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BIOMATERIALS AND BIOCOMPATIBILITY

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BIOMATERIALS

Biomaterials is a term used to indicate materials that constitute parts of medical implants, extracorporeal devices, and disposables that have been utilized in medicine, surgery, dentistry, and veterinary medicine as well as in every aspect of patient health care. The National Institutes of Health Consensus Development Conference of November 1982 defined a biomaterial as ‘‘any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body’’ (Boretos and Eden, 1984). The common denominator in all the definitions that have been proposed for ‘‘biomaterials’’ is the undisputed recognition that biomaterials are distinct from other classes of materials because of the special biocompatibility criteria they must meet. Biomaterials are devices or materials that are used in the treatment of physiological, anatomical or biochemical disorders which cannot be corrected by other therapies or procedures. They are used for developing body implants or interfaces which interact with the living tissues and physiological systems of the patient for a significant duration. Therefore, the assessment of the overall safety of the device is of importance so as to minimize the risk to the patient treated with the device. The term biocompatibility refers to the interaction between a biomedical device and the tissues of the patient and it depends on several factors like the chemical and physical nature of its components, the types of patient tissue that will be exposed to the device and the duration of that exposure.

HISTORY

The introduction of non-biological materials into the human body was noted far back in prehistory. The remains of a human found near Kennewick, Washington, USA (often referred to as the "Kennewick Man") was dated to be 9000 years old. This individual, described by archeologists as a tall, healthy, active person, wandered through the region now known as southern Washington with a spear point embedded in his hip. It had apparently healed in and did not significantly impede his activity. This unintended implant illustrates the body's capacity to deal with implanted foreign materials. The spear point has little resemblance to modern biomaterials, but it was a tolerated foreign material implant, just the same.

Unlike the spear point described above, dental implants were devised as implants and used early in history. The Mayan people fashioned nacre teeth from sea shells in roughly 600 A.D.and apparently achieved a bone integration, basically a seamless integration into the bone (Bobbio, 1972). Similarly, an iron dental implant in a corpse dated 200 A.D. was found in Europe (Crubezy et al., 1998). This implant, too, was described as properly bone integrated. There was no materials science, biological understanding, or medicine behind these procedures. Still, their success (and longevity) is impressive and highlights two points: the forgiving nature of the human body and the pressing drive, even in prehistoric times, to address the loss of physiologic/anatomic function with an implant.

There is evidence that sutures may have been used as long as 32,000 years ago (Scott, 1983). Large wounds were closed early in history by one of two methods—cautery or sutures. Linen sutures were used by the early Egyptians. Catgut was used in the Middle Ages in Europe. Metallic sutures are first mentioned in early Greek literature. Galen of Pergamon (circa 130–200A.D.) described ligatures of gold wire.

Recent well documented history of biomaterials is also dated as old 2000 years ago, where in Romans, Chinese and Aztec used gold in dentistry. In 1816, Philip Physick, University of Pennsylvania Professor of Surgery, suggested the use of lead wire sutures noting little reaction. In 1849, J. Marion Sims, of Alabama, had a jeweler fabricate sutures of silver wire and performed many successful operations with this metal. Consider the problems that must have been experienced with sutures in eras with no knowledge of sterilization, toxicology, immunological reaction to extraneous biological materials, inflammation, and biodegradation. Yet sutures were a relatively common fabricated or manufactured biomaterial

for thousands of years. Development of aseptic surgical technique by Lister in 1860's gave pulse and momentum to all medico scientific fields including biomaterial science.

The twentieth century hence becomes a blossomed bud of biomaterials. Certain highlights in the last century are given below.

- Early 1900's: Bone plates used to fix fractures.
- 1930's: Introduction of stainless steel, cobalt chromium alloys

Turn of century was synthetic implants become available.

- 1937: Poly (methyl methacrylate) (PMMA) introduced in dentistry.
- 1938: First total hip prosthesis (P. Wiles).

In the World War II, shards of PMMA unintentionally got lodged into eyes of aviators and parachute cloth used for vascular prosthesis.

- 1940's: Polymers in medicine: PMMA bone repair; cellulose for dialysis; nylon sutures.
- 1952: Mechanical heart valve.
- 1953: Dacron (polymer fiber) vascular grafts.
- 1958: Cemented (PMMA) joint replacement.
- 1958: Rob suggests Dacron Fabrics can be used to fabricate an arterial prosthetic.
- 1960: First commercial heart valves.
- 1960: Charnley uses PMMA, ultrahigh-molecular-weight polyethylene, and stainless steel for total hip replacement.

