Evolution of Biomaterials

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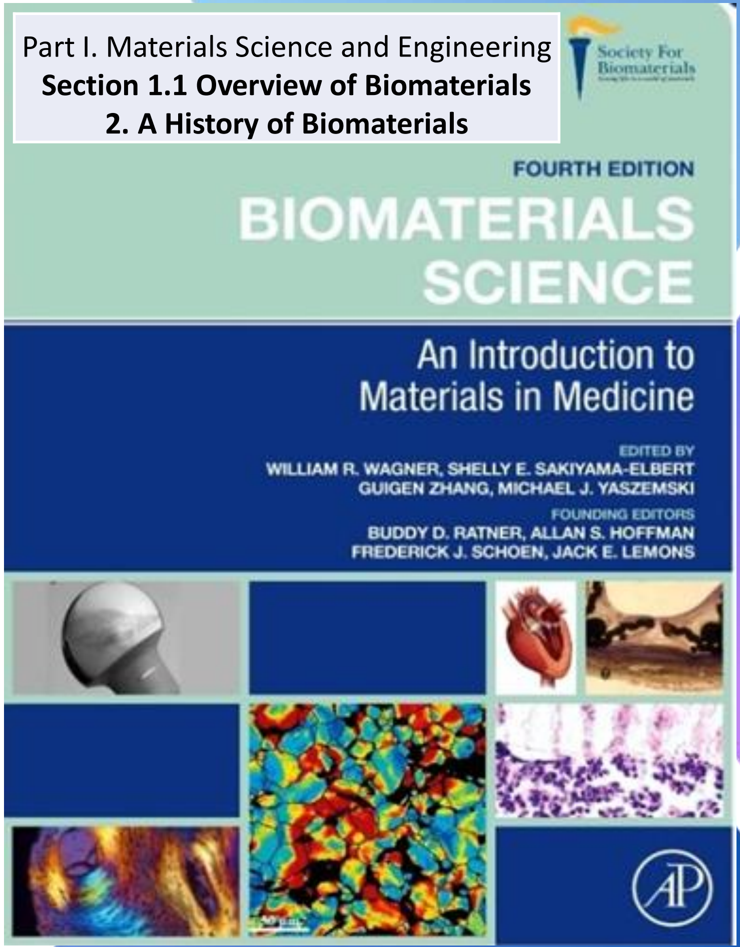


What Are Biomaterials?

Biomaterials as we think of them today did not exist just 70 years ago.

- No specific word "biomaterial" in use.
- No medical device manufacturers (except external prosthetics).
- No formalized regulatory approval processes.
- No understanding of biocompatibility.
- No academic courses on biomaterials.

However, biomaterials were used throughout history, generally with poor to mixed results.

Eras of Biomaterials Evolution

Eras of Biomaterials Evolution

Pre-history

Prehistory: Earliest uses (spear points, tattoos, skin grafts)

Surgeon-Hero Era

World War II to Modern Era: Surgeon-Hero

Designed Biomaterials & Engineered Devices

Materials designed specifically for medical applications

Contemporary Era

Contemporary Era: Into the New Millennium

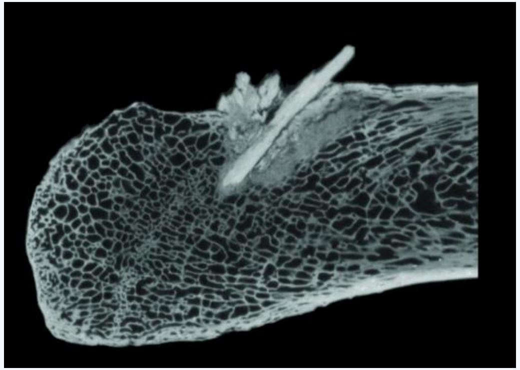
Emphasis: Experiments and studies that set the foundation for the field, largely between 1920 and 1980.

Biomaterials Before World War II

The introduction of nonbiological materials into the human body took place throughout history.

This section broadly traces the history of biomaterials from the earliest days of human civilization up to World War II.

Unintended & Intentional Early Implants



Unintended Implants:

- Kennewick Man (9000 years old): Spear point embedded in hip, healed in, illustrates body's capacity to tolerate foreign materials.

Intentional Early Foreign Material Introduction:

- Tattoos (over 5000 years ago): Carbon particles likely caused foreign-body reaction.

- Skin Grafts (circa 600 BC): Documented repair of torn earlobes and reconstruction of noses with skin flaps, arguably the first written record of such techniques.

Early Dental Implants

- Mayan people (circa 600 AD): Fashioned nacre teeth from sea shells, achieving what is now called osseointegration (seamless integration into bone).
- France (200 AD): A wrought iron dental implant in a corpse was found to be properly osseointegrated.

Significance of Early Dental Implants:

- Success (and longevity) achieved without modern materials science, biological understanding, or medicine.
- Highlights the adaptive nature of the human body and the pressing drive to restore lost functions with implants, even in prehistoric times.

Evolution of Sutures

History of Sutures

- Neolithic Period: Loose evidence suggests sutures may have been used.
- Early Methods: Large wounds were closed by cautery or sutures.

Early Materials:

- Linen: Used by early Egyptians.
- Catgut: Used in the Middle Ages in Europe.
- Ant Heads: In South Africa and India, large, biting ants were used to clamp wound edges.

Evolution of Sutures

History of Sutures

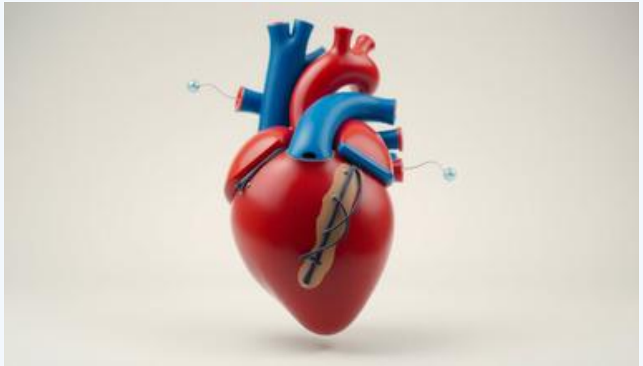
Metallic Sutures:

- Early Greek literature mentions metallic sutures.
- Galen of Pergamon (ca. 130-200 AD): Described ligatures of gold wire.
- Philip Physick (1816): Suggested lead wire sutures, noting little reaction.
- J. Marion Sims (1849): Used silver wire sutures, performing many successful operations.

Challenges:

- These early uses predated knowledge of sterilization, toxicology, immunological reaction, inflammation, and biodegradation.

