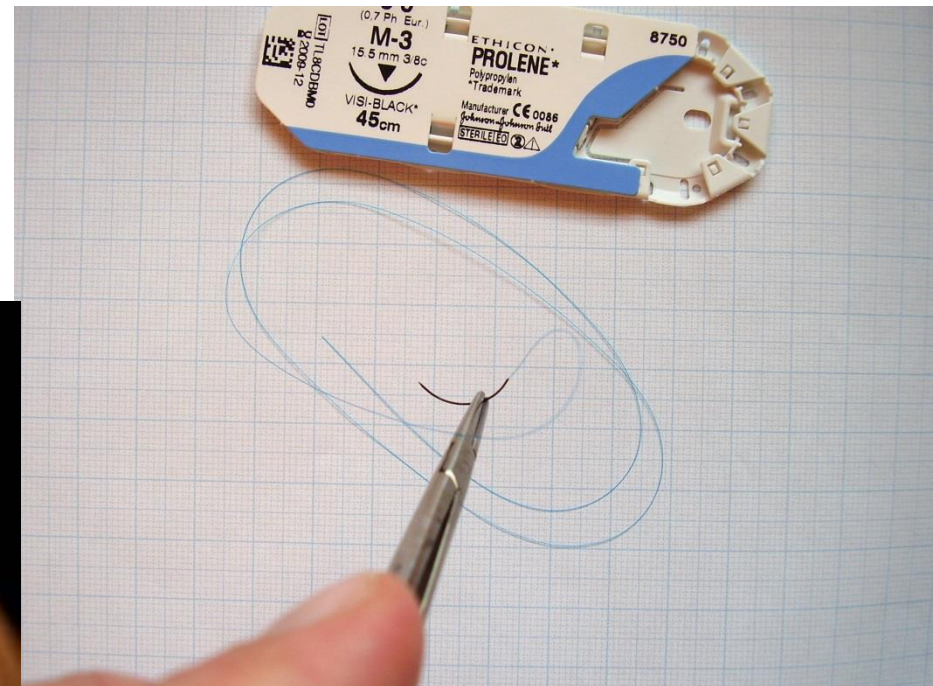
Golden wires were used as sutures in ancient Greece.

Lead and silver wire sutures were successfully used in the US after 1800s.

Obviously the application of sutures then must have been problematic with no knowledge of sterilization, toxicology, inflammation, immunological reactions, and biodegradation.

The success of these crude biomaterials shows us:

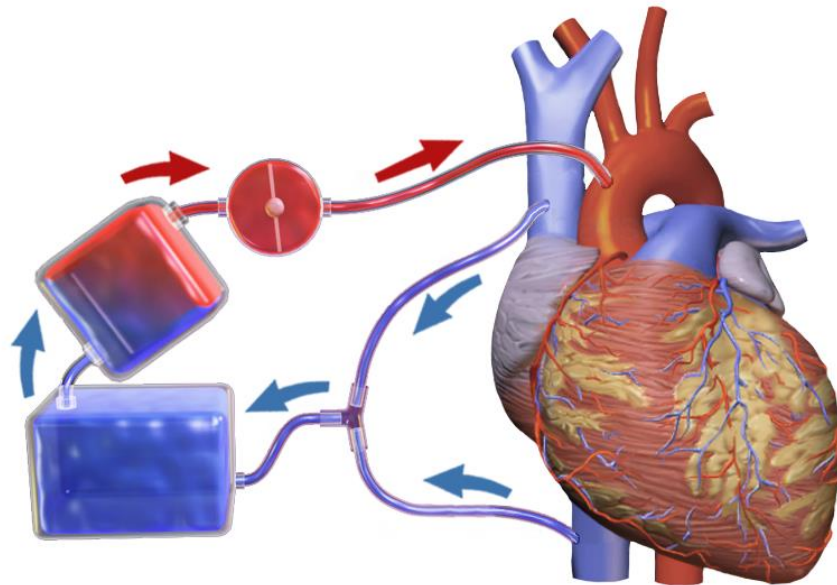
1. The forgiving nature of the human body
2. The strong drive to address the loss of physiological/anatomical function with an implant.



The heart was described as a pump in 1628 by English physician William Harvey as “The heart’s one role is the transmission of the blood and its propulsion by means of the arteries to the extremities everywhere”

Design issues on artificial heart pumps were addressed in *The Culture of Organs* by Lindbergh and Carrell in 1938.

The first artificial heart patent was issued in 1950s and was tested in animals by Dr. Willem Kolff in 1957.



Artificial hearts are also used for organ perfusion – keeping organs alive by pumping blood through them. Theoretical and experimental work on organ perfusion were performed in from 1812 to 1881.

The contact lens concept was developed by Leonardo DaVinci in 1508.

Sir John Herschel suggested in 1827 that a glass lens could protect the eye.

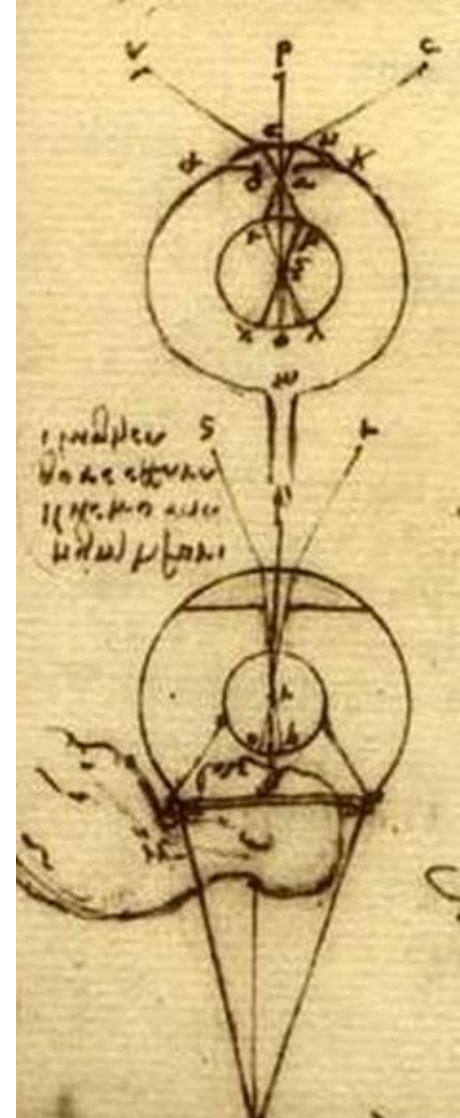
Adolf Fick, known for his laws of diffusion, successfully applied a glass contact lens for the first time in 1860.

Spectacles That Fit Over Your Eyeballs



The New "Contact" Glasses Now Being Tested by Eye-Specialists. They Fit Directly Over the Eyeballs Without Frames. The Photograph Shows Their Actual Size.