Late 1960 – early 1970's biomaterial field solidified.

- 1975: Society for Biomaterials formed.
- 1970's: PEO (polyethylene oxide) protein resistant thin film coating.
- 1976: FDA amendment governing testing & production of biomaterials /devices.
- 1976: Artificial heart (W. Kolff, Prof. Emeritus U of U).

DEVELOPMENT THROUGH AGES

- **First Generation Implants**

These were actually "ad hoc" implants, specified by physicians using common and borrowed materials and most successes were accidental rather than by design.

Eg: gold fillings, wooden teeth, PMMA dental prosthesis, steel, gold, ivory, etc., bone plates, glass eyes and other body parts, dacron and parachute cloth vascular implants.

- **Second Generation Implants**

Here engineered implants using common and borrowed materials were performed, many new materials are developed through collaborations of physicians and engineers, built on first generation experiences and used advances in materials science (from other fields).

Eg: titanium alloy dental and orthopaedic implants, cobalt-chromium-molybdinum orthopaedic implants, UHMW polyethylene bearing surfaces for total joint replacements, heart valves and pacemakers.

- **Third Generation Implants**

Bioengineering techniques and knowledge are applied on implants, modified and devised new polymeric devices, many under development.

Eg: tissue engineered implants designed to regrow rather than replace tissues, Integra Life Sciences artificial skin, Genzyme cartilage cell procedure, some resorbable bone repair cements, genetically engineered "biological" components (Genetics Institute and Creative Biomolecules BMPs).

CLASSIFICATION OF BIOMATERIALS

Different classifications of biomaterials are made based on different criteria.
According to the **chemical composition**, these are broadly classified as.

- **Metals**

Metals have been used almost exclusively for load-bearing implants, such as hip and knee prostheses and fracture fixation wires, pins, screws, and plates. Metals have also been used as parts of artificial heart valves, as vascular stents, and as pacemaker leads. Although pure metals are sometimes used, alloys (metals containing two or more elements) frequently provide improvement in material properties, such as strength and corrosion resistance. Three material groups dominate biomedical metals: 316L stainless steel, gold, nickel-titanium alloy, cobalt-chromium alloy, cobalt-chromium-molybdenum alloy and pure titanium and titanium alloys are the most commonly metals used as biomaterials.

The main considerations in selecting metals and alloys for biomedical applications are biocompatibility, appropriate mechanical properties, corrosion resistance, and reasonable cost. The main advantages of metals are that they are strong and are resistant to fatigue degradation. They have shape memory and can be sterilized easily before use. The main

disadvantage is that metal can corrode due to chemical reaction with the body enzymes and acids. It also can cause metal ion toxicity in the body.

- **Polymers (natural and artificial)**

Polymers are the most widely used materials in biomedical applications. They are the materials of choice for cardiovascular devices as well as for replacement and augmentation of various soft tissues. Polymers also are used in drug delivery systems, in diagnostic aids, and as a scaffolding material for tissue engineering applications. Examples of current applications include vascular grafts, heart valves, artificial hearts, breast implants, contact lenses, intraocular lenses, components of extracorporeal oxygenators, dialyzers and plasmapheresis units, coatings for pharmaceutical tablets and capsules, sutures, adhesives, and blood substitutes Polymers include collagen, nylon and silicones. They are used in tissue repair, heart valves and breast implants.

Polymers can be manufactured and modified easily to adapt to their use. They are also biodegradable, which is both an advantage and a disadvantage. Due to the intensive interaction with the body, they can leach, leading to wear and tear. They also can absorb important nutrients and water from the blood.

- **Ceramics**

Ceramics and glasses are used as components of hip implants, dental implants, middle ear implants, and heart valves. These biomaterials have been used less extensively than either metals or polymers. Alumina, zirconia and pyrolitic carbon are some of the ceramics used as biomaterials in applications such as orthopedic and dental implants.

The main advantage is that they are strong and chemically inert. They have high compressive strength, which is necessary for bone implants. Some ceramic materials are also biodegradable. Difficulty in manufacturing forms the main disadvantage. They also can minimize bone ingrowth. Sometimes, implants can loosen over time and become dislodged.