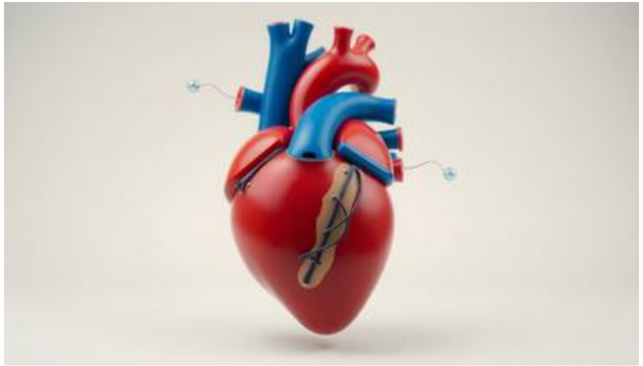
Early Artificial Hearts & Perfusion



Early Understanding of the Heart:

- Aristotle (4th century BC) called the heart the most important organ.
- William Harvey (1628) espoused a modern view of the heart as a pump.
- This appreciation led to the logical idea of replacing the heart with an artificial pump.

Early Artificial Hearts & Perfusion



- Le Gallois (1812): French physiologist, proposed organs could be kept alive by pumping blood through them.

- Organ Perfusion Experiments (1828-1868): A number of experiments were performed.

Étienne-Jules Marey (1881): Described an artificial heart device, primarily oriented to studying the beating of the heart.

Lindbergh & Carrel's Impact

Lindbergh & Carrel's Contributions

- "The Culture of Organs" (1938): Visionary book by aviator Charles Lindbergh and surgeon Alexis Carrel.
- Addressed key issues:
- Pump design (Lindbergh pump).
- Sterility.
- Blood damage.
- Nutritional needs of perfused organs.
- Mechanics.
- This book is considered a seminal document in the history of artificial organs.

Mid-20th Century Artificial Heart Developments:

- Paul Winchell (mid-1950s): Ventriloquist who patented an artificial heart.
- Dr. Willem Kolff and Team (1957): Tested artificial hearts in animals.

Early Contact Lenses

Early Contact Lenses

- Leonardo DaVinci (1508): Developed the concept of contact lenses.
- Rene Descartes (1632): Credited with the idea of the corneal contact lens.
- Sir John F.W. Herschel (1827): Suggested a glass lens could protect the eye.

Adolf Gaston Eugen Fick's Contribution:

- Optometrist (nephew of Fick's law fame).
- Invented a glass contact lens (circa 1860), possibly the first offering real success.
- Experimented with contact lenses on both animals and humans.

Modern Contact Lenses:

- 1936 to 1948: Plastic contact lenses were developed, primarily from poly(methyl methacrylate) (PMMA).

Basic Biocompatibility Concepts

Basic Concepts of Biocompatibility

Prior to 1950, most implants had a low probability of success.

- This was largely due to a poor understanding of biocompatibility and sterilization.

Factors Contributing to Biocompatibility:

- The chemistry of the implant.
- Leachables (substances that leach out of the material).
- Shape.
- Mechanics.
- Design.

Early studies, especially with metals, focused on chemical explanations for observed bioreactions.

Early Bioreactivity Studies

Early Bioreactivity Studies: Metals

- H.S. Levert (1829): Performed possibly the first study assessing in vivo bioreactivity of implant materials.
- Studied gold, silver, lead, and platinum in dogs.
- Platinum, in particular, was found to be well tolerated.

Early Bioreactivity Studies

19th and Early 20th Century Metallic Implants:

- 1886: Bone fixation plates of nickel-plated sheet steel with nickel-plated screws were studied.
- A. Zierold (1924): Published a study on tissue reaction to various materials in dogs.
- Iron and steel corroded rapidly, causing bone resorption.
- Copper, magnesium, aluminum alloy, zinc, and nickel discolored surrounding tissue.
- Gold, silver, lead, and aluminum were tolerated but lacked mechanical strength.

Biocompatible Alloys

Development of Biocompatible Alloys

Stellite: A Co-Cr-Mo alloy, found to be well tolerated and strong.

M. Large (1926): Noted the inertness displayed by 18-8 stainless steel containing molybdenum.

Vitallium Alloy (1929): A 65% Co - 30% Cr - 5% Mo alloy, developed and used with success in dentistry.

J. Cotton (1947): Discussed the possible use of titanium and its alloys for medical implants.

***These discoveries marked a shift towards materials with both good mechanical properties and improved tissue tolerance*.**

Early Plastic Implants

Early Plastic Implants

- The history of plastics as implantation materials is shorter than metals, as few plastics existed before the 1940s.

Pioneering Plastic Implants:

- Nylon: Possibly the first paper on the implantation of a modern synthetic polymer, nylon, as a suture appeared in 1941.
- Cellophane: Papers as early as 1939 documented its use as a wrap for blood vessels, describing a "marked fibrotic reaction."
- Poly(methyl methacrylate) (PMMA) and Nylon: Papers in the early 1940s discussed the tissue reaction to these implanted materials.

Polyethylene & Teflon

Polyethylene & Teflon in Implants

- Polyethylene:
- First paper on polyethylene as a synthetic implant material was published in 1947 by Ingraham et al.
- Noted good results (i.e., a mild foreign-body reaction), attributed to the high purity of the polymer due to a new high-pressure polymerization technique.
- LeVeen and Barberio (1949): Commented that additives in many plastics caused strong biological reactions by "sweating out."

Polyethylene & Teflon

Polyethylene & Teflon in Implants

Teflon (Polytetrafluoroethylene):

- LeVeen and Barberio (1949) found a vigorous foreign-body reaction to cellophane, Lucite, and nylon, but an extremely mild reaction to Teflon.
- They concluded that purity was key, raising questions about unpolymerized chemicals or minute amounts of plastic itself causing reactions.

WWII to Modern Era: Surgeon-Hero

Transition from Wartime to Peacetime:

- After World War I, and particularly post-WWII, newly developed high-performance metal, ceramic, and polymeric materials became available.
- Materials originally manufactured for airplanes, automobiles, clocks, and radios were taken "off the shelf" by surgeons and applied to medical problems.

Early Biomaterials Used:

- Silicones
- Polyurethanes
- Teflon
- Nylon
- Methacrylates
- Titanium
- Stainless Steel

Context of Surgeon-Hero Era

Context of the Surgeon-Hero Era

1. Limited Collaboration: Just after WWII, there was little precedent for surgeons to collaborate with scientists and engineers.
2. Necessity as Invention: Medical and dental practitioners invented and improvised when a patient's life or functionality was at stake.
3. Minimal Regulation: Government regulatory activity was minimal.
4. Non-Existent Human Subject Protections: The concept of human subject protections as known today did not exist.