Plastic contact lenses were developed between 1936 to 1948 using poly(methyl methacrylate)



The first study assessing the bioreactivity of implant materials was performed by H. Levert in 1829. Gold, silver, lead and platinum specimens were studied in dogs and platinum was found to be well tolerated.

In 1924, A. Zierold published a study on tissue reaction to various materials in dogs. Iron and steel were found to corrode rapidly, leading to resorption of adjacent bone. Copper, magnesium, aluminum alloy, zinc and nickel discolored the surrounding tissue. Gold, silver, lead and aluminum were tolerated but inadequate mechanically. A Co-Cr-Mo alloy was well tolerated and strong.

Inertness of 18-8 stainless steel containing molybdenum was found in 1926. Vitallium alloy (65% Co- 30% Cr- 5% Mo) was developed in 1929 and used in dentistry with success. Titanium and its alloys were found useful for medical implants in 1947 by J. Cotton.





Biomaterials science experienced a huge leap in the US after the end of the World War II.

Many high-performance materials developed for the army were made available to the surgeons and medical practitioners.

Silicones, polyurethanes, Teflon, nylon, methacrylates, titanium and stainless steel were the early biomaterials that surgeons immediately took and used in the operating room to repair the patient.



Medical and dental practitioners of this era felt it was appropriate to improvise on their own where the life of their patient was at stake.

Due to minimal government regulatory activity and minimal patient protection, the doctors had much more freedom than is seen today to take heroic action where there were no other options.

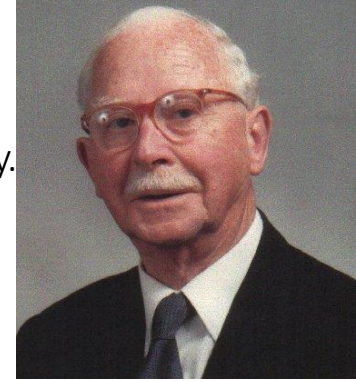
These high-risk trials sometimes succeeded and a foundation of biomaterials and ideas was built by the courageous, creative doctors of the era.

A new order was developed in scientific/engineering input, government quality controls and sharing of decisions prior to attempting high-risk, novel procedures.



Modern intraocular lenses were developed after the World War II by Sir Harold Ridley.

Dr. Ridley examined pilots of Spitfire and Hurricane planes who were unintentionally implanted in their eyes with pieces of plastic from shattered windows of the planes. These pilots had lived for years with plastic fragments in their eyes which were seen to be healed in place when looked into their eyes.



The conventional wisdom at that time was that the human body would not tolerate implanted foreign objects, especially in the eye. (The body's reaction to a bullet was cited as an example of the difficulty of implanting materials in the body)

Dr. Ridley found the material of the windows (ICI Perspex poly(methyl methacrylate)), and ordered sheets of it to make implant lenses.

The lenses were successful and first implanted in a human in 1949 to treat cataract.

The intraocular lense industry could not develop until 1980 due to the opposition in scientific community that spoke against implanting foreign materials in eyes.

Now more than 10 million intraocular lenses are implanted in the world every year and cataract is no longer a serious problem.

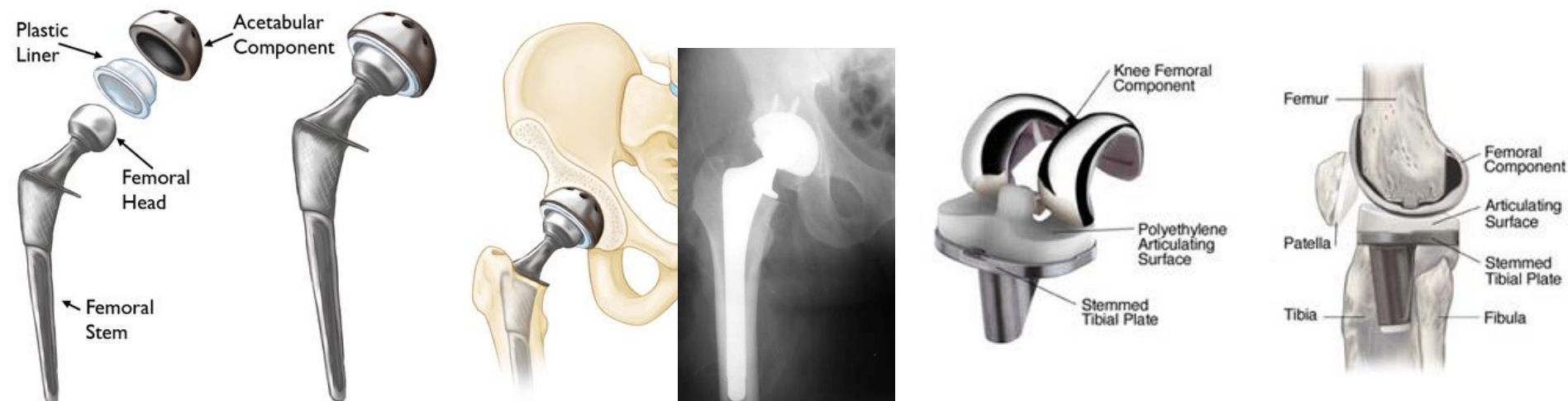
Hip replacement prostheses were researched in early 1900s however the results were poor due to the poor durability, loosening and wear of the materials.

In 1953 Dr. E. Haboush invented the idea of using fast-setting dental acrylics to anchor prosthetics to bone.

A total hip replacement with an acetabular cup of metal that was cemented in place was developed in 1956. Metal-on-metal wear products led to high complication rates.

Sir John Charnley working at a tuberculosis sanatorium invented the first successful hip joint prosthesis consisting of the femoral stem, ball head and plastic acetabular cup in 1958.

Initially used Teflon acetabular cup produced too much wear debris. So Dr. Charnley used a HMW polyethylene cup which he learned from a salesman selling novel plastic gears. Finally poly(methyl methacrylate) cements developed in the dental community were used to anchor the cup to the hip. Total knee replacements were developed based on the technology on the hip prosthesis and successful clinical results were obtained first in 1969.



Crude dental implants were developed in the prehistory and 1800s but the used materials gave poor long term results so the procedure was not widely adopted.



