Module -3

Hard Tissue Replacements: Bone repair and joint implants-long bone repair and joint replacements, dental implants- effects of material selection, effects of surface properties, surface chemistry.

Preservation Techniques For Biomaterials: Phase behavior, nonfreezing storage-hypothermic, freeze-thaw technology, freeze drying, and vitrification.

Artificial Organs: Introduction: Substitutive medicine, outlook for organ replacement, design consideration, evaluation process.

HARD TISSUE REPLACEMENTS

LONG BONE AND JOINT REPLACEMENT REPAIR

- Nature provides different types of mechanisms to repair fractures in order to be able to cope with different mechanical environments about a For example, incomplete fractures (cracks), which only allow micromotion between the fracture fragments, heal with a small amount of fracture-line callus, known as primary healing.
- In contrast, complete fractures which are unstable, and therefore generate macromotion, heal with a voluminous callus stemming from the sides of the bone, known as secondary healing
- The goals of fracture treatment are obtaining rapid healing, restoring function, and preserving cosmesis without general or local complications.
- Implicit in the selection of the treatment method is the need to avoid potentially deleterious conditions, for example, the presence of excessive motion between bone fragments which may delay or prevent fracture healing.
- **Wires:**
- Surgical wires are used to reattach large fragments of bone, like the greater trochanter, which is often detached during total hip replacement.

- They are also used to provide additional stability in long-oblique or spiral fractures of long bones which have already been stabilized by other means.
- Braided multistrain (multifilament) wire is an attractive alternative because it has a similar tensile strength than a monofilament wire of equal diameter, but more flexibility and higher fatigue strength.

- **Pins:**
- Straight wires are called Steinmann pins; however if the pin diameter is less than 2.38 mm, it is called Kirschner wire.
- They are widely used primarily to hold fragments of bones together provisionally or permanently and to guide large screws during insertion.
- Screws are the most widely used devices for fixation of bone fragments. There are two types of bone screws: (1) cortical bone screws, which have small threads, and (2) cancellous screws, which have large threads to get more thread-to-bone contact. They may have either V or buttress threads
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- The cortical screws are subclassified further according to their ability to penetrate, into self-tapping and nonself-tapping.
- The self-tapping screws have cutting flutes which thread the pilot drill-hole during insertion. In contrast, the non-self-tapping screws require a tapped pilot drill-hole for insertion.

- The holding power of screws can be affected by the size of the pilot drill-hole, the depth of screw engagement, the outside diameter of the screw, and quality of the bone
- Therefore, the selection of the screw type should be based on the assessment of the quality of the bone at the time of insertion. Under identical conditions, self-tapping screws provide a slightly greater holding power than non-self-tapping screw.
- Screw pullout strength varies with time after insertion in vivo, and it depends on the growth of bone into the screw threads and/or resorption of the surrounding bone.
- The bone immediately adjacent to the screw often undergoes necrosis initially, but if the screw is firmly fixed, when the bone revascularizes, permanent secure fixation may be achieved.
- This is particularly true for titanium alloy screws or screws with a roughened thread surface, with which bone ongrowth results in an increase in removal torque.
- **Plates**
- Compression between the fracture fragments can be achieved with a special type of plate called a dynamic compression plate (DCP).
- The dynamic compression plate has elliptic shape screw holes with its long axis oriented parallel to that of the plate. The screw hole has a sliding ramp to the long axis of the plate.
- The principle of the dynamic compression plate. Bone plates are often contoured in the operating room in order to conform to an irregular bone shape to achieve maximum contact of the fracture fragments. However, excessive bending decreases the service life of the plate.
- The most common failure modes of a bone plate-screw fixation are screw loosening and plate failure. The latter typically occurs through a screw hole due to fatigue and/or crevice corrosion.

- In the vicinity of the joints, where the diameter of long bones is wider, the cortex thinner, and cancellous bone abundant, plates are often used as a buttress or retaining wall. A buttress plate applies force to the bone perpendicular to the surface of the plate, and prevents shearing or sliding at the fracture site.
- Buttress plates are designed to fit specific anatomic locations and often incorporate other methods of fixation besides cortical or cancellous screws, for example, a large lag screw or an I-beam.
- For the fusion of vertebral bodies following diskectomy, spinal plates are used along with bone grafts. These plates are secured to the vertebral bodies using screws .
- Similar approaches have been employed to restore stability in the thoracolumbar and cervical spine region as well.