This era was characterized by individual initiative and risk-taking.

Surgeon-Hero Philosophy

The "Surgeon-Hero" Philosophy

- Trust and Freedom: The physician was implicitly entrusted with the patient's life and health, having much more freedom to take heroic action.
- Inspired by Materials Science: Surgeons were aware of post-WWII material advancements and envisioned replacements for body parts.
- High-Risk Trials: Many materials were tried on the spur of the moment, often when other options were unavailable.
- Building the Foundation: Courageous, fiercely committed, and creative individuals built the foundation of ideas and materials for the biomaterials field.

Regulatory Example:

- Willem Kolff's Pump Oxygenator: Insisted on 10 consecutive, successful animal operations before clinical human use (Kolff, 1998).

Intraocular Lenses: Ridley

Intraocular Lenses (IOLs): Sir Harold Ridley

Early Observations:

- Sir Harold Ridley (1906-2001) invented the plastic intraocular lens.
- After WWII, he examined aviators with plastic shards in their eyes from shattered Spitfire and Hurricane canopies.
- Conventional wisdom: human body would not tolerate foreign objects, especially in the eye.

Ridley's finding: The shards healed in place with no further reaction, indicating they were

Ridley's IOL Innovation

Ridley's Innovation & Impact

- Material Source: Based on his observations, Ridley traced the plastic to ICI Perspex poly(methyl methacrylate).
- Lens Fabrication: He used this material to fabricate implant lenses (intraocular lenses) which functioned reasonably in humans as replacements for cataract-clouded natural lenses.
- First Human Implantation: November 29, 1949.

Ridley's IOL Innovation

Impact and Legacy:

- Controversy: Ridley faced fierce controversy for challenging established medical dogma.
- Industry Growth: The IOL industry did not instantly arise; it became a major force in the biomedical device market by the early 1980s.
- Millions of Lives Transformed: His concept, using a biocompatible plastic, led to an industry that now implants over 7 million lenses annually, significantly improving the quality of life for millions suffering from cataracts.

Early Hip & Knee Prostheses

Hip & Knee Prostheses: Early Efforts

- Theodore Gluck (1891): Performed possibly the first hip replacement using a cemented ivory ball, but it was unsuccessful.
- Numerous attempts (1920-1950) to develop hip replacement prostheses.
- M.N. Smith-Petersen (1925): Explored a glass hemisphere over the hip joint ball, but it failed due to poor durability.

Early Hip & Knee Prostheses

Hip & Knee Prostheses: Early Efforts

Material Improvements:

- Chrome-cobalt alloys and stainless steel offered improved mechanical properties.
- Judet brothers (1938): Explored an acrylic surface for hip procedures, but it had a tendency to loosen.
- Dr. Edward J. Haboush (1953): Developed the idea of using fast-setting dental acrylics to glue prosthetics to bone.

John Charnley's Hip Prosthesis

John Charnley's Breakthrough

Pioneer of Successful Hip Replacement:

- John Charnley (1911-82), working in an isolated sanatorium in England, invented the first really successful hip joint prosthesis.
- His design included a femoral stem, ball head, and a plastic acetabular cup, proving a reasonable solution for damaged joint replacement.

John Charnley's Hip Prosthesis

John Charnley's Breakthrough

Material Evolution:

- 1958: Initially used a Teflon acetabular cup, which led to poor outcomes due to wear debris.
- 1961: Switched to a high molecular weight polyethylene cup, achieving much higher success rates.
- Learned about high molecular weight polyethylene from a salesman of plastic gears.

Collaboration: Dr. Dennis Smith introduced Charnley to poly(methyl methacrylate) cements from dentistry, optimizing them for hip replacement.

Knee Replacements: Total knee replacements borrowed from hip prosthesis technology, with successful results obtained by Frank Gunston and John Insall (1968-72).

Modern Dental Implants

Dental Implants: Modern Evolution

- Maggiolo (1809): Implanted a gold post anchor into fresh extraction sockets, then affixed a tooth after healing. This bears remarkable similarity to modern procedures.
- 1887: This procedure was used with a platinum post.
- Gold and platinum posts generally yielded poor long-term results, preventing widespread adoption.

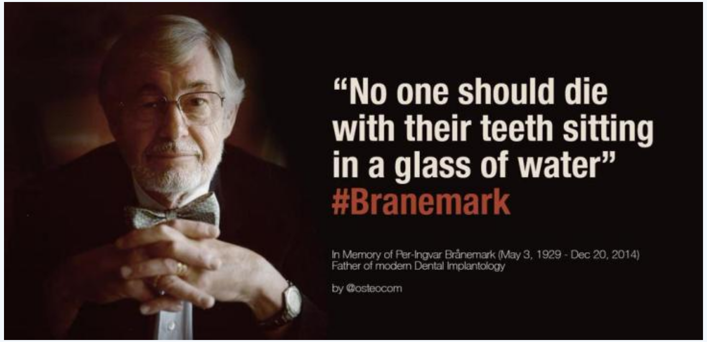
Advancements in Materials:

- Venable (1937): Used surgical Vitallium and Co-Cr-Mo alloy for implants.
- Strock (circa 1937, Harvard): Used a screw-type implant of Vitallium, possibly the first successful dental implant.

Brånemark & Osseointegration

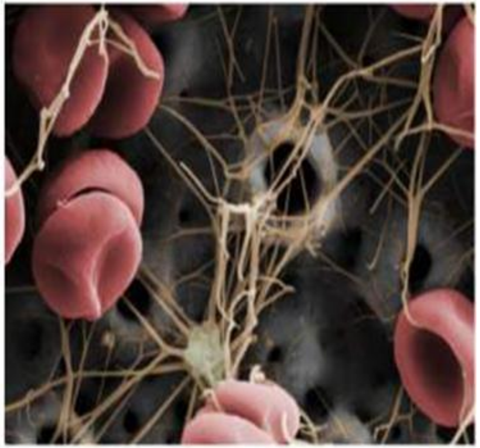
"Osseointegration": Brånemark named this phenomenon,

- Fortuitous Discovery (1952): Per-Ingvar Brånemark, an orthopedic surgeon in Sweden, implanted an experimental titanium cylinder (cage device) into rabbit bone to observe healing reactions.
- Unexpected Integration: After several months, he tried to remove the device and found it was tightly integrated into the bone.



Brånemark & Osseointegration

Concept & Application:



- Coined "Osseointegration": Brånemark named this phenomenon defining it as a direct structural and functional connection between living bone and the surface of a load-carrying implant.
- Clinical Application: He explored the application of titanium implants to surgical and dental procedures.