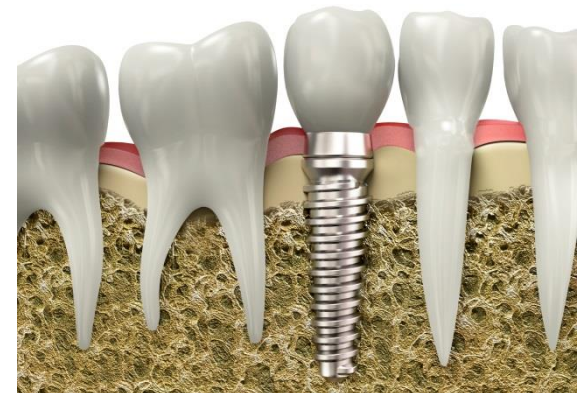
Vitallium was used as a screw-type implant successfully for the first time in 1937.

A number of important developments in surgical procedure and implant design took place after the World War II.

The discovery of titanium as a biomaterial was made by Per Ingvar Branemark, an orthopedic surgeon in Sweden in 1952. He implanted an experimental titanium cage into rabbit bone to observe healing reactions and found it to be tightly integrated to the bone.

Dr. Branemark named the phenomenon osseointegration and explored the applications of titanium implants to surgical and dental procedures.

Now most dental implants and many orthopedic implants are made of titanium and its alloys.



Until the middle of the 20th century, kidney failure resulted in unpleasant death of patients.

The first attempts to remove toxins from blood were made in John Hopkins Hospital in 1910 using rabbit blood.

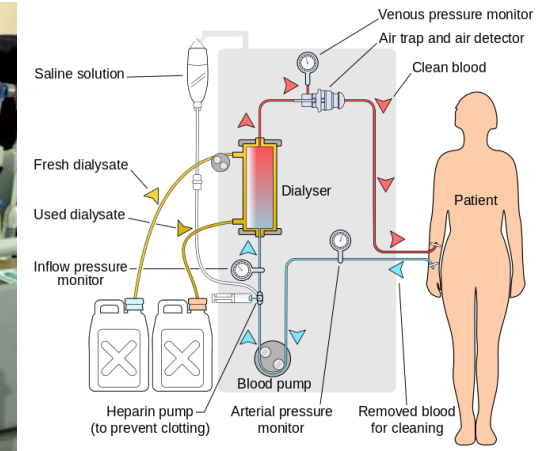
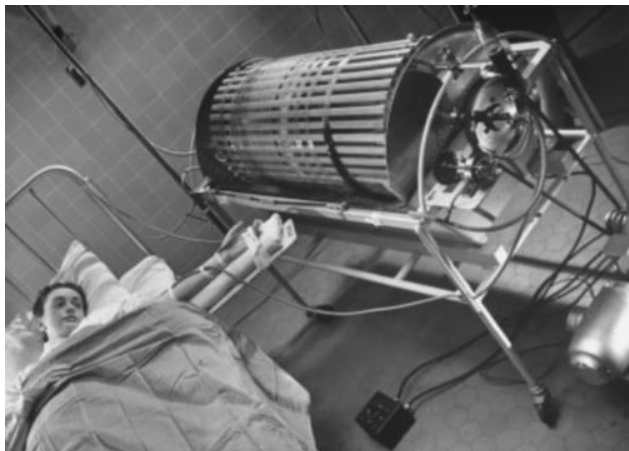
A drum dialyzer system from a 100 liter tank, wood and sausage-casing cellulose as the dialysis membrane was built by Willem Kolff in Holland in 1943.

Dr. Kolff took his idea to the US and developed a washing machine artificial kidney at the Cleveland Clinic in 1960.

Major advances were made to the system by Belding Scribner by devising a method to routinely access the bloodstream

When Dr. Scribner heard about the new plastic, Teflon, he envisioned how to get the blood out of and into the blood vessels. His device used Teflon tubes to access the vessels, a Dacron sewing cuff through the skin, and a silicone rubber tube for blood flow.

These advances made dialysis possible saved more than a million patients.



Partially blocked coronary arteries lead to diminished heart functionality and myocardial infarction (death of a section of the heart muscle) when the artery is completely clogged. Bypass operations take a section of vein from another part of the body and replace the clogged artery.

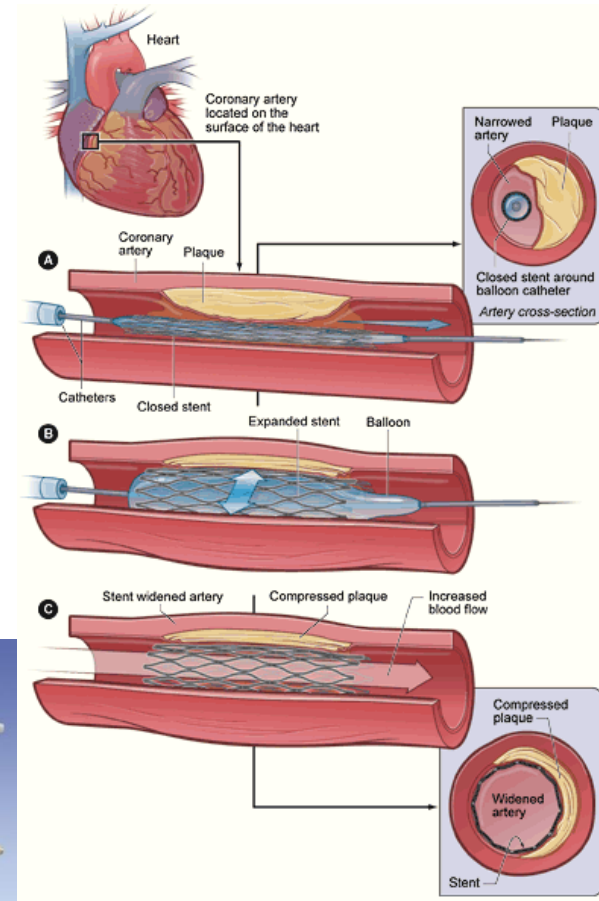
An alternative to this hard surgery is percutaneous transluminal coronary angioplasty (PTCA) where a balloon is threaded on a catheter into the coronary artery and then inflated to open the clogging vessel. In many cases the artery can spasm and close due to the trauma of the procedure.

The coronary stent, an expandable metal mesh that holds the vessel open after PTCA was invented by Dr. J. Palmaz in 1978 in the US. His words on the discovery:

“In a presentation of a doctor on coronary balloon angioplasty, the idea of using some sort of support, such as used in mine tunnels or in oil well drilling came to my mind. Since the coronary balloon goes in small like a folded umbrella and is inflated to about 3-4 times its initial diameter, my idealistic support device needed to go in small and expand at the site of blockage with the balloon. I thought one way to solve this was a malleable, tubular criss-cross mesh. I started making crude prototypes with copper wire and lead solder which I first tested on rubber tubes similar to arteries. I called the device a balloon-expandable intravascular graft. However the reviewers of my first submitted paper wanted to call it a stent, after Charles Stent, a British dentist who invented a wax material to make dental molds for dentures”

The word ‘stent’ was then generically used for any device intended to keep tissues in place while healing.

