Artificial Organ

Introduction

An artificial organ is a man-made device that is implanted or integrated into a human body to replace a natural organ or restoring a specific function so the patient may return to as normal a life as possible. They can be used both for functions that are essential to life and also for purposes that are not related to survival but do improve a person's quality of life. The organs that can be replaced artificially are quite numerous (including the ears, ovaries, and even the heart and brain), eg. artificial heart, pacemaker, artificial kidney machine, heart-lung machine, etc. Perhaps the most common manifestation of an artificial organ is hearing aids that are used to improve a person's ability to hear and distinguish sounds.

The replaced function doesn't necessarily have to be related to life support, but the ultimate goal of artificial organ research and development is fully functional created organs that can be integrated into the body which fully replaces the natural organ and remains functional for a lifetime. Many steps have been taken towards this goal, and it is very likely that the field will continue to change and develop.

The reasons to construct and install an artificial organ might include:

- Life support to prevent imminent death while awaiting a transplant (e.g. artificial heart)
- Dramatic improvement of the patient's ability for self care (e.g. artificial limb)
- Improvement of the patient's ability to interact socially (e.g. cochlear implant)
- Cosmetic restoration after cancer surgery or accident

Previously, an artificial organ would be created completely out of synthetic material, such as plastics or metals. These mechanical organs had some problems, such as difficulty replacing all the functions of a biological organ and a tendency to only work on a temporary basis. A significant amount of current research focuses on biological or hybrid bio-mechanical material and processes.

The main goal is to develop and define technologies that will maintain, improve or even restore the function of diseased organs. The growing need for these technologies is substantial. Improved health care has resulted in an increased life span for the general population and, when coupled with a growing shortage of donor organs, makes it clear that organ assistance and substitution devices will play a larger role in managing patients with end-stage disease by providing a bridge to recovery or transplantation.

A thorough knowledge of the physical, chemical and flow properties of blood is essential for understanding and modeling capillary transport phenomena and circulatory system dynamics in the body. Similarly, in the design and development of extracorporeal devices (i.e., those external to the body) such as artificial kidneys, blood oxygenators and blood pumps, the same knowledge is critical. Many of the major practical problems involved in artificial organ applications result, in fact, from the sensitivity of blood to the unfamiliar shear stresses imposed by such devices, stress that cause blood cell rupture and clotting problems.

[Man-made devices designed to replace, duplicate, or augment, functionally or cosmetically, a missing, diseased, or otherwise incompetent part of the body either temporarily or permanently, and which require a non-biologic material interface with living tissue.]

Design considerations and evaluation process:
Artificial organs can only replace those bodily functions which have been incorporated into their design. Therefore, in the design of an artificial organ, the first task is to establish the specification for the device i.e. 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.

Defining specifications and constraints is the first step in the conceptualization of an artificial organ. Only when this is done can one think realistically about design alternatives, the limitations of available materials, and the clinical constraints which will apply, of which the key ones are connections to the body and duration of expected service.

Once all these considerations have been integrated, the next step is typically the construction of a prototype. Ideally the device should achieve everything it was expected to do, but usually it exhibits some level of performance and durability which falls short of design specifications, either because of some misjudgement in terms of required function or because of some unanticipated problem arising at the interface between the device and the body.

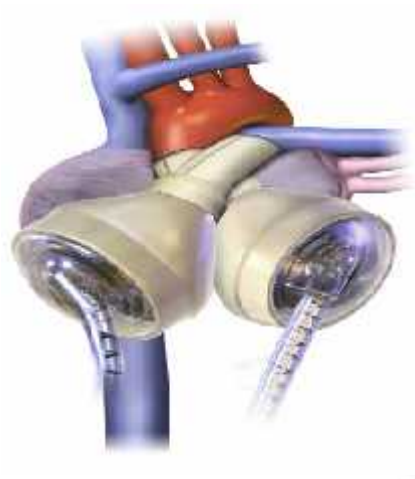
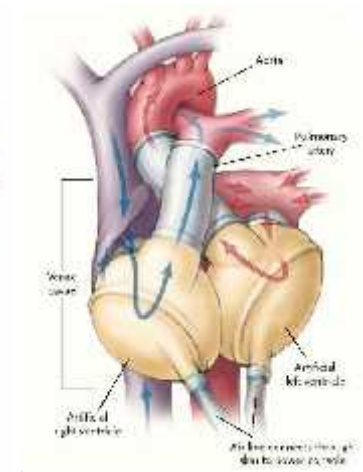
The following step of development may be called optimization. At this point, new experiments are needed to establish the reliability and effectiveness of the device in animal models. This is the stage of validation of the device, which is first conducted in acute experiments and must later be extended to periods of observation approximating the duration of intended use in humans.

The final stage of design, for many artificial organs, is individualization, that is, the ability to fit the needs of diverse individuals. Human come in a wide range of body sizes. In some cases, the prostheses must fit very strict dimensional criteria, which imply that they must be fabricated over an extended range of sizes.

Evaluation process:
The evaluation process of an artificial organ typically is done in six phase:

1. In vitro bench testing
2. Ex vivo appraisal
3. In vivo studies with health experimental animals
4. In vivo studies with animal models of disease
5. General clinical use.

Artificial heart
An artificial heart is a prosthetic device that is implanted into the body to replace the function of original biological heart. It is distinct from a cardiac pump, which is an external device used to provide the functions of both the heart and the lungs. Thus, the cardiac pump need not be connected to both blood circuits.
A total artificial heart (TAH) is a device that replaces the two lower chambers of the heart. These chambers are called ventricles (VEN-trih-kuls). Heart failure is a condition in which the heart can't pump enough blood to meet the body's needs. "End stage" means the condition has become so severe that all treatments, except heart transplant, have failed. (A heart transplant is surgery to remove a person's diseased heart and replace it with a healthy heart from a deceased donor.)

One of the best known devices is the "Jarvik-7" artificial heart, named for its designer Robert K. Jarvik, an American physician. Designed to function like the natural heart, the Jarvik-7 has two pumps (like the ventricles), each with a disk-shaped mechanism that pushes the blood from the inlet valve to the outlet valve.

The action of the artificial heart is entirely similar to the action of the natural heart. There is, however, one huge difference: the natural heart is living muscle, while the artificial heart is plastic, aluminum, and Dacron polyester. As a result, the artificial heart needs some external source of "life." An external power system energizes and regulates the pump through a system of compressed air hoses that enter the heart through the chest. Since the system is cumbersome and open to infection, the use of an artificial heart is meant to be temporary. Artificial hearts are typically used to bridge the time to heart transplantation, or to permanently replace the heart in case heart transplantation is impossible.

Engineering design:

Designing is the intellectual attempt to meet certain demands in the best possible way. It is an engineering activity that impinges on nearly every sphere of human life, relies on the discoveries and laws of science, and creates the conditions for applying these laws to the manufacturer of useful products. The engineering design process can be broken down into at least four stages:

1. Define the problem - clarification of the task.
    1.1 Fit of the system – the device must first “fit” the patient. One must consider the volume and mass of the device, as well as any critical dimension such as the length, width, or height and the location of any tubes, conduits or connectors. The device should not project heat in such a way that surface in contact with tissue or blood are subjected to a temperature rise 5^0C above core temp. on a chronic basis. The effect of device movement and vibration should be considered in the design specification. The acceptable sound levels at various frequencies must be specific. A device should meet existing standards for electromagnetic interference and susceptibility.
    1.2 Pump performance –pump performance must be specified in terms of cardiac output range. A heart assist or total artificial heart device must be able to pump a cardiac output ranging up to 8 litres/min with physiologic inlet and outlet artery pressure.
    1.3 Biocompatibility- the device must not cause excessive damage to the biologic system. Specifically, the device must be minimally thrombogenic and haemolytic.

It should have a minimal effect on the immune system. It should not promote infection, calcification, or tissue necrosis.

1.4 Reliability- the design specification must assign a target reliability for the device. The design specification must state which components of the system could be changed if necessary. The reliability issue is very complex and involves moral, ethical, legal, and scientific issues.

1.5 Quality of life-the design specification must address the quality of life for the patient.

2. Conceptual design – plan treatment
3. Detailed design – execute the plan
4. Learn and generalize – finally, after the design is complete, the designer should be able to learn and generalize from the design. This educational process will include manufacturing of prototypes and testing. General concepts and principles may be gleaned from the design process that can be applied to further designs.

Circulatory assist devices were initially designed to support patients in hemodynamic collapse, but are now used for a wide range of clinical conditions ranging from prophylactic insertion for invasive procedures to cardiogenic shock or cardiopulmonary arrest. There are three major types of percutaneous devices (as well as surgically-implanted ventricular assist devices):

- Counterpulsation devices (intraaortic balloon pump [IABP] and noninvasive counterpulsation)
- Cardiopulmonary assist devices (Cardiopulmonary support or CPS)
- Left ventricular assist devices (eg, Impella)

An intra-aortic balloon pump (IABP) is a mechanical device that is inserted into the aorta, the body's largest artery. It is a long, thin tube called a catheter with a balloon on the end of it. It is used to assist the heart to pump more blood around the body and also improves the delivery of oxygen to the heart.

The IABP is the most commonly used mechanical support device. It has a long clinical record of success, is simple, is inserted easily and rapidly, is the least expensive of all the devices, and does not require constant monitoring by technical support personnel.

Working of IABP

The IABP is connected to a long catheter (tube) that is inserted via the groin using a small incision made under local anaesthetic. The catheter is then carefully guided up a large blood vessel until it is near the heart. The IABP machine is synchronised to the patient's heart rhythm and pumps gas into a balloon at the end of this catheter. This balloon rhythmically inflates and deflates pushing blood forward around the body and also pushes blood back into the coronary arteries of the heart. In this way both the body and the heart get improved blood circulation and oxygen delivery.

Counterpulsation is a term that describes balloon inflation in diastole and deflation in early systole. Balloon inflation causes 'volume displacement' of blood within the aorta, both proximally and distally. This leads to a potential increase in coronary blood flow and potential improvements in systemic perfusion by augmentation of the intrinsic 'Windkessel effect', whereby potential energy stored in the aortic root during systole is converted to kinetic energy with the elastic recoil of the aortic root.

Physiological effects of IABP therapy

The primary goal of IABP treatment is to improve the ventricular performance of the failing heart by facilitating an increase in myocardial oxygen supply and a decrease in myocardial oxygen demand. Although these effects are predominately associated with enhancement of LV performance, IABP may also have favourable effects on right ventricular (RV) function by complex mechanisms including accentuation of RV myocardial blood flow, unloading the left ventricle causing reduction in left atrial and pulmonary vascular pressures and RV afterload. IABP inflates at the onset of diastole, thereby increasing diastolic pressure and deflates just before systole, thus reducing LV afterload. The magnitude of these effects depends upon:

Balloon volume: the amount of blood displaced is proportional to the volume of the balloon.

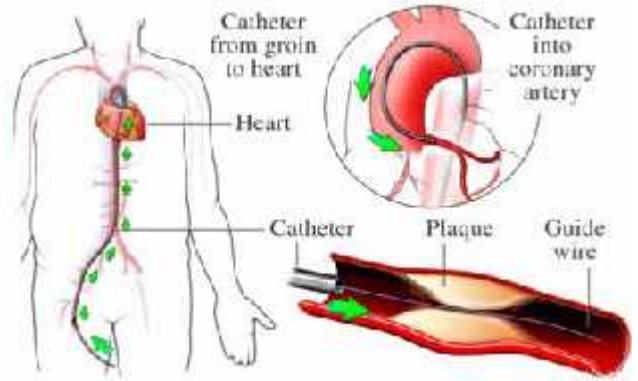
Heart rate: LV and aortic diastolic filling times are inversely proportional to heart rate; shorter diastolic time produces lesser balloon augmentation per unit time.

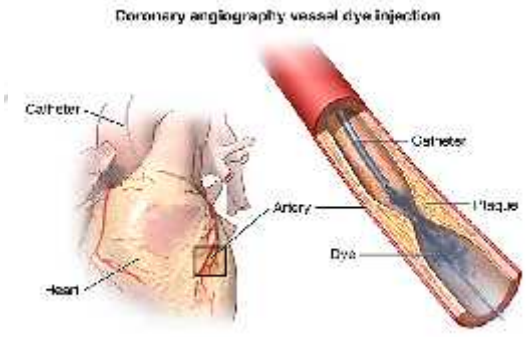
Aortic compliance: as aortic compliance increases (or SVR decreases), the magnitude of diastolic augmentation decreases.

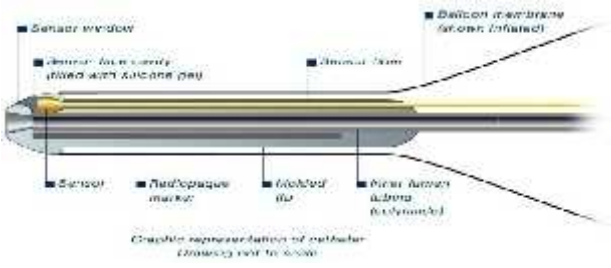
Cardiac catheterization

Cardiac catheterization (KATH-eh-ter-ih-ZA-shun) is a medical procedure used to diagnose and treat some heart conditions. Cardiac catheterization involves passing a thin long flexible tube (catheter) into the right or left side of the heart, usually from the groin or the arm. Through the catheter, doctor can do diagnostic tests and treatments on heart. The test may last 30 - 60 minutes.

For example, doctor may put a special type of dye in the catheter. The dye will flow through your bloodstream to heart. Then, doctor will take x-ray pictures of heart. The dye will make coronary (heart) arteries visible on the pictures. This test is called coronary angiography (an-jee-OG-rah-fee). The dye can show whether a waxy substance called plaque (plak) has built up inside coronary arteries. Plaque can narrow or block the arteries and restrict blood flow to heart. The build up of plaque in the coronary arteries is called coronary heart disease (CHD) or coronary artery disease.

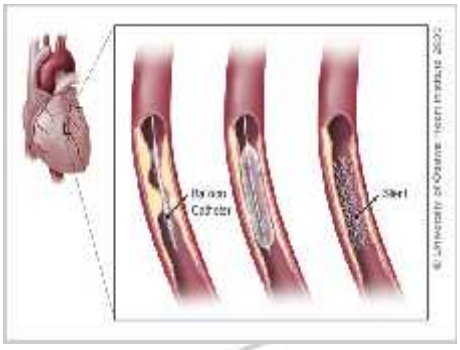


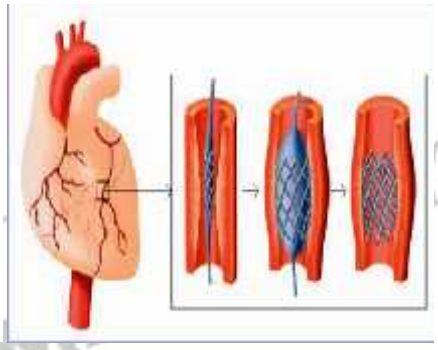




Catheter

Stent: A stent is a small mesh tube that's used to treat narrow or weak arteries. Arteries are blood vessels that carry blood away from heart to other parts of the body. A stent is placed in an artery as part of a procedure called percutaneous (per-ku-TA-ne-us) coronary intervention (PCI), sometimes referred to as coronary angioplasty (AN-jee-oh-plas-tee). PCI restores blood flow through narrow or blocked arteries. A stent helps support the inner wall of the artery in the months or years after PCI.



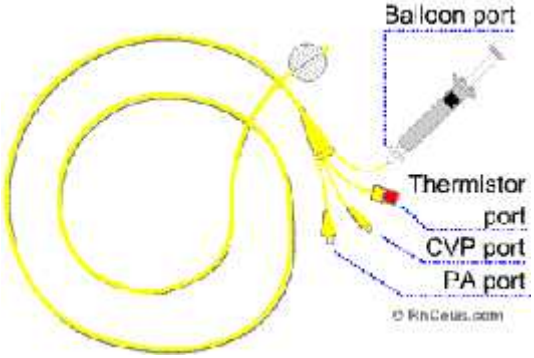


Doctors also may place stents in weak arteries to improve blood flow and help prevent the arteries from bursting. Stents usually are made of metal mesh, but sometimes they're made of fabric. Fabric stents, also called stent grafts, are used in larger arteries. Some stents are coated with medicine that is slowly and continuously released into the artery. These stents are called drug-eluting stents. The medicine helps prevent the artery from becoming blocked again.

SWAN Catherter

The Swan-Ganz balloon flotation catheter was introduced in 1970. It can be placed at the bedside within a few minutes even in critically ill patients. Although placement of these catheters is not difficult, some training and experience are required to avoid complications and for proper interpretation of the hemodynamic data that can be obtained by pulmonary artery catheterization. Its purpose is diagnostic; it is used to detect heart failure or sepsis, monitor therapy, and evaluate the effects of drugs. The pulmonary artery catheter allows direct, simultaneous measurement of pressures in the right atrium, right ventricle, pulmonary artery, and the filling pressure ("wedge" pressure) of the left atrium.

The swan catheter itself floats down into the right side of the heart and into the pulmonary artery. This artery is the one that leads to the lungs. When properly positioned, a swan can monitor a CVP (central venous pressure), PAP (pulmonary artery pressure), cardiac output and index, and SVO2.



Advanced Hemodynamic Monitoring

The CVP is important in acutely ill patients and cardiac patients. It allows the doctors and nurses to monitor fluid volume. A low CVP usually means the patient needs some maintenance fluids or a fluid bolus, whereas a high CVP might indicate the need for diuretics such as lasix or bumex.

PAP monitor the pressure in the pulmonary artery. Increased PAP can indicate pulmonary hypertension and also be useful as a diagnostic tool for other conditions.

Cardiac output, in a nutshell, is how much blood your heart is pumping a minute. Cardiac index is how much blood your heart is pumping in relation to your body weight. These are very important numbers as they directly tell the health care provider how well your heart is performing. And finally SVO2 is the oxygenation of a mixture of all the blood from your body. It tells the healthcare provider how much oxygen the patient's body is using.

Surgical Site Infection (SSI)

A surgical site infection is an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs, or implanted material. A surgical site infection occurs when micro-organisms get into the part of the body that has been operated on and multiply in the tissues.

Artificial blood:

Artificial blood can be defined as a liquid that can carry large amounts of oxygen and can serve as a temporary substitute for blood. Artificial blood also called "blood substitutes" that are used to fill fluid volume and/or carry oxygen and other gases in the cardiovascular system.

Blood substitutes can be divided into two categories:

A. *Volume expanders*: inert and merely increase blood volume. These may be crystalloid-based (Ringer's lactate, normal saline, D5W (dextrose 5% in water)) or colloid-based (Haemaccel, Gelofusin).

B. *Oxygen therapeutics*: mimic human blood's oxygen transport ability. Examples: Hemopure, Oxygent, PolyHeme.

Artificial blood is supposed to fulfill some functions of biological blood, especially in humans. The oxygen transport function of blood is most important and it is very difficult to reproduce. The initial goal of oxygen carrying blood substitutes is merely to mimic blood's oxygen transport capacity. Artificial blood based on oxygen therapeutics are broken into two categories: (a) haemoglobin solutions and (b) perfluorocarbon (PFC) emulsions.

Haemoglobin solutions:

Hb derived from humans, animals or artificially via recombinant technology. Different types of haemoglobin solutions: (i) purified Hb solution & (ii) modified Hb solutions : (a) polymerized Hb, (b) polymer conjugated Hb (P-L-P conjugated polymerized Hb), (c) intra-molecular cross-linked Hb (DCL Hb- diaspirin cross-linked Hb), (d) recombinant Hb (a few parts of an amino acid sequence of human Hb are replaced to prevent the dissociation into dimmers and to maintain adequate oxygen affinity –γHb 1:1) & (e) Hb vesicles (purified Hb & lipid – phospholipids encapsulated Hb, eg. PEH, LEH-liposome encapsulated Hb). Substances called perfluorochemicals (PFC) have the ability to carry oxygen and carbon dioxide.

Perfluorocarbons :

PFC are chemically inert compounds consisting of fluorine-substituted hydrocarbons. It increases oxygen solubility in plasma and facilitates effortless transport of oxygen in circulation. Perfluorochemicals will not mix with blood; therefore emulsions must be made by dispersing small drops of PFC in water. This liquid is then mixed with antibiotics, vitamins, nutrients, and salts, producing a mixture that contains about 80 different components, and performs many of the vital functions of natural blood. PFC particles are about 40 times smaller than the diameter of a red blood cells (RBC). This small size can enable PFC particles to traverse capillaries through which no RBCs are flowing. In theory this can benefit damaged, blood-starved tissues, which conventional red cells cannot reach. PFC solutions can carry oxygen so well that mammals and humans can survive breathing liquid PFC solution, called liquid breathing.

1st generation PFCs : Perfluorodecalin (PFD, perfluorotrypropylamine (FTPA)

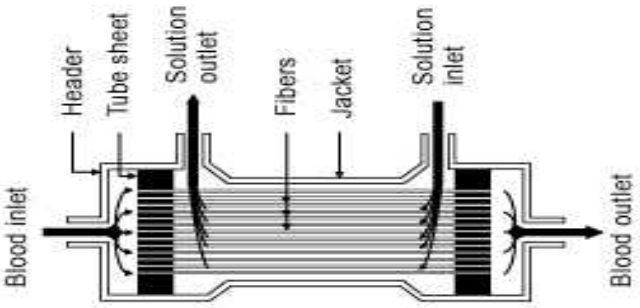
2nd generation PFCs : Perfluorooxtyl bromide (PFOB), Bis (perfluorobutyl) ethylene.

Liver Support System / Liver Assist Devices (LAD) / Bio-artificial LAD

Artificial extracorporeal liver support is a detoxification treatment for liver failure patients and is based / worked on the same principles of hemodialysis. The main aim is to mimic the primary functions of liver, such as detoxification, synthesis and regulation. The liver support system is design in such a way that it can able to remove the lipophilic, albumin-bound substances such as bilirubin, bile acids, metabolites of aromatic amino acids, medium chain fatty acids and cytokines.

The liver function includes the breakdown, synthesis, modification, storage and regulated release of carbohydrates, lipids, amino acids, proteins and nucleic acids. It produces bile and delivers to the intestine for digestion and excretion of wastes.

Bio-artificial liver assist devices apply mechanical principles to the biologically active models for the "global" replacement of primary liver functions. Among various configurations, hollow-fiber bioreactors have been actually used in human patient. Hollow-fiber bioreactors, similar to hemodialysis devices, contain numerous numbers of hollow fibers of a semipermeable material. Cultured or seed hepatocytes (liver cells / porcine hepatocytes) are filled in the extracapillary space (ECS) of hollow-fiber bioreactor. These hepatocytes secrete bile that perfuse through the membrane and mixed with patient's blood or plasma in the intracapillary space (ICS). A membrane oxygenator and heater are included in the artificial liver assist devices. The heater keeps the patient's blood / plasma at body temperature. The membrane oxygenator provides the house hepatocytes with the oxygen they require for proper function. A complete operation last for 6 - 8 hours.



Bio-artificial LAD

Artificial Pancreas (Biopancreas)

The artificial pancreas is a technology developed to help diabetes people. It automatically controls blood glucose level by providing the substitute endocrine functionality of a healthy pancreas. There are several important exocrine (digestive) and endocrine (hormonal) functions of the pancreas, but it is the lack of insulin production, which is the motivation to develop a substitute.

Different approaches (Different insulin administration systems of artificial pancreas) under consideration include:

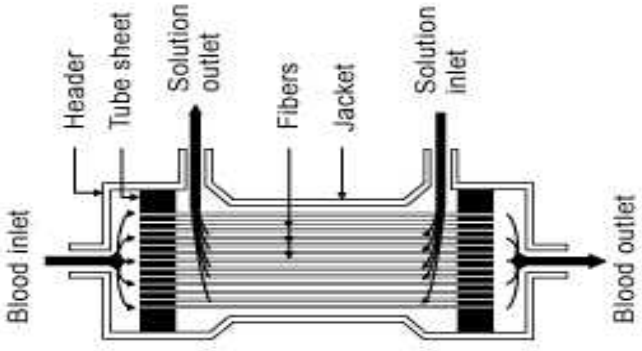
1. The medical equipment approach (Insulin pump) -- using an insulin pump under closed loop control & real-time data from a continuous blood glucose sensor.
2. The bioengineering approach (The Bio-artificial pancreas): -- the development of a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years.
3. The gene therapy approach -- the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells.

Bio-artificial pancreas:

This involves harvesting insulin-producing cells from pigs, encapsulating the cells in dissolvable "microreactors" (a tiny, dissolvable, spherical cage) and then injecting them into the abdomens of people with diabetes. The microreactors float freely and producing insulin as needed. This is a living drug-delivery system where pancreatic cells have a biochemical mechanism that continuously monitors blood glucose, releasing only enough insulin to keep blood sugar within a normal range. The microreactors permit life-sustaining oxygen and nutrients to flow in and wastes and insulin to flow out, keeping cells healthy and nourished.

Capillary Bio-artificial Pancreas (Extracorporeal artificial pancreas):