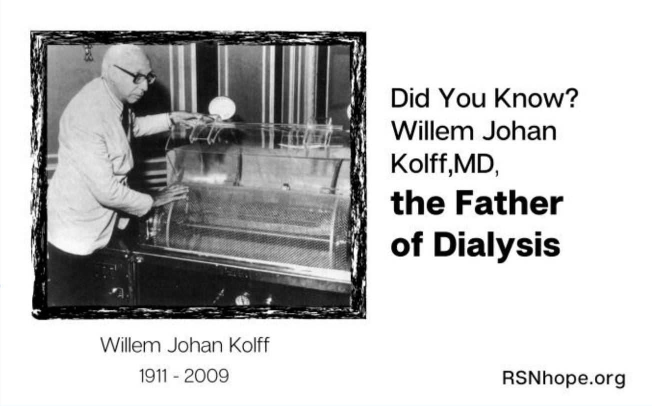
- Surgical Protocols: Developed low-impact surgical protocols for tooth implantation, which reduced tissue necrosis and enhanced successful outcomes.

Impact: Most dental and many other orthopedic implants today are made of titanium and its alloys due to this discovery.

Artificial Kidney: Early Concepts

1. Kidney failure throughout history was a sentence to an unpleasant death, typically lasting about a month.
2. John Jacob Abel (1910, Johns Hopkins University): Made the first attempts to remove toxins from blood.
3. Experiments were conducted with rabbit blood.
4. At this time, it was not possible to perform this procedure on humans.

Willem Kolff's Dialyzer



Pioneering Work (1943): In Nazi-occupied Holland, Willem Kolff, a physician, built a drum dialyzer system.

Materials: Constructed from a 100-liter tank, wood slats, and 130 feet of cellulose sausage casing tubing as the dialysis membrane.

Early Successes: Achieved some successes in saving lives that previously had only one outcome: death from kidney failure.

Innovation in the US:

- Kolff brought his ideas to the United States.
- 1960 (Cleveland Clinic): Developed a "washing machine artificial kidney," utilizing Maytag washing machines purchased from Sears.

Belding Scribner & Dialysis

Breakthrough in Access:

- Dr. Belding Scribner at the University of Washington made major advances.
- Devised a method to routinely access the bloodstream for dialysis treatments.
- Prior to this, access sites quickly ran out, limiting dialysis treatments.

The "U" Shunt Concept:

- Scribner conceived an idea for easy blood access: a shunt implanted between an artery and vein that emerged through the skin as a "U."
- This exposed portion allowed ready blood access.

Quinton-Scribner Shunt

- Material Inspiration: When Dr. Scribner learned about the new plastic, Teflon, he envisioned how to get blood in and out of vessels.
- Collaboration: His device was built with the assistance of Wayne Quinton.

Components:

- Teflon tubes: To access the blood vessels.
- Dacron sewing cuff: Through the skin.
- Silicone rubber tube: For blood flow.

- Impact: The Quinton-Scribner shunt made chronic dialysis possible, credited with saving millions of lives.
- Philanthropy: Dr. Scribner famously refused to patent his invention due to its critical importance to medical care.

Artificial Kidney: Developments

1. Chemical Engineering Contributions: Professor Les Babb (University of Washington), working with Scribner, improved dialysis performance and invented a proportioning mixer for the dialysate fluid.

2. First Dialysis Center: The first dialysis center was opened in Seattle, leveraging these technological advances.

- Bioethics: The early experience with dialyzing patients, where demand outstripped the availability of dialyzers, made important contributions to bioethics associated with medical devices (Blagg, 1998).

- This era highlighted the ethical dilemmas introduced by life-saving, but scarce, medical technologies.

Artificial Heart Development

- Willem Kolff's Pioneering Work:
- 1957: Implanted the first artificial heart in the Western hemisphere in a dog (a Russian artificial heart was implanted in a dog in the late 1930s).
- His artificial heart was made of thermosetting poly(vinyl chloride), cast inside hollow molds to prevent seams.

Heart-Lung Machine:

- John Gibbon (1953): Invented the heart-lung machine, which was useful for acute treatments, such as during open-heart surgery.

National Goals:

- 1964: The National Heart and Lung Institute of the National Institutes of Health set a goal to develop a total artificial heart by 1970.

Implantable Artificial Hearts

- Dr. Michael DeBakey (1966): Implanted a left ventricular assist device in a human.

- Dr. Denton Cooley and Dr. William Hall (1969): Implanted a polyurethane total artificial heart.

Jarvik Hearts:

- Dr. William DeVries (1982-85): Implanted a number of Jarvik hearts, based on designs originated by Drs. Clifford Kwan-Gett and Donald Lyman.
- Patients lived up to 620 days on the Jarvik 7 device.

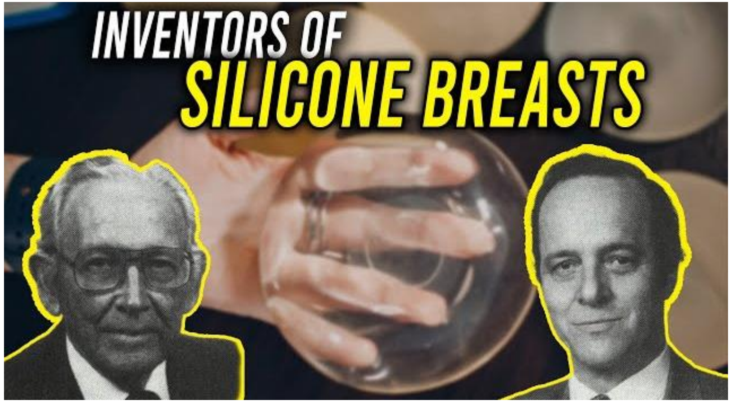
These developments marked significant progress in long-term cardiac support.

Breast Implants Evolution

Breast Implants: Evolution

- Addressing Poor Results: The breast implant evolved to overcome the poor outcomes associated with direct injection of substances into the breast for augmentation.
- Silicone Injections: In the 1960s, direct silicone injections were even classified as a criminal offense in California and Utah due to severe complications.
- Poly(vinyl alcohol) Sponges: In the 1950s, these sponges were implanted as breast prostheses, but also yielded poor results.