Coronary artery stents are now used in over 10 million procedures every year using various metals.

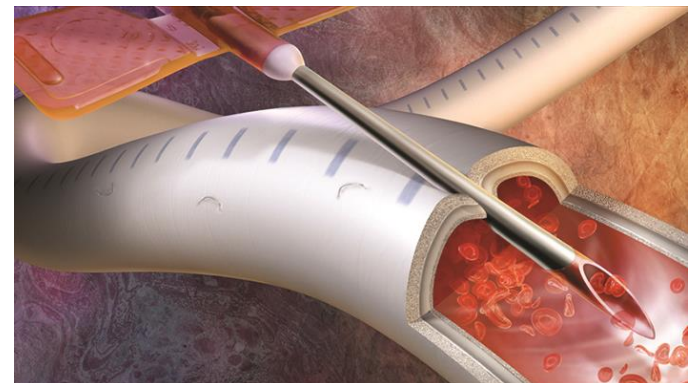


In contrast to the development of biomaterials after the World War II from readily available materials, biomaterials were developed after 1960s specifically for biomedical applications. Some key classes of biomaterials developed in this era and their evolution from commodity materials to engineered biomaterials are given below:

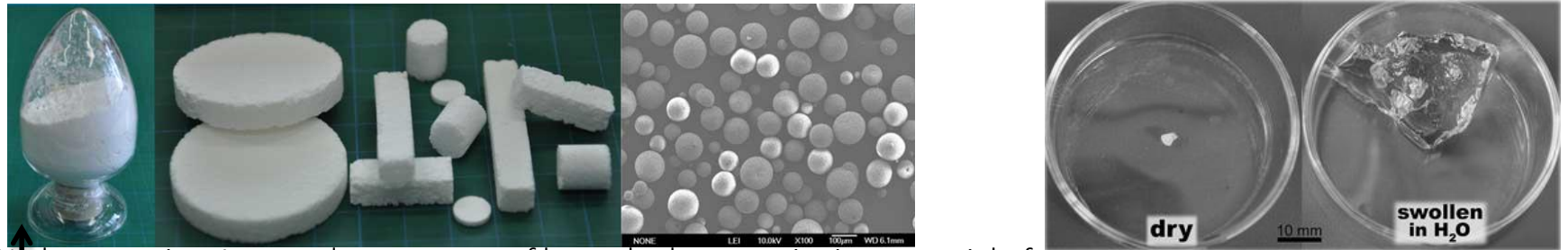
Silicones: Commercial production of silicones was initiated by E. Rochow of GE in 1946. It was known at that time that silicones had low toxicity. Physiological response to silicones was then researched and reported in 1954 in a book by McGregor. Silicone rubber was used extensively in tubing of the first artificial kidneys.

Polyurethanes: These polymers were invented in 1937 by Otto Bayer in Germany. The first class of polymers to exhibit rubber elasticity without covalent cross-linking were used as heart valves in 1959. A subclass of polyurethanes with good biocompatibility and durability were developed in the mid-1960s and used as the pump diaphragms in artificial hearts.

Teflon: Polytetrafluoroethylene was discovered by Roy Plunkett of DuPont in 1938. From inert wire insulation to porous membranes, Teflon had been used in a wide range of applications. Porous Teflon has become the leading synthetic vascular graft and has numerous applications in surgery and biotechnology.

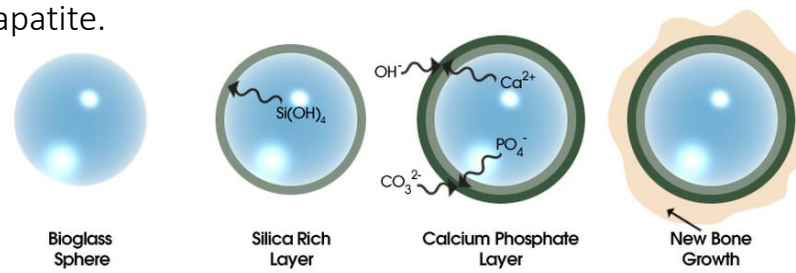


Hydrogels: Hydrated, swollen natural polymers have been found in nature since the beginning of life as bacterial biofilms, hydrated tissues and plant structures. Gelatin and agar were known to early men. The modern history of hydrogels as biomaterials started in 1936 when DuPont scientists synthesized methacrylic polymers. These were hard, brittle, glassy polymers. After a long time a new polymerization of poly(hydroxyethyl methacrylate) monomer and a new cross-linking agent in the presence of water was discovered in 1960. The new form of the polymer was a soft, water-swollen, elastic, clear gel which created the soft contact lens industry and the modern field of biomedical hydrogels. Another important hydrogel is Poly(ethylene glycol) with high bacterial resistance.



Hydroxyapatite: A natural component of bone, hydroxyapatite is a material of ancient history and a synthetic biomaterial with a modern history. It is simple to synthesize this ceramic powder in the lab. The first biomedical application of hydroxyapatite was done in 1969 by hot-pressing into useful shapes for biological testing. It is the most widely studied material for healing bone.

Bioglass: Like hydroxyapatite, bioglass is one of the most important bone healing materials. It was developed by Larry Hench, a researcher specialized in glasses, in 1967. An army colonel asked him to develop a material to heal the wounded soldiers in Vietnam. In his first try Dr. Hench made small rectangles of 45S5 glass with 44.5% SiO_2 and the remaining calcium, phosphates. Implanted samples did not come out of the rabbit bones. Later studies by Hench showed that the surface of the bioglass transformed from a silicate-rich composition to a phosphate-rich structure in biological fluids as in hydroxyapatite.



The modern era in the history of biomaterials is enabled by rapid developments in modern biology.

The biomaterials community has been quick to embrace and make use of new ideas from biology such as cell-surface receptors, growth factors, control of protein expression and phenotype, cell attachment proteins, gene delivery; and new ideas from materials science such as phase separation, anodization, self-assembly, surface modification and surface analysis.



Hence biomaterials science in the modern era is able to engineer and design biomaterials to control specific biological reactions.