- **Intramedullary Nails**

- Intramedullary devices (IM nails) are used as internal struts to stabilize long bone fractures. IM nails are also used for fixation of femoral neck or intertrochanteric bone fractures; however, this application requires the addition of long screws.

- A gamut of designs are available, going from solid to cylindrical, with shapes such as cloverleaf, diamond, and “C” (slotted cylinders).

DENTAL IMPLANTS

- **Metals and Alloys**

- more suitable surface for tissue integration. Early work by Johansson and coworkers [1989] reported that sputtercoated Ti alloy surfaces resulted in wide (5000 Å) amorphous zones devoid of collagen filaments, compared to the thinner 200–400 Å collagen-free amorphous zone surrounding cpTi surfaces.

- Subsequent studies revealed differences in the oxide characteristics between these sputtercoated cpTi and Ti alloy surfaces used for histologic and ultrastructural interfacial analyses.
- Significant surface contamination and the presence of V was observed in the Ti alloy surface, which led to an overall woven bone interface compared to the cpTi surface which had a more compact bone interface.
- **Ceramics and Ceramic Coatings** The use of single crystal sapphire or Al2O3 ceramic implants has remained an important component in the dental implant field.
- Although this material demonstrates excellent biologic compatibility, implants fabricated from Al2O3 have not reached a high degree of popularity in the United States.
- Morphologic analyses of the soft tissue interface with Al2O3 revealed a hemidesmosomal external lamina attachment adjacent to the junctional epithelium—implant interface.
- This ultrastructural description is often used for comparison purposes when determining the extent of soft tissue interaction with dental implants.

EFFECTS OF MATERIAL SELECTION

- The cellular events which take place and lead to the interfacial ultrastructure with bone tissue and ceramic surfaces are under current investigation.
- Based upon preliminary findings, the advantageous properties of HA coatings do not appear to be related to recruitment of additional cells during the early attachment phase of healing.
- Although recent work indicated that bone cells and tissue form normal cellular focal contacts during attachment to HA coatings, the level of initial in vitro attachment generally only approximates that observed with Ti

- Rather, the mechanisms for the enhanced in vitro cell responses appear to be related, to a certain degree, to the degradation properties and release of Ca+2 and PO–3 4 ions into the biologic milieu.
- This surface corrosion is associated with highly degradable amorphous components of the coating and leads to surface irregularities which may enhance the quality of cell adhesion to these roughened.
- Cellular events which occur following attachment may be influenced by the nature of the ceramic surface.
- Emerging evidence from a number of laboratories suggests that cellularmediated events, including proliferation, matrix expression, and bone formation are enhanced following attachment to HA coatings and appear to be related to the gene expression of osteoblasts when cultured on different ceramic materials.
- **Joint Replacements**
- Our ability to replace damaged joints with prosthetic implants has brought relief to millions of patients who would otherwise have been severely limited in their most basic activities and doomed to a life in pain.
- It is estimated that about 16 million people in the U.S. are affected by osteoarthritis, one of the various conditions that may cause joint degeneration and may lead a patient to a total joint replacement.
- Bone Plates: (a) dynamic compression plate, (b) hybrid compression plate (lower part has dynamic compression screw holes), (c) reconstruction bone plate (easy contouring), (d) buttress bone plate, (e) L shaped buttress plate, (f) nail plate (for condylar fracture), and (g) dynamic compression hip screw. Degeneration is the end-stage of a process of destruction of the articular cartilage, which results in severe pain, loss of motion, and occasionally, an angular deformity of the extremity .
- Unlike bone, cartilage has a very limited capacity for repair.

- Therefore, when exposed to a severe mechanical, chemical, or metabolic injury, the damage is permanent and often progressive.
- Under normal conditions, the functions of cartilage are to provide a congruent articulation between bones, to transmit load across the joint, and to allow low-friction movements between opposing joint surfaces.
- The sophisticated way in which these functions are performed becomes evident from some of the mechanical characteristics of normal cartilage.
- For example, due to the leverage geometry of the muscles and the dynamic nature of human activity, the cartilage of the hip is exposed to about eight times body weight during fast walking
- Over a period of 10 years, an active person may subject the cartilage of the hip to more than 17 million weight bearing cycles From the point of view of the optimal lubrication provided by synovial fluid, cartilage's extremely low frictional resistance makes it 15 times easier to move opposing joint surfaces than to move an ice-skate on ice.
- Cartilage functions as a unit with subchondral bone, which contributes to shock absorption by undergoing viscoelastic deformation of its fine trabecular structure.
- Although some joints, like the hip, are intrinsically stable by virtue of their shape, the majority require an elaborate combination of ligaments, meniscus, tendons, and muscles for stability.
- Because of the large multidirectional forces that pass through the joint, its stability is a dynamic process
- Receptors within the ligaments fire when stretched during motion, producing an integrated muscular contraction that provides stability for that specific displacement. Therefore, the ligaments are not passive joint restraints as once believed.

- The extreme complexity and high level of performance of biologic joints determine the standard to be met by artificial implants.
- Total joint replacements are permanent implants, unlike those used to treat fractures, and the extensive bone and cartilage removed during implantation makes this procedure irreversible.
- Intramedullary devices: (a) Gross-Kempf (slotted), (b) Uniflex (Ti alloy, slotted), (c) Kuntscher, (d) Samson, (e) Harris, (f) Brooker-Wills distal locking pin, and (g) Enders pins.
- The design of an implant for joint replacement should be based on the kinematics and dynamic load transfer characteristic of the joint.
- The material properties shape, and methods used for fixation of the implant to the patient determines the load transfer characteristics. This is one of the most important elements that determine long-term survival of the implant, since bone responds to changes in load transfer with a remodeling process, mentioned earlier as Wollff's law.
- Overloading the implant-bone interface or shielding it from load transfer may result in bone resorption and subsequent loosening of the implant
- The articulating surfaces of the joint should function with minimum friction and produce the least amount of wear products

EFFECTS OF SUFACE PROPERTIES

- Effects of Surface Properties Surface Topography The effects of surface topography are different than the overall three-dimensional design or geometry of the implant,
- This important consideration in overall biologic response to implants is discussed later in this chapter. In this discussion the concept of surface topography refers to the surface texture on a microlevel.

- It is on this microscopic level that the intimate cell and tissue interactions leading. The effects of surface topography on in vitro and in vivo cell and tissue responses have been a field of intense study in recent years.
- The overall goal of these studies is to identify surface topographies which mimic the natural substrata in order to permit tissue integration and improve clinical performance of the implant. In terms of cell attachment,
- Established that levels of short-term osteoblast cell attachment were higher on rough compared to smooth surfaces and cell morphology was directly related to the nature of the underlying substrate.
- After initial attachment, in many cases, cells of various origin often take on the morphology of the substrate as shown in Fig. 44.15. Increased surface roughness produced by such techniques as sand or grit blasting or by rough polishing, provided the rugosity necessary for optimum cell behavior.

SURFACE CHEMISTRY

- Depending upon the purity of the autoclave water, contaminants have been observed on the metal oxide and are correlated with poor tissue responses. The role of multiple sterilization regimens on the practice of implant utilization is also under scrutiny.
- Many implants and especially bone plate systems are designed for repackaging if the kit is not exhausted. However, early evidence indicates that this practice is faulty and, depending on the method of sterilization, may affect the integrity of the metal oxide surface chemistry.
- In vitro experiments have verified that multiple-steam-autoclaved and ethylene-oxide-treated implant surfaces adversely affected cellular and morphologic integration.
- However, the effects of these treatments on long-term biological responses including in vivo situations remain to be clarified. Other more recently introduced techniques such as radiofrequency argon plasma cleaning treatments have succeeded in altering metal oxide chemistry.

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Other more recently introduced techniques such as radiofrequency argon plasma cleaning treatments have succeeded in altering metal oxide chemistry and. Numerous studies have demonstrated that PC treatments produce a relatively contaminant-free surface with improved surface energy (wettability), but conflicting biologic results have been reported with these surfaces. Recent in vitro studies have demonstrated that these highly energetic surfaces do not necessarily improve cellular responses such as attachment and cell expression. This has been confirmed by in vivo studies which indicate that the overall histologic and ultrastructural morphology of the bone-implant interface is similar for plasma-cleaned and dry-heat-sterilized implant .Another promising technique for the sterilization of implant materials is the exposure of the implant surface to ultraviolet light or gamma irradiation. Both these methods of sterilization produce a relatively contaminant-free thin oxide layer which fosters high levels of cell attachment and inflammatory-free long-term in vivo. Currently, gamma irradiation procedures are widely used for the sterilization of metallic dental implant devices.

PRESERVATION TECHNIQUES OF BIOMATERIALS

PHASE BEHAVIOR

- Crystallization is one example of this type of phase transformation and is a **two-step process of nucleation of the new phase and its subsequent growth.** If the formation of the new phase is catalyzed from the surface of foreign particles or a substrate, the growth process is triggered by heterogeneous nucleation (THET).

- If, however, the new phase develops from the clustering of individual water molecules, **growth of the new phase occurs from homogeneous nucleation (THOM)** .

- The latter type of nucleation requires higher activation energies than heterogeneous nucleation and thus occurs at lower temperatures.
- The melting-temperature curve shows the melting-point depression of a crystalline sample relative to solute concentration.
- The glass-transition curves signifies the temperatures for which a **supercooled solution** becomes glassy during cooling. The final curve in demonstrates the devitrification temperature profile and illustrates the conditions for which a substance may experience crystallization damage during warming.
- For glasslike solids, damage is incurred as the glass transforms to a crystalline form at TD, while for previously **crystalline or partially vitrified solids, recrystallization (the coalescence of small crystals during warming) produces damage.**

NON-FREEZING STORAGE

- There are essentially **two techniques** for hypothermic preservation of organs for subsequent transplantation. **The first is static cold storage** by ice immersion at ~4°C—to reduce metabolism as much as possible without the formation of deleterious ice crystals
- The second procedure is **continuous cold machine perfusion** at ~10°C to provide diminished metabolism and to remove deleterious end products.
- The perfusate used for static cold storage mimics the intracellular ionic composition of the organ and has impermeant solutes added to prevent cell swelling.
- However, for perfusion preservation techniques in general, modified plasma or solutions of plasma-like composition usually have been preferred. This is presumably due to the slightly higher temperatures used in perfusion techniques that permit some degree of metabolism to occur during storage.

FREEZE DRYING

- Lyophilization is a dual stage process that consists of rapidly cooling the liquid material to its solid form and subsequent drying (or removing) of the solidified solvent. The intricacies of the procedures employed directly influence the shelf life of the final dehydrated product.
- The drying stage of the process utilizes vacuum sublimation (transformation of a solid phase directly to the vapor phase) and may itself consist of multiple steps. The complexities of the drying procedure are determined by the continuity of the ice phase throughout the frozen specimen that the quality of the final lyophilized product partially depends on the freezing protocol experienced by the original sample,
- the size and distribution of the resultant ice crystals, the degree of heterogeneity, the presence or absence of amorphous regions, and the conditions imposed on the sample during drying.
- As one might expect, these factors can produce differentiations between the desired goals of the freeze-drying process and the actual final product. The effects of the freezing protocol and the size and distribution of the resultant crystals are important for the reasons discussed previously
- It should be mentioned that in the case of protein lyophilization, carbohydrates are often added for protection, while for cells, glycerol is a common lyoprotectant.

VITRIFICATION

- It requires the rapid cooling of the liquid to the glass-transition temperature TG and is most easily achieved in high-viscosity liquids.
- The molecular configuration of the supercooled liquid ($T \geq TG$) is the same as that of the glass ($T \leq TG$). Hence rapid cooling is necessary to prevent the supercooled liquid molecules from reorganizing into a regular (e.g., lattice) configuration.

- Vitrification is a second-order phase transition. Hence, by definition, the specific volumes of both phases (near TG) are identical, although the thermodynamic property values.
- The difficulty in successfully vitrifying a material lies in reaching its glass transition temperature TG prior to crystal formation. Hence reducing the distance between TM and TG by increasing the solute concentration increases the probability that a given liquid will form a glass. Two alternative ways to achieve glassy state are
- (1) to cool biomaterials at ultrarapid rates such that TG is reached before nucleation can proceed and
- (2) to increase the pressure of the system such that the intersection of THOM and TG occurs at lower CPA concentrations .
- Since glass formation circumvents the deleterious effects of freeze injury during cooling, it is becoming an increasingly important biomaterial storage technique.

FREEZE THAW TECHNOLOGY

- In work with sperm, they were the first to report the protective effects of additives or cryoprotectant agents (CPAs), i.e., glycerol, on biomaterials at low temperatures.
- The mechanisms by which CPAs protect cells from freeze injury are of fundamental importance but are, unfortunately poorly understood. There are four major protective actions of these compounds.
- First, CPAs act to stabilize the proteins of biomaterials under low-temperature conditions. Experimental evidence indicates that for cells, this effect results from the interaction of sugars with the polar head groups of phospholipids.

- Second, CPAs lower the electrolyte concentration of the suspending medium of the cell at a given temperature by altering the phase relationship during cooling.
- Third, CPAs reduce the temperature at which cells undergo lethal intracellular ice formation.
- Fourth, CPAs promote the formation of the vitreous, rather than crystalline, phases inside the cell during cooling and help prevent intracellular ice formation.

ARTIFICIAL ORGANS

Substitutive medicine

- The fundamental tenet of substitutive medicine is that beyond a certain stage of failure, it is more effective to remove and replace a malfunctioning organ than to seek in vain to cure it. This ambitious proposition is not easy to accept.
- It goes against the grain of holistic views of the integrity of the person.
- It seems at odds with the main stream of twentieth-century scientific medicine, which strives to elucidate pathophysiologic mechanisms at the cellular and molecular level and then to correct them through a specific biochemical key.
- The technology of organ replacement rivals that of space travel in complexity and fanfare and strikes the O popular imagination by its daring, its triumphs, and its excesses.
- Although the artificial organ approach does not reach the fundamental objective of medicine, which is to understand and correct the disease process, it is considerably more effective than drug therapy or corrective surgery in the treatment of many conditions, e.g., cardiac valve disease, heart block, malignant arrhythmia, arterial obstruction, cataract.

- A priori, functional disabilities due to the destruction or wear of body parts can be addressed in two ways: the implantation of prosthetic devices or the transplantation of natural organs.
- For a natural organ transplant, we typically borrow a spare part from a living being or from an equally generous donor who before death volunteered to help those suffering from terminal organ failure.
- Transplanted organs benefit from refinements acquired over thousands of years of evolution.
- They are overdesigned, which means they will provide sufficient functional support even though the donated part may not be in perfect condition at the time of transfer to another person.
- They have the same shape and the same attachment needs as the body part they replace which means that surgical techniques are straightforward. The critical problem is the shortage of donors, and therefore only a small minority of patients currently benefit from this approach.
- Artificial organs have different limitations. Seen on the scale of human evolution, they are still primitive devices, tested for 40 years at most.
- Yet they have transformed the prognosis of many heretofore fatal diseases, which are now allowed to evolve past what used to be their natural termination point.
- In order to design artificial organs, inventive engineers, physiologists, and surgeons think in terms of functional results, not anatomical structures. As a result, artificial organs have but a distant similarity to natural ones.
- They are mostly made of synthetic materials (often called biomaterials) which do not exist in nature.
- They use different mechanical, electrical, or chemical processes to achieve the same functional objectives as natural organs.
- They adapt but imperfectly to the changing demands of human activity. They cannot easily accommodate body growth and therefore are more beneficial to adults than to children.

- Most critically, artificial organs, as is the case for all machines, have a limited service expectancy because of friction, wear, or decay of construction materials in the warm, humid, and corrosive environment of the human body.
- Such considerations limit their use to patients whose life expectancy matches the expected service life of the replacement part or to clinical situations where repeated implantations are technically feasible.
- In spite of these obstacles, the astonishing reality is that millions of people are currently alive thanks to cardiac pacemakers, cardiac valves, artificial kidneys, or hydrocephalus drainage systems, all of which address life-threatening conditions.
- An even larger number of people enjoy the benefits of hip and knee prostheses, vascular grafts, intraocular lenses, and dental implants, which correct dysfunction, pain, inconvenience, or merely appearance.
- In short, the clinical demonstration of the central dogma of substitutive medicine over the span of two generations can be viewed demographically as the first step in a evolutionary jump which humans cannot yet fully appreciate.
- Hybrid artificial organs, or bioartificial organs, are more recent systems which include living elements (organelles, cells, or tissues) as part of a device made of synthetic materials.
- They integrate the technology of natural organ transplantation and the refinements which living structures have gained through millions of years of evolution with the purposeful design approach of engineering science and the promises of newly developed synthetic materials
- Depending upon medical needs and anticipated duration of use, artificial organs can be located outside of the body yet attached to it (paracorporeal prostheses or assist devices) or implanted inside the body in a appropriate location (internal artificial organs or implants).
- The application of artificial organs may be temporary, i.e., a bridge procedure to sustain life or a specific biologic activity while waiting for either recovery of natural function (e.g., the heart-lung machine), or permanent organ replacement (e.g., left ventricular assist devices). It

can be intermittent and repeated at intervals over extended periods of time when there is no biologic necessity for continuous replacement of the missing body functions (e.g., artificial kidney).

- It can pretend to be permanent, at least within the limits of a finite life span. Up to 1950, organ replacement technology was relatively crude and unimaginative.
- Wooden legs, corrective glasses, and dental prostheses formed the bulk of artificial organs.
- Blood transfusion was the only accepted form of transplantation of living tissue. Suddenly, within a decade, the artificial kidney, the heart-lung machine, the cardiac pacemaker, the arterial graft, the prosthetic cardiac valve, and the artificial hip joint provided the first sophisticated examples of engineering in medicine.
- More recently, the membrane lung, the implantable lens, finger and tendon prostheses, total knee replacements, and soft-tissue implants for maxillo-facial, ear, or mammary reconstruction have reached the stage of broad clinical application.
- Ventricular assist devices and the total artificial heart have been extensively tested in animals and validated for clinical evaluation. Artificial skin is increasingly used in the treatment of ulcers and burns.
- Soft- and hard-tissue substitutes function effectively for several years. Sexual and sensory prostheses offer promises for the replacement of complex human functions.
- Interfacing of devices with the peripheral and central nervous systems appears as promising today as cardiovascular devices were 30 years ago.
- Perhaps the brightest future belongs to “information prostheses” which bring to the human body, signals which the organism can no longer generate by itself (e.g., pacemaker functions), signals which need to be modulated differently to correct a disease state (e.g., electronic blood pressure regulators) or signals which cannot be perceived by the nervous system through its usual channels of information gathering (e.g., artificial eye or artificial ear).

Outlook for Organ Replacement

- 1.Cellular transplants for continuing secretion of bioactive substances (e.g., transplants of insulinproducing xenograft tissue protected against immune rejection by permselective envelopes)
- 2. Composites of synthetic materials with living cells (often called organoids) to accelerate implant integration within the body (e.g. endothelial cell-lined polymer conduits designed for vascular grafts)
- 3. Replacement parts in which natural tissue regeneration is activated by the presence of supportive cells (e.g., Schwann cell-seeded nerve guidance channels)
- 4. Vehicles for gene therapy in which continued gene expression is enhanced by a synthetic polymer substrate with appropriate mechanical, chemical, or drug release properties (e.g., epicardial transplants of genetically modified skeletal or cardiac muscle grown on a distensible polymer matrix)

Design Considerations

- Natural organ transplants, if ideally preserved, should be able to fulfill all functions of the original body part except for those mediated by the nervous system, since a transplanted organ is by definition a denervated structure.
- In actuality, transplants always present some degree of ischemic damage caused by interruption of the blood supply during transfer from donor to recipient.
- In the long run, transplanted organs may also exhibit functional alterations because of cell or tissue damage associated with an underlying systemic disease.

- They may be damaged by the immuno-suppression protocol, which at the current stage is needed for all organ replacements except for autografts, identical-twin homografts, and some types of fetal tissue transplants.
- The second-order limitations of transplanted organs are usually ignored, and the assumption is made that all original functions are restored in the recipient.
- Artificial organs, however, can only replace those bodily functions which have been incorporated into their design because these functions were scientifically described and known to be important.
- Therefore, in the design of an artificial organ, the first task is to establish the specifications for the device, i.e., to describe in quantitative terms the function or functions which must be fulfilled by a human-made construct and the physical constraints that apply because the device must interface with the human body.
- Each human organ fulfills multiple functions of unequal importance in terms of survival. Consequently, it is critical to distinguish the essential functions which must be incorporated into an effective spare part from those which can be neglected.

Evaluation process

- The evaluation of an artificial organ typically is done in six phases:
- 1. In vitro bench testing
- 2. Ex vivo appraisal
- 3. In vivo studies with healthy experimental animals
- 4. In vivo studies with animal models of disease
- 5. Controlled clinical trials
- 6. General clinical use

- **In Vitro Bench Testing In vitro bench testing of a completed prototype has three major purposes**:
- To observe the mode of operation of the device and assess its performance under tightly controlled circumstances
- To define performance in quantitative terms over a wide range of environmental or input conditions
- To assess the device's reliability and durability in a manner which can be extrapolated to the intended clinical use