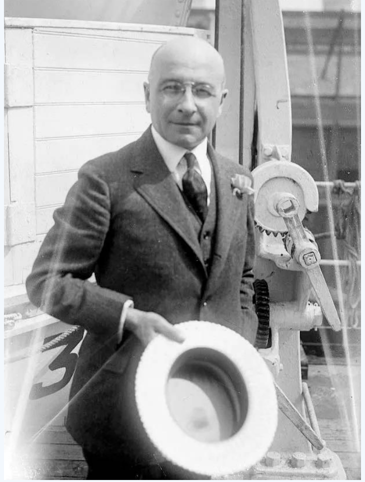
Breast Implants Evolution



First Silicone Breast Implant:

- Early 1960s: University of Texas plastic surgeons Thomas Cronin and Frank Gerow invented the first silicone breast implant.
- Design: Consisted of a silicone shell filled with silicone gel.
- Variations: Many variations were tried, including cladding with polyurethane foam (e.g., the Natural Y implant), which proved problematic.
- Acceptability: The basic silicone rubber-silicone gel breast implant was generally acceptable in performance.

Vascular Grafts: Early Solutions



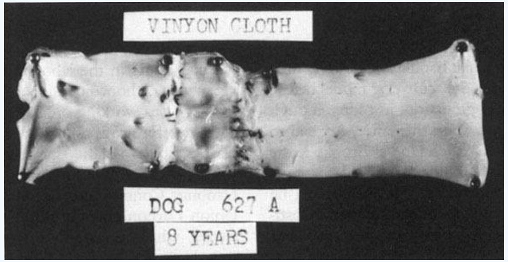
Vascular Grafts: Early Solutions

- The need for methods and materials to repair damaged and diseased blood vessels has long existed for surgeons.
- Dr. Alexis Carrel (1912 Nobel Prize in Medicine): Developed pioneering methods to anastomose (suture) blood vessels, a critical achievement for vascular surgery.

Early Implant Materials:

- Blackmore (1942): Used Vitallium metal tubes to bridge arterial defects in war-wounded soldiers.
- This demonstrated an early use of metallic biomaterials for vascular repair.

Voorhees & Fabric Grafts



- An Observation Leads to an Idea: Arthur Voorhees (1947), a Columbia University surgical intern, noticed during a postmortem that tissue had grown around a silk suture left inside a lab animal.
- The "Cloth Tube" Concept: This observation stimulated the idea that a cloth tube might also heal by being populated by the body's tissues, potentially serving as an artery replacement.
- First Experimental Grafts: Voorhees sewed his first experimental vascular grafts from a silk handkerchief and then parachute fabric (Vinyon N) using his wife's sewing machine.

Voorhees & Fabric Grafts

- First Human Implant: In 1952, the first human implant of a prosthetic vascular graft was performed, with the patient living many years, inspiring widespread adoption.
- Porous vs. Solid: A 1954 paper (Egdahl et al.) established the clear benefit of a porous (fabric) tube over a solid polyethylene tube.

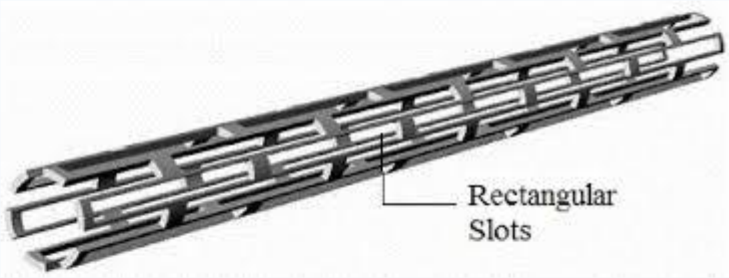
Simple Construction (1958 Textbook): "The Terylene, Orlon or nylon cloth is bought from a draper's shop and cut with pinking shears to the required shape. It is then sewn with thread of similar material into a tube and sterilized by autoclaving before use."

Stents: Problem & Solution

- The Problem: Partially occluded coronary arteries lead to angina, diminished heart functionality, and eventually myocardial infarction (heart attack).
- Current Solutions (Pre-Stent):
- Bypass operations: Taking a vein section from another part of the body to replace the occluded artery. This is major, invasive, and expensive surgery.
- Synthetic Vascular Grafts: Small diameter (3mm) grafts suitable for coronary arteries tend to thrombose (clot), making them unusable.
- Percutaneous Transluminal Coronary Angioplasty (PTCA): A balloon is threaded on a catheter into the coronary artery and inflated to open the vessel.
- Problem with PTCA: In many cases, the coronary artery could spasm and close due to elastic recoil or delamination of the vessel wall layers after the procedure, often requiring emergency bypass surgery.

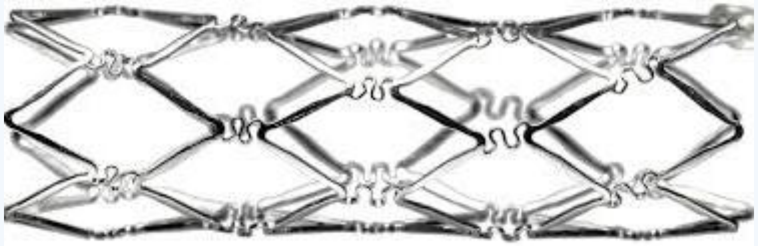
Palmaz & Stent Concept

Dr. Julio Palmaz & Stent Concept



- 1978: Dr. Julio Palmaz heard Dr. Andreas Gruntzig discuss the reclosure problem after PTCA.

Using a support structure, similar to those in mine tunnels or oil well drilling, to keep the lumen open.



Design Requirements:

- The device needed to go in small (folded like an umbrella) and expand at the site of blockage with the balloon.
- He envisioned a malleable, tubular, crisscross mesh.

Early Prototypes: Palmaz created crude prototypes using copper wire and lead solder, testing them in rubber tubes mimicking arteries.

The Name "Stent" & Development

- Original Name: Palmaz called his device a BEIS (balloon-expandable intravascular graft).
- The Term "Stent": Reviewers of his first submitted paper wanted to call it a stent.
- Etymology: The word "stent" derives from Charles Stent, a British dentist (died turn of 20th century) who invented a wax material for dental molds. This material was later used by plastic surgeons to keep tissues in place while healing.
- The term became generic for any device intended to keep tissues in place while healing.

Early Material and Testing:

- Early experimental device was made of stainless steel wire soldered with silver.
- 1983-1986: Bench and animal testing at University of Texas Health Science Center in San Antonio showed promise.

Stent Efficacy & Impact

Microscopic Observations: After weeks to months post-implantation, the stent remained open and the metal mesh was covered with translucent, glistening tissue similar to a normal vessel lining.

Atherosclerotic Vessels: Tested in an atherosclerotic rabbit model, new tissue free of atherosclerotic plaque encapsulated the stent wires, even on a high cholesterol diet.

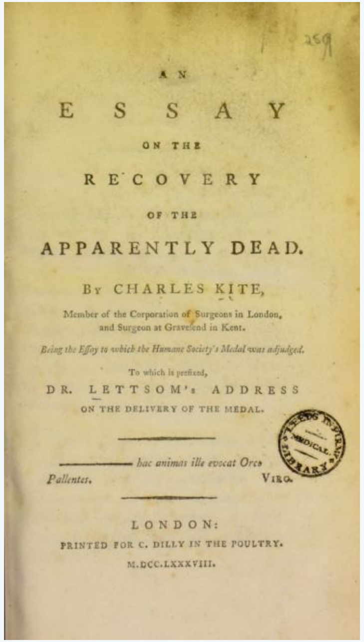
Commercialization: Johnson & Johnson adopted the project, and clinical trials were instituted under FDA scrutiny.

Widespread Adoption: Coronary artery stenting is now performed in well over 1.5 million procedures per year, revolutionizing the treatment of coronary occlusive disease.

Pacemakers: Early Concepts

Pacemakers: Early Concepts

1. Charles Kite (London, 1788): Wrote "An Essay Upon the Recovery of the Apparently Dead," discussing electrical discharges to the chest for heart resuscitation.
2. 1820-1880: It was known that electric shocks could modulate the heartbeat (e.g., Frankenstein story era).

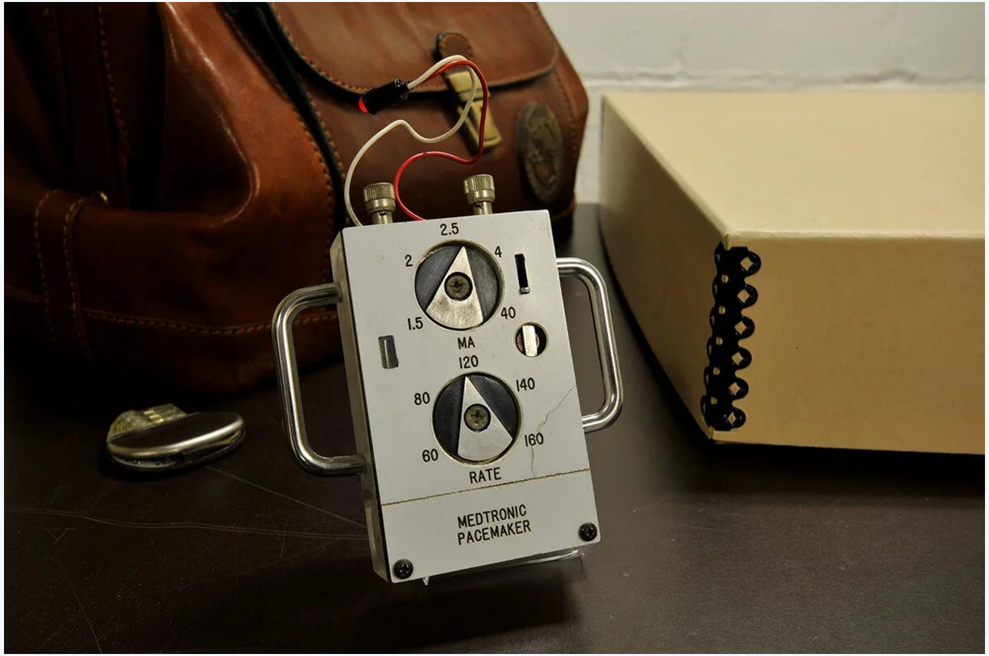

AN
ESSAY
ON THE
RECOVERY
OF THE
APPARENTLY DEAD.
By CHARLES KITE,
Member of the Corporation of Surgeons in London, and Surgeon at Gravesend in Kent.
Being the Essay to which the Humane Society's Medal was adjudged.
To which is prefixed,
DR. LETTSOM's ADDRESS
ON THE DELIVERY OF THE MEDAL.
—— *hac animas ille evocat Orco*
Pallentes. VIRG.
LONDON:
PRINTED FOR C. DILLY IN THE POULTRY.
M.DCC.LXXXVIII.

These early observations laid the groundwork for understanding the heart's electrical activity and its potential for modulation.

Early Portable Pacemakers

Simultaneous Invention (1930-31):

- Dr. Albert S. Hyman (USA) and Dr. Mark C. Lidwill (Australia, with physicist Major Edgar Booth) may have independently invented the portable pacemaker almost simultaneously.
- Early pacemakers were hardly portable by modern standards, but represented a significant step forward.



Modern Pacemaker Development

John Hopps (1949): Canadian electrical engineer, invented an early cardiac pacemaker while researching hypothermia. Discovered that a cooled heart could be electrically restarted.

His work led to a vacuum tube cardiac pacemaker in 1950.

Paul M. Zoll (1952): Developed a pacemaker in conjunction with the Electrodyne Company.

This device was about the size of a small microwave oven, powered externally, and stimulated the heart via electrodes on the chest. It caused pain and burns but could pace the heart.

Wearable & Implantable Pacemakers

Wearable & Implantable Pacemakers

1. Earl E. Bakken (Medtronics, 1957-58): Developed the first wearable transistorized (external) pacemaker at the request of heart surgeon Dr. C. Walton Lillehei.
2. Bakken quickly produced a prototype used on children with post-surgery heart block.
3. Medtronic commercially produced this unit as the 5800 pacemaker.

Wearable & Implantable Pacemakers

- Wilson Greatbatch & W.M. Chardack (1959): Developed the first fully implantable pacemaker.
- Utilized two Texas Instruments transistors, enabling small size and low power drain.
- Encased in epoxy to protect against body fluids.

Heart Valves: Challenges

Heart Valves: Early Challenges

Development of prosthetic heart valves closely paralleled advancements in cardiac surgery.

A key challenge was that valve replacement was extremely difficult until the heart could be stopped and blood flow diverted.

Heart Valves: Challenges

Early Attempts:

- Charles Hufnagel (1952): Implanted a valve consisting of a poly(methyl methacrylate) tube and a nylon ball in a beating heart.

- This was a heroic operation but largely unsuccessful, though it inspired cardiac surgeons to consider valve prostheses possible.

The 1953 development of the heart-lung machine by John Gibbon allowed the next stage in heart valve evolution.

Starr-Edwards & Tissue Valves

- Starr-Edwards Valve (1960): Albert Starr (surgeon) and Lowell Edwards (engineer) performed the first successful mitral valve replacement in a human.
- Design: Consisted of a silicone ball and a poly(methyl methacrylate) cage (later replaced by stainless steel).
- Quote: Starr famously said, "Let's make a valve that works and not worry about its looks."
- Impact: Prior to this, no human had lived with a prosthetic heart valve longer than 3 months. The Starr-Edwards valve significantly improved patient survival.

Key Issues: Major challenges in this era were thrombosis (blood clotting) and durability.

Pyrolytic Carbon Discovery

Pyrolytic Carbon: An Accidental Discovery

Definition: Pyrolytic carbon (PyC) is a manmade material formed from the thermal decomposition of hydrocarbons in the absence of oxygen.

Accidental Discovery: According to Professor Robert E. Baier, PyC's use as leaflets for blood contact was accidental (2016).

Context: In 1967-68, Jack Bokros of General Atomic Corp. sent PyC samples to Dr. Vincent Gott for testing as "positive" (clot-provoking) controls against traditional graphite coatings on artificial heart valves.

- ***Unexpected Results: Despite predictions of clotting, the naked PyC rings stayed clean in canine vena cavae, even after weeks.***

Pyrolytic Carbon Impact

Pyrolytic Carbon: Mechanism & Impact

- Mechanism of Biocompatibility: Robert Baier showed that PyC uniquely bound one of the blood's proteins in a configuration that triggered the least thrombosis and coagulation.
- It adsorbed a layer of blood proteins rapidly without denaturing them, which typically triggers the clotting cascade.
- Other researchers confirmed this unique interaction (e.g., Emery Nyilas on heat of adsorption, Andrade and Kim on protein adsorption mode).

Pyrolytic Carbon Impact

Commercial Impact:

- This discovery led to the development of CarboMedics and Medical Carbon Research Institute.
- A large fraction of the world's synthetic heart valves are now made from PyC.
- St. Jude Medical's success (and subsequent acquisition for $25 billion) is largely attributed to its pioneering use of PyC in heart valves.
- Over 15 million successful PyC heart valve implants to date.

Drug Delivery & Controlled Release

- Traditional Drug Administration: For most of history, drugs were administered orally or by hypodermic syringe, without effort to modulate release rate.
- Wurster Process (1949): Dale Wurster invented a process allowing pills and tablets to be encapsulated to slow their release rate.

Modern Controlled Release Concepts:

- Judah Folkman: Noted dyes penetrated silicone rubber and surmised drugs could too.
- 1964: Sealed isoproterenol into silicone tubes and implanted them into dogs' hearts, observing delayed release.
- Later applied this to birth control steroid delivery, donating the development patent-free to the World Population Council.

Drug Delivery & Controlled Release

Commercialization:

- Alejandro Zaffaroni (1970): Chemist who heard of Folkman's work and launched Alza (originally Pharmetrics) to develop these ideas for pharmaceuticals.
- Alza developed new polymers and delivery strategies, leading the new field of controlled release.

Designed Biomaterials: Intro

1. In contrast to the "surgeon-hero" era, where largely off-the-shelf materials were repurposed for medical devices, the 1960s onward saw a shift.
2. This new era focused on the development of materials specifically designed for biomaterials applications.
3. This section highlights key classes of materials and their evolution from commodity substances to engineered/synthesized biomaterials.

Designed Biomaterials: Silicones

- Commercial Development: While silicones were explored for years, Eugene Rochow (General Electric) pioneered their commercial scale-up and manufacture in the early 1940s.
- Low Toxicity: In his 1946 book, "The Chemistry of Silicones," Rochow anecdotally commented on the low toxicity of silicones, though without proposing medical applications.
- Early Medical Reports:
- Possibly the first report of silicones for implantation was by Lahey (1946).
- A 1954 book by McGregor, "Silicones and Their Uses," included a chapter titled "Physiological Response to Silicones," citing toxicological studies and mentioning silicone rubber applications in artificial kidneys and silicone-coated grids for dialysis membranes (Skeggs and Leonards, 1948).

Designed Biomaterials: Polyurethanes

- Invention: Polyurethane was invented by Otto Bayer and colleagues in Germany in 1937.
- Versatile Chemistry: Its intrinsic chemistry offered a wide range of synthetic options, leading to hard plastics, flexible films, or elastomers.
- Unique Property: This was the first class of polymers to exhibit rubber elasticity without covalent cross-linking.
- Early Biomedical Applications:
- 1959: Polyurethanes were explored for biomedical applications, specifically heart valves (Akutsu et al.).
- Mid-1960s: Segmented polyurethanes were developed, demonstrating both good biocompatibility and outstanding flex life in biological solutions at 37°C (Boretos and Pierce, 1967).

Designed Biomaterials: Teflon

- Discovery: DuPont chemist Roy Plunkett discovered Teflon (polytetrafluoroethylene, PTFE), a remarkably inert polymer, in 1938.
- Commercial Application: William L. Gore and his wife, Vieve, started a company in 1958 to apply Teflon for wire insulation.
- Expanded PTFE (ePTFE) - Goretex:
- 1969: Their son, Bob Gore, found that Teflon, if heated and stretched, forms a porous membrane with attractive physical and chemical properties.
- Inspiration: Bob Gore recounted showing a piece of porous Teflon tubing to a physician on a ski lift, who immediately asked for a specimen to try as a vascular prosthesis.
- Leading Material: Today, Goretex porous Teflon and similar expanded PTFEs are leading synthetic vascular grafts, widely used in various surgical and biotechnology applications.

Designed Biomaterials: Hydrogels

Designed Biomaterials: Hydrogels

1. Natural Occurrence: Hydrogels are ubiquitous in nature (e.g., bacterial biofilms, hydrated extracellular matrix, plant structures). Gelatin and agar were also known and used early in human history.

2. Modern History Traceable: The modern history of hydrogels specifically designed for medical applications is well-documented.

Designed Biomaterials: Hydrogels

PolyHEMA Discovery:

- 1936: DuPont scientists mentioned poly(2-hydroxyethyl methacrylate) (polyHEMA) as a hard, brittle, glassy polymer, without recognizing its full potential.

- 1960: Otto Wichterle and Drahoslav Lim published a paper in Nature describing the polymerization of HEMA monomer with a cross-linking agent in the presence of water and other solvents. This yielded a soft, water-swollen, elastic, clear gel, not a brittle polymer.

Designed Biomaterials: Hydrogels

Innovation: Wichterle developed an apparatus (originally from a children's construction set) for centrifugally casting the hydrogel into contact lenses. This led to the soft contact lens industry and the modern field of biomedical hydrogels.

Early Applications: Included acrylamide gels for electrophoresis, poly(vinyl alcohol) porous sponges (Ivalon) as implants, various hydrogel formulations for soft contact lenses, and alginate gels for cell encapsulation.

Designed Biomaterials: PEG

Designed Biomaterials: Poly(Ethylene Glycol)

- Definition: Poly(ethylene glycol) (PEG), also known as poly(ethylene oxide) in its high molecular weight form, can function as a hydrogel when crosslinked.
- Broad Applications: PEG has numerous other applications and implementations, warranting its own section due to widespread use.
- Low Reactivity: Its low reactivity with living organisms was known since at least 1944, when it was examined as a vehicle for intravenously administering fat-soluble hormones (Friedman).

Designed Biomaterials: PEG

Key Developments:

- Frank Davis and Colleagues (mid-1970s): Discovered that attaching PEG chains to enzymes and proteins significantly extended their functional residence time in vivo (PEGylation).
- Professor Edward Merrill (MIT, early 1980s): Concluded that surface-immobilized PEG would resist protein and cell adhesion, which his research group confirmed.
- Dr. Milton Harris (University of Alabama, Huntsville): His synthetic chemistry developments significantly accelerated the application of PEGs to a wide range of biomedical problems.

Designed Biomaterials: PLGA

Designed Biomaterials: Poly(Lactic-Glycolic Acid)

- Discovery: Originally discovered in 1833.
- Modern Synthesis: Anionic polymerization from the cyclic lactide monomer in the early 1960s made it possible to create materials with mechanical properties comparable to Dacron.
- Biodegradable Implants:
- Kulkarni et al. (1966): First publication on poly(lactic acid) in medicine, demonstrating its slow degradation after implantation in guinea pigs or rats and good toleration.
- Cutright et al. (1971): First to apply this polymer for orthopedic fixation.

Designed Biomaterials: PLGA

Related Polymers:

- Poly(glycolic acid) and copolymers of lactic and glycolic acid were subsequently developed.

Key Applications:

- Sutures: Early clinical applications, based on work by Joe Frazza and Ed Schmitt at David & Geck, Inc (1971).
- Controlled Release: Widely applied for controlled release of drugs and proteins.
- Tissue Engineering: Professor Robert Langer's group at MIT pioneered the development of these polymers in the form of porous scaffolds for tissue engineering (1993).

Designed Biomaterials: Hydroxyapatite

- Definition: Hydroxyapatite is a naturally occurring mineral, a major component of bone, and a synthesized material with wide application in medicine.
- Formulation: It can be easily made as a powder.
- Early Biomedical Application:
- Levitt et al. (1969): One of the first papers to describe biomedical applications, in which they hot-pressed hydroxyapatite powder into useful shapes for biological experimentation.
- Extensive Research: This early appreciation of hydroxyapatite's materials science aspect led to thousands of research papers.
- Mechanism: The effectiveness of ancient nacre implants (described earlier) may be due to hydroxyapatite, as nacre's calcium carbonate can transform into hydroxyapatite in phosphate solutions (Ni and Ratner, 2003).

Designed Biomaterials: Titanium

- Discovery: William Gregor (1791) extracted an impure oxide of titanium from ore.
- Commercial Extraction: After 1932, a process developed by William Kroll permitted the commercial extraction of titanium from mineral sources.
- Post-WWII Transition: At the end of World War II, titanium metallurgy methods and materials shifted from military to peacetime uses.
- Early Biomedical Use: By 1940, satisfactory results had already been achieved with titanium implants (Bothe et al., 1940).
- Major Breakthrough: The Brånemark discovery of osseointegration (discussed in the dental implants section) was the major breakthrough for using titanium in bony tissue implants.

Designed Biomaterials: Bioglass

Designed Biomaterials: Bioglass

- Significance: Bioglass is one of the first completely synthetic materials known to seamlessly bond to bone.
- Development: Developed by Professor Larry Hench and colleagues.
- Inspiration (1967): Hench, then an Assistant Professor at the University of Florida working on glass materials, was challenged by a US Army colonel returning from Vietnam to "make a material the body won't resist" for implant applications, as metals and polymers were being rejected.

Designed Biomaterials: Bioglass

The Breakthrough Moment:

- Project Funding: In October 1969, a project was funded to test if silicate-based glasses with critical amounts of Ca and P ions would be accepted by bone.
- First Experiment (Nov 1969): Hench made small rectangles of 45S5 glass (44.5 wt% SiO2), which Ted Greenlee (Assistant Professor of Orthopedic Surgery) implanted in rat femurs.
- Remarkable Result: Six weeks later, Greenlee reported that the samples would not come out of the bone, as they were strongly bonded in place. "Bioglass was born, and with the first composition studied!"
- Mechanism: Later studies by Hench using surface analysis showed that Bioglass transformed from a silicate-rich composition to a phosphate-rich structure (possibly hydroxyapatite) in biological fluids (Clark et al., 1976).

Contemporary Era: Intro

- Defining Feature: The modern era of biomaterials is characterized by biomaterials engineered to control specific biological reactions, driven by rapid developments in modern biology.
- Integration of Concepts: While first-generation biomaterials still evolve, they now incorporate concepts and approaches from later generations.
- Emerging Biological Concepts (1960s): When the field's foundations were laid, ideas like cell-surface receptors, growth factors, nuclear control of protein expression, cell attachment proteins, stem cells, and gene delivery were either controversial or undiscovered. Pioneers could not design with these in mind.
- The biomaterials community quickly embraced and exploited new ideas from biology.
- New Materials Science Ideas: Concepts like phase separation, anodization, self-assembly, surface modification, and surface analysis were rapidly assimilated into the biomaterials scientists' toolbox.

Key Ideas in Modern Biomaterials

- Protein adsorption
- Biospecific biomaterials
- Nonfouling materials
- Healing and the foreign-body reaction
- Controlled release (programmed release)
- Tissue engineering
- Immunoengineering
- Regenerative materials
- Nanotechnology

These topics are crucial to modern biomaterials science and are explored in detail in relevant literature (e.g., "Biomaterials Science: An Introduction to Materials in Medicine, fourth edition").

The field continues to evolve, constantly integrating new discoveries and approaches.

Conclusions

Evolution of the Field: Biomaterials has progressed from adventurous practices by "surgeon-heroes" (sometimes with engineers) to a field dominated by engineers, chemists, and physicists, and now into a modern era where biologists and bioengineers are key players.

Pioneers: Many individuals who pioneered the field in its formative days are still alive, offering first-hand accounts of its roots.

Preserving History: Readers are encouraged to document conversations with these pioneers to preserve the exciting stories and accidental discoveries that shaped this intellectually stimulating field.

Ongoing History: The practice of biomaterials today is deeply immersed within this continuously evolving history.