Modern biomaterials research is mainly concentrated on the following ideas:

Protein adsorption

Biospecific biomaterials

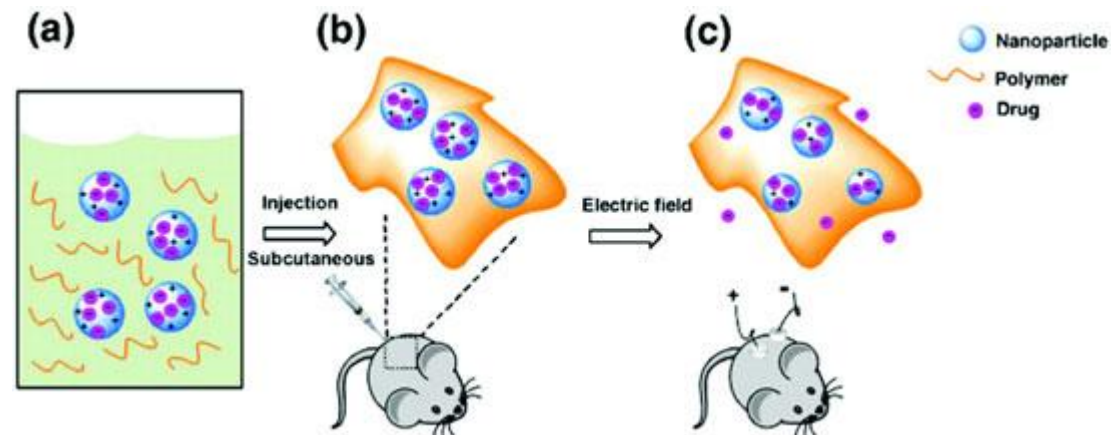
Nonfouling materials

Healing and the foreign-body reaction

Controlled release

Tissue engineering

Regenerative medicine



MME4506 Biomaterials

Scope of the course: The properties and applications of synthetic and natural biomaterials that are used in contact with biological systems.

Definition: “A biomaterial is a nonviable material used in a medical device, intended to interact with biological systems”, Williams, 1987

Applications: medical implants, growing cells in culture, assaying for blood proteins in the clinical laboratory, processing biomolecules, implants in cattle to regulate fertility, diagnostic gene arrays, aquaculturing of oysters or fish, investigational cell-silicon biochips

Scientific and engineering fundamentals behind materials and their applications will be covered with an emphasis on their interaction with biological systems.



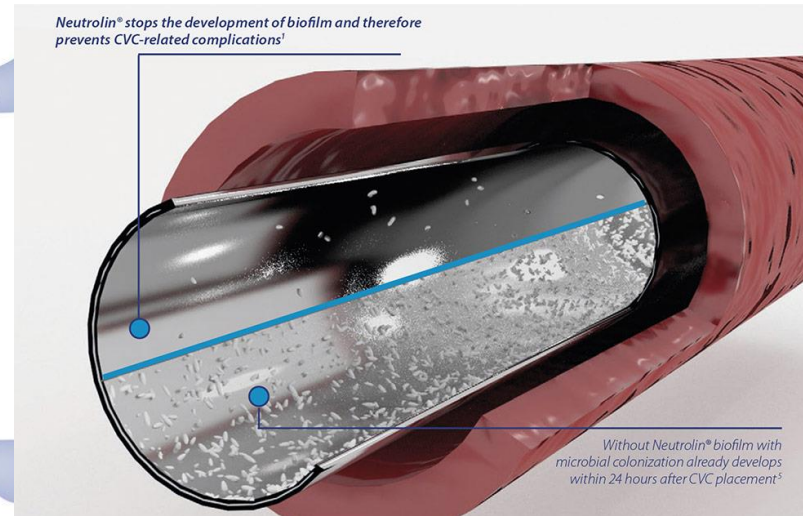
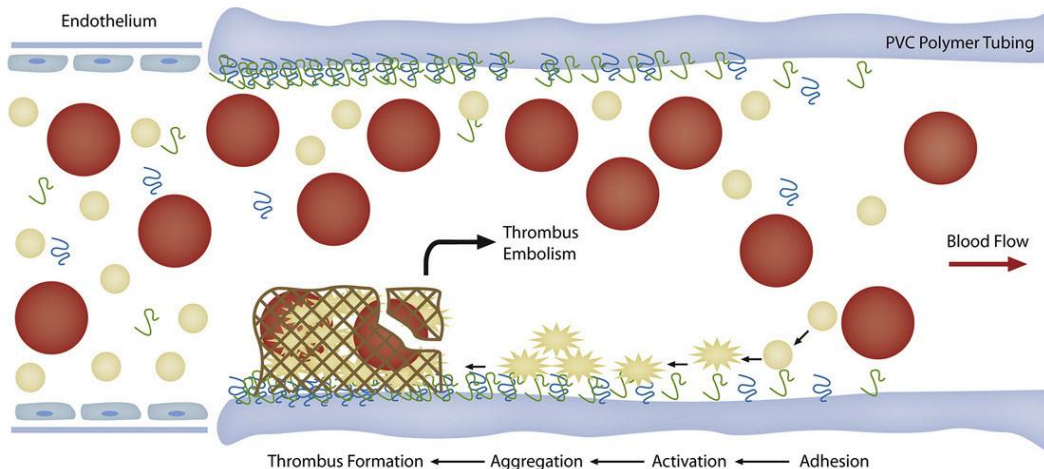
Biomaterials science research focuses on the synthesis, optimization, characterization, testing of biomaterials, and the biology of host-material interactions.

The most important research subject in the recent years has been the modification of biomaterial surfaces to modulate their biocompatibility.

Definition: *“Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application”*. Williams, 1987

Biomaterial surfaces are engineered to induce rapid and precise reactions with cells and proteins, tailored to a specific application.

For example: Resistance to blood clotting in a hemodialysis membrane, resistance to bacterial colonization in a urinary catheter, normal and uncomplicated healing in a hip-joint replacement prosthesis



Biocompatibility sets biomaterials apart from all other materials studied in materials science and engineering

Some applications of synthetic and modified natural materials in medicine:

Hip and knee replacements (1 Million each year in the US) – Titanium, Ti-Al-V alloy, stainless steel, polyethylene

Bone-plate for fracture fixation – Stainless steel, Co-Cr alloy

Bone cement – Poly(methyl methacrylate), Calcium phosphate cement

Bony defect repair – Hydroxyapatite

Artificial tendon and ligament – Teflon, Dacron

Dental implant for tooth fixation (2 M each year in the US) – Titanium, Ti-Al-V alloy, stainless steel, polyethylene, alumina, calcium phosphates

Blood vessel prosthesis (600000 each year in the US) – Dacron, Teflon, polyurethane

Heart valve (200000 each year in the US) – Reprocessed tissue, stainless steel, carbon

Coronary stents (3 M each year in the US) – Stainless steel, gold, titanium, cobalt-chromium alloy, tantalum alloy, polymer coating

Catheter (400 M each year in the US) – Silicone rubber, Teflon, polyurethane

Blood bag (80 M each year in the US) – Silicone rubber, Teflon, polyurethane

Pacemaker (800000 each year in the US)– Polyurethane

Skin repair template – Silicone-collagen composite

Artificial kidney (Hemodialyzer, 700000 each year in the US) – Cellulose, polyacrylonitrile

Heart-lung machine (Oxygenator, 600000 each year in the US) – Silicone rubber

Cochlear sensor replacement – Platinum electrodes

Intraocular lens (5 M each year in the US) – Poly(methyl methacrylate), silicone rubber, hydrogel

Contact lens (60 M each year in the US) – Silicone, acrylates, hydrogel

Corneal bandage – Collagen, hydrogel

Breast prostheses (500000 each year in the US) – Silicone rubber and gel

A biomaterial should not be toxic (mostly the case) unless it is specifically engineered for such a requirement.