- **Composites**

Composite materials are solids which contain two or more distinct constituent materials or phases, on a scale larger than the atomic. The term “composite” is usually reserved for those materials in which the distinct phases are separated on a scale larger than the atomic, and in which properties such as the elastic modulus are significantly altered in comparison with

those of a homogeneous material. Accordingly, reinforced plastics such as fiberglass as well as natural materials such as bone are viewed as composite materials, but alloys such as brass are not. A foam is a composite in which one phase is empty space. Natural biological materials tend to be composites. Natural composites include bone, wood, dentin, cartilage, and skin. Natural foams include lung, cancellous bone, and wood. Natural composites often exhibit hierarchical structures in which particulate, porous, and fibrous structural features are seen on different micro-scales [Katz, 1980; Lakes, 1993]. In this segment, composite material fundamentals and applications in biomaterials [Park and Lakes, 1986] are explored. Composite materials offer a variety of advantages in comparison with homogeneous materials. These include the ability for the scientist or engineer to exercise considerable control over material properties. There is the potential for stiff, strong, lightweight materials as well as for highly resilient and compliant materials. In biomaterials, it is important that each constituent of the composite be biocompatible. Moreover, the interface between constituents should not be degraded by the body environment.

According to the mechanisms of interaction inside body or the functional host response initiation, a novel functional classification is made, which includes.

- **Bio inert Biomaterials**

The term bio inert refers to any material that once placed in the human body has minimal interaction with its surrounding tissue. Generally a fibrous capsule might form around bio inert implants hence its bio functionality relies on tissue integration through the implant.

Examples of these are stainless steel, titanium, alumina, partially stabilized zirconia, and ultra-high molecular weight polyethylene.

- **Bioactive Biomaterials**

Bioactive refers to a material, which upon being placed within the human body interacts with the surrounding bone and in some cases, even soft tissue. This occurs through a time–dependent kinetic modification of the surface, triggered by their implantation within the living bone. An ion-exchange reaction between the bioactive implant and the surrounding body fluids-results in the formation of a biologically active carbonate apatite (CHAp) layer on the implant that is chemically and crystallographically equivalent to the mineral phase in bone.

Prime examples of these materials are synthetic hydroxyapatite [Ca_{10} $(PO_4)_6(OH)_2$], glass ceramic and bioglass.

- **Bio resorbable Biomaterials**

Bio resorbable refers to a material that upon placement within the human body starts to dissolve and slowly replaced by advancing tissue (such as bone).

Common examples of bio resorbable materials are tricalcium phosphate [Ca_3 $(PO_4)_2$] and polylactic- polyglycolic acid copolymers. Calcium oxide, calcium carbonate and gypsum are other common materials that have been utilized during the last three decades.

IMPORTANCE

The need for biomaterials stems from an inability to treat many diseases, injuries and conditions with other therapies or procedures.

- Replacement of body part that has lost function (total hip, heart)
- Correct abnormalities (spinal rod)
- Improve function (pacemaker, stent)
- Assist in healing (structural, pharmaceutical effects: sutures, drug release)

Apart from improvising the quality and longevity of life, biomaterial science is a very vast field of multidisciplinary interventions. Nevertheless mention it is a billion dollar industry, which grows at minimum 5-7% per annum.

CONTEMPLATION

Since biomaterials are used inside the body, and are used as a supporting element to improve the quality of life and prolong the life, it should be designed thinking few considerations:

- ✓ Contact time period inside body (A tongue depressor may be used for a few seconds but an artificial lens goes over 30 years inside)
- ✓ Adequate mechanical properties (strength, stiffness, and fatigue properties); appropriate optical properties (used in the eye, skin, or tooth); appropriate density; manufacturability; and appropriate engineering design Integration into surrounding tissue without extensive inflammatory response or support of infection
- ✓ Host response to the material
- ✓ Immune acceptance
- ✓ Biocompatibility

- ✓ Bio stability
- ✓ Economics and utility

BIOCOMPATIBILITY

Biocompatibility is defined as the property of being biologically compatible by not producing a toxic, injurious, or immunological response in living tissue. The human body has an extraordinary ability to be able to tell whether an object is foreign or not. This is part of the body's protection against invasion from an outside organism. If a substance is placed in the body and the body can tell it is foreign, then an immune system response will be generated. When an object is incorporated into the body without any immune responses it is said to be biocompatible. In order for a device to be biocompatible, it must follow a very stringent set of demands from the body.