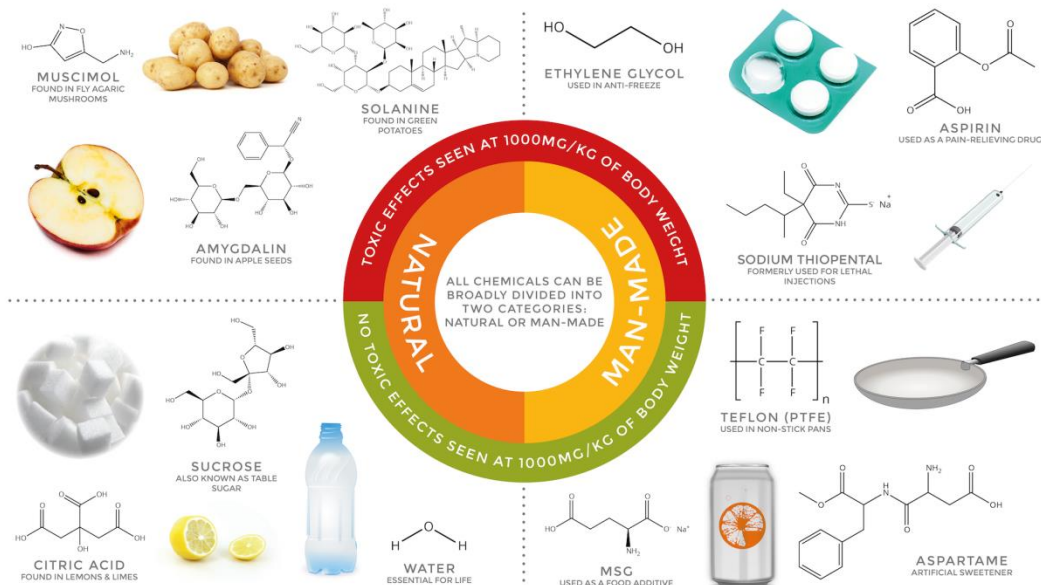
Toxicity deals with the substances that migrate out of biomaterials and the methods to evaluate the above criterion for new biomaterials

Generally applicable requirement is that a biomaterial should not give off anything from its mass unless it is specifically designed to do so.

For example, for polymers many low-molecular-weight leachables exhibit some level of physiologic activity and cell toxicity.

NATURAL & MAN-MADE CHEMICALS

A COMMON MISCONCEPTION IS THAT ALL MAN-MADE CHEMICALS ARE HARMFUL, AND ALL NATURAL CHEMICALS ARE GOOD FOR US. HOWEVER, MANY NATURAL CHEMICALS ARE JUST AS HARMFUL TO HUMAN HEALTH, IF NOT MORE SO, THAN MAN-MADE CHEMICALS.

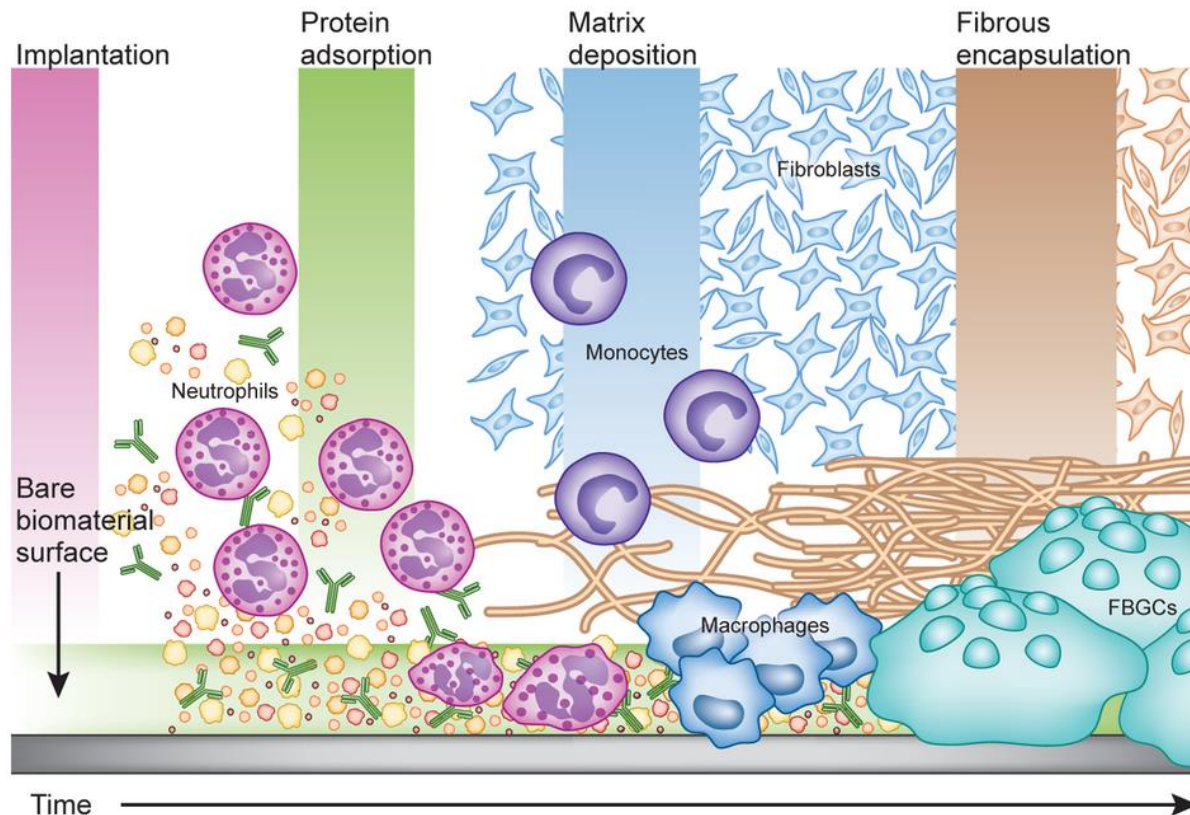


Special processes are invoked when a material or device heals in the body.

Injury to tissue stimulates the inflammatory reaction sequence that leads to healing.

Where a foreign body is present in the wound site, the reaction sequence is referred to as the foreign-body reaction which is different than the normal response of the body.

The reaction will differ in intensity and duration depending upon the anatomical site involved.



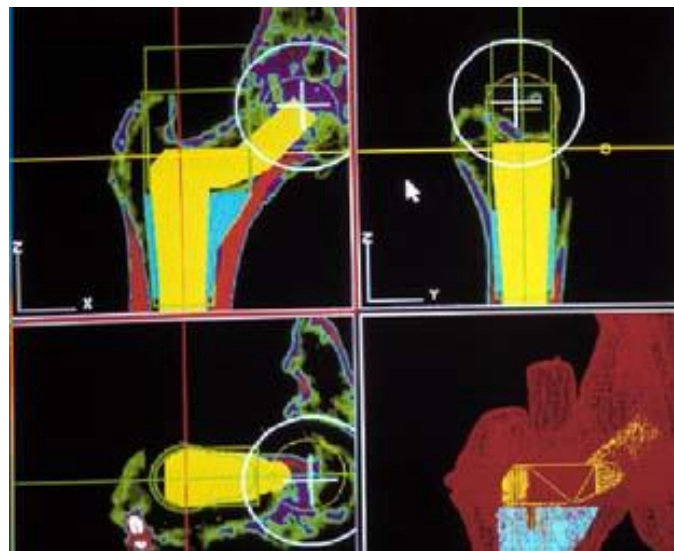
The mechanical and performance requirements for a biomaterial or device originate from the need to perform a physiological function.

Examples to three categories of requirements:

Mechanical performance requirement: A hip-prosthesis must be strong and rigid; a tendon material must be strong and flexible; a heart valve leaflet must be flexible and tough; a dialysis membrane must be strong and flexible but not elastomeric.

Mechanical durability requirements: A catheter has a performance period of only 3 days; a bone plate 6 months or more; A heart valve leaflet more than 10 years, a hip-prosthesis more than 10 years

Bulk physical property requirements: the dialysis membrane should be permeable; the articular cup of the hip joint should have high lubricity; the intraocular lens should have be clear and refracting.



Biomaterials science is a new field and we have been only learning about the fundamentals of bio-interaction based on significant research effort driven by the industry.

Industry manufactures millions of devices that are not perfect due to the demand from the medical practitioner to minimize suffering and death.

As a result of considerable experience we know a set of biomaterials that performs satisfactorily in the body. Their performance in the patient is acceptable because complications associated with the devices are less than the complications of the original diseases.

Hence there exists a complex balance in the field between the desire to minimize suffering and death; the excitement of new scientific ideas, the corporate imperative to gain profit; the risk/benefit relationship; and the requirements of the regulatory agencies to protect the public.

The industrial side of the biomaterials field raises questions about the ethics due to large investments in the development, manufacture, quality control, clinical testing, regulatory acceptance, and distribution of medical devices.

Some ethical concerns relevant to biomaterials science is given at the end of the course.



Facts and stats from the US (Global numbers are typically 3x the US number):

Total number of employees in the medical device industry: 500000

Registered medical device manufacturers: 20000

Total medical device market: 150 Billion dollars

Total biomaterials market: 9 B dollars

Total disposable medical supplies market: 100 B dollars

Total health research and development: 160 B dollars

Some applications with high success rate are presented in the following slides

These devices have widespread applications in many anatomical sites and made of a broad range of materials.

The mechanisms by which the body responds to foreign bodies and heals wounds are observed in each case.

Problems, concerns and unexplained observations for each device are noted by doctors, manufacturing companies and regulatory agencies.

Companies use these data to improve device performance and the quality of the treatment while keeping a balance between the quality and profits.

Regulatory agencies observe the device performance to make policy intended to control the industry and protect the patient.

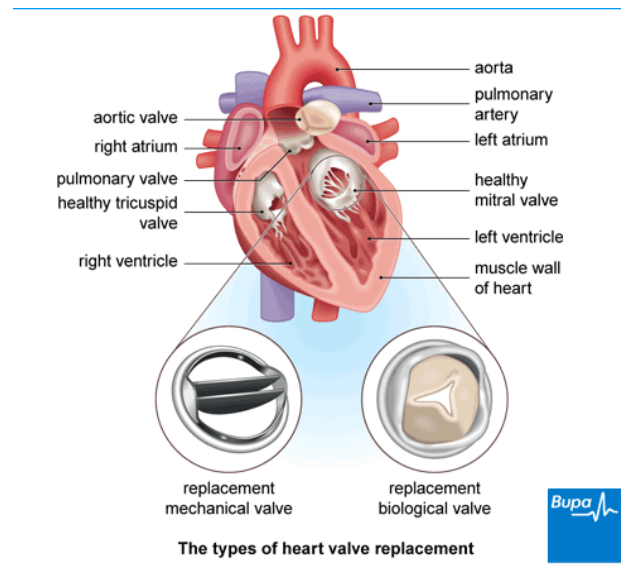
Heart valve prosthesis: Implants are required due to acquired damage to the natural valve and congenital heart anomalies

Heart valves open and close many times: $60\text{bpm} \times 60 \times 24 \times 365 = 31560000$ each year

Many types of prostheses from carbon, metals, elastomers, plastics, fabrics, animal or human tissues chemically pretreated to reduce their immunologic reactivity

Generally as soon as the valve is implanted, cardiac function is restored to normal levels.

Common problems that may differ with different types of heart valves: induction of blood clots, degeneration of tissue, mechanical failure, infection



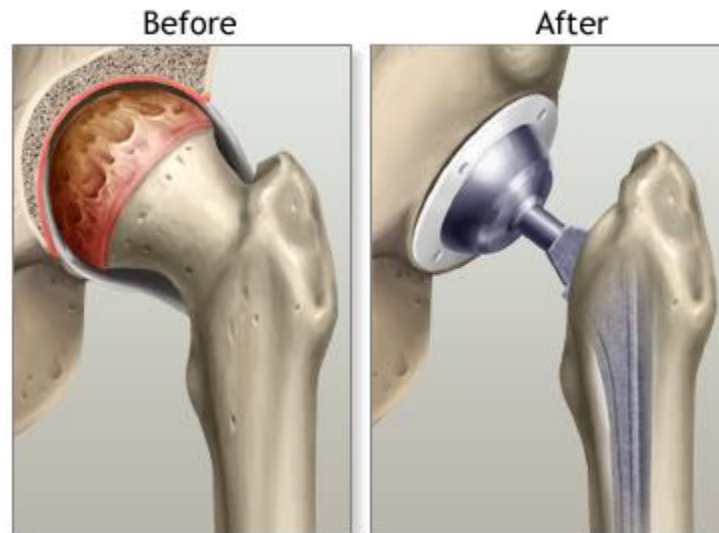
Artificial hip joints: The natural joint wears out due to high levels of mechanical cyclic stress or degenerative or rheumatological disease after 50 years.

The mobility is restored by hip-joint prostheses from titanium, stainless steel, high-strength alloys, ceramics, composites and ultrahigh-molecular-weight polyethylene.

Poly(methyl methacrylate) cement is used in some types to speed up the integration with bone and the patient recovers after a few days. A longer healing and integration takes place for other types before the joint can bear the full weight of the body.

Generally good function is restored so that the patient can return to athletic activities.

Common problem with the prostheses is loosening after 10-15 years which necessitates another operation.

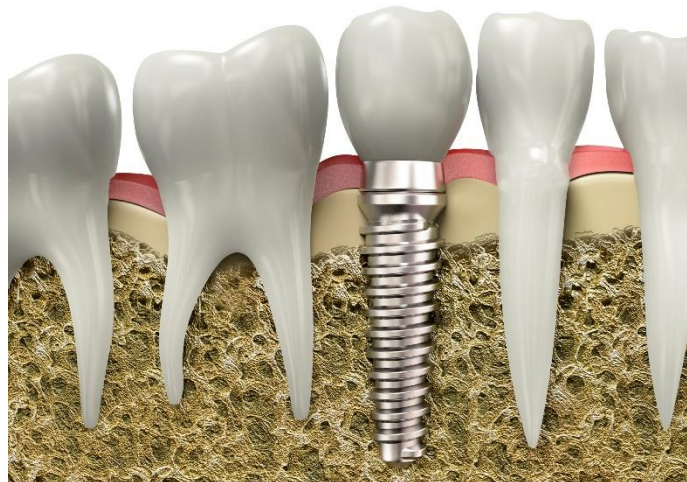


Dental implants: Titanium implants form an artificial tooth anchor upon which a crown is affixed.

The primary advantage of titanium implant is its strong integration with the jaw bone by a tight mechanical fit.

A special requirement of a material in this application is the ability to form a tight seal against bacterial invasion around the contact point with the gum so that the implant surface is engineered to be hydrophilic.

Generally the artificial teeth function well for a long time and some patients receive up to 12 implants. The common problems are loss of tissue support due to loosening, infection and weakness of unalloyed titanium subjected to long-term cyclic loading.



Intraocular lenses

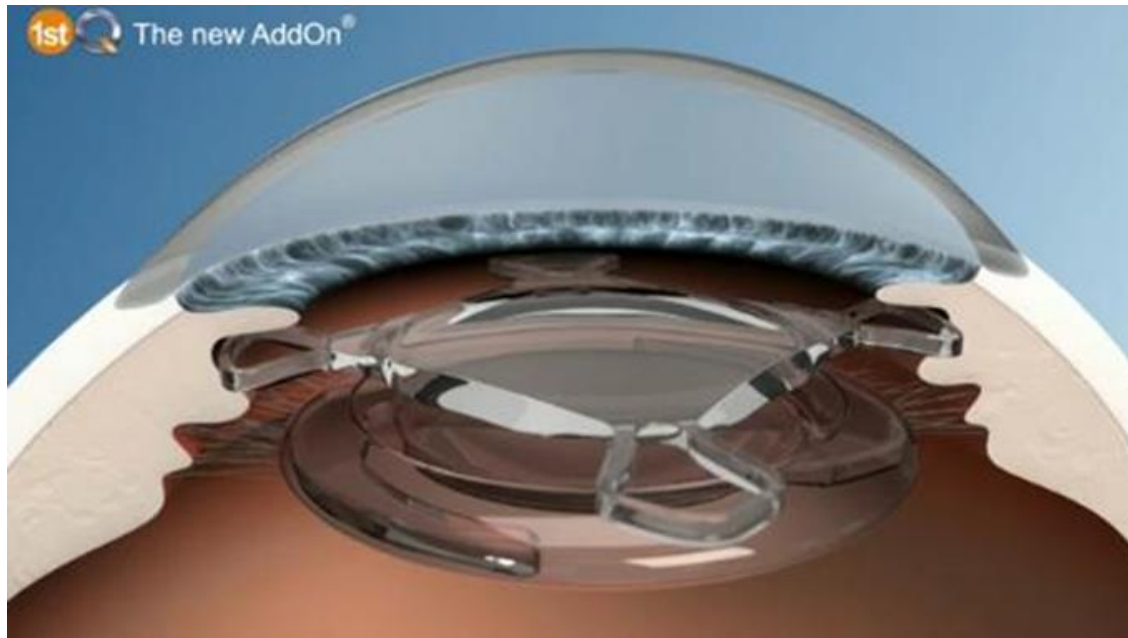
More than 50% of the population suffers from cataract by the age of 75.

IOL implantation restores good vision almost immediately after the operation.

A variety of IOLs have been fabricated of poly(methyl methacrylate), silicone elastomer, soft acrylic polymers and hydrogels.

Like materials implanted at other sites of the body, inflammatory cells migrate to the surface of the lenses on the cornea after implantation.

A common problem is the outgrowth of cells from the surface which can cloud the vision.



Left Ventricular Assist Device

Each year about 100000 people suffer from seriously failing hearts and about 5000 donor hearts are available for transplantation.

LVADs that can be considered as one half of a total artificial heart are used to maintain a patient with a failing heart while the patient awaits the availability of a transplant heart.

Patients have lived on LVAD support for more than 4 years so the LVAD is also used as a permanent therapy.

The complications that may arise are infection and serious blood clot formation within the device which could break off and obstruct blood flow to a vital organ.





Ethical concerns regarding biomaterials

- Is the experiment well designed and important so that the data obtained will justify the suffering and sacrifice of the life of a living creature?
- How should research using humans be conducted to minimize risk to the patient and offer a reasonable risk-to-benefit ratio?
- How can the needs of the patient be best balanced with the financial goals of a company?
- Since the motivation of the researcher for a successful biomedical device is to benefit financially, how can the investigator be made to report truly?
- What is the trade-off between sustaining life and the quality of life with a life-sustaining device for the patient? Can the patient be allowed to end the treatment if the quality of life is not satisfactory?
- Do the government regulatory agencies have sufficient information to define adequate tests for materials and devices while there are so many unanswered questions about the basic science of biomaterials?
- Should the government or private insurers pay for the health care of patients receiving devices that have not yet been formally approved by the FDA?
- Should an orthopedic appliance company manufacture two models of hip joint prostheses: one with an expected lifetime of 20 years for young, active recipients and another that costs $\frac{1}{4}$ as much with an expected lifetime of 7 years for older patients, with the goal of saving resources so that more individuals can receive the appropriate care?