The device must be very strong so it does not break inside the body. Depending on the circumstances, it may need to be either very hard or very flexible. Anything placed into the body must be able to take a constant physical beating from one's body. For instance, the valves in a heart open and close about 70 - 80 times a minute. Over the course of years and years this adds up to millions of pumps. If the artificial valve cannot meet these standards and fails, the person will die.

The term biocompatibility refers to the interaction between a biomedical device and the tissues of the patient and it depends on several factors like the chemical and physical nature of its components, the types of patient tissue that will be exposed to the device and the duration of that exposure.

Medical devices and their component materials may leach compounds or have surface characteristics that may produce undesirable effects when used clinically. The selection and evaluation of materials and devices intended for use in humans requires a structured program of assessment to establish biocompatibility and safety. Current regulations, whether in accordance with the U.S. Food and Drug Administration (FDA), the International Organization for Standardization (ISO), or the Japanese Ministry of Health and Welfare (JMHW), require that manufacturers conduct adequate safety testing of their finished devices through pre-clinical and clinical phases as part of the regulatory clearance process.

The ISO, JMHW and FDA guidelines provide a general testing framework to aid manufacturers in the assessment of device biocompatibility. The number and type of specific safety tests required to assess product safety and compliance are dependent on the individual characteristics of the device, its component materials, and its intended clinical use.

INTERNATIONAL STANDARDS

The development of a risk management system for biomaterials was developed in the framework of the following international standards.

- ASTM Standard
- ISO 14971 « Medical devices – Risk management
- ISO 10993 « Biological evaluation of Medical Devices which specifies requirements and gives guidance on procedures to be followed in the evaluation of the potential for medical (or dental) materials to cause adverse health effect.

The ISO 10993 standard plays an important role in the assessment of biocompatibility of a medical device. In principle a great number of tests have to be undertaken depending on the intended use of the medical device.

The standard describes tests on toxicity, carcinogenicity, haemocompatibility, etc. Some of these tests are simple in-vitro tests, while others require extensive animal experiments. This standard gives a more precise description of non-invasive and invasive use. In general three categories of contact with a human being are distinguished.

1) Surface devices, where contact is made with the skin, intact mucosal membranes and breached or compromised surfaces, for example ECG electrodes
2) External communicating devices, where indirect contact is made with blood, tissue or bone, for example dental filling materials.
3) Implant devices, where direct contact is made with blood, tissue or bone, for example breast implants.

Depending on the time table and the category the necessary test are determined.

In ISO 10993 the specificity of nano-biomaterials is not taken into account.

- ISO 13121 « Nano materials used in biomaterial science

Nano materials are well suited for targeted drug delivery, molecular diagnostics, and imaging applications (both magnetic resonance imaging and X-ray imaging). Nano porous materials

will have applications in implants, as membranes (for example, for dialysis machines), and also in drug delivery. Nanostructured materials can enhance the biocompatibility and mechanical properties of medical devices, whereas drugs and nanostructured polymers can be combined to control the rate at which the drug is released in yet another drug-delivery application. The unique mechanical properties of nanostructured and Nano composite materials (such as high strength and shape-memory properties) are also invaluable for implants and catheter devices (Helmus, 2007).

During the development of the biological testing strategy of a product, it is necessary to discuss the regulatory requirements for the evaluation of the product. Risk assessments may be obtained by testing according to recognized guidelines, including those described in FDAG95-1, ISO 10993, and Japanese Guidelines for Basic Biological Tests for Medical Devices and Materials. Other testing guidelines may include OECD, ASTM, USP, BP, etc. Risk assessments can most accurately be predicted through the diligent use of these methods. The testing strategy developed for the medical devices should be developed to immaculate the intended final use of the product and to utilize the most diligent pathway while minimizing the use of laboratory animals.

Hence, biocompatibility can be redefined as.
Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy.

Biomaterials are subjected to a battery of *in vitro* and *in vivo* tests described under the collective heading of biocompatibility testing. The *in vivo* tests based on International Organisation of Standardisation (ISO) standard ISO 10993-1: 1992 done directly on the biomaterials comprise systemic acute and chronic toxicity tests, short term and long term implantation tests, sensitisation tests and carcinogenicity tests.

CONCLUSION

Biomaterial science is a very vast field of study, which is highly evolved, yet potentially unexplored. Biocompatibility plays the key role in the development of medical devices, even for scientific purposes. The complete medical device must be judged for its biocompatibility

and one must keep in mind that there is no list of biocompatible materials, although a preferred list exists. Newer materials are keeping on evolving and a new paradigm will hopefully be set up for the biocompatibility platform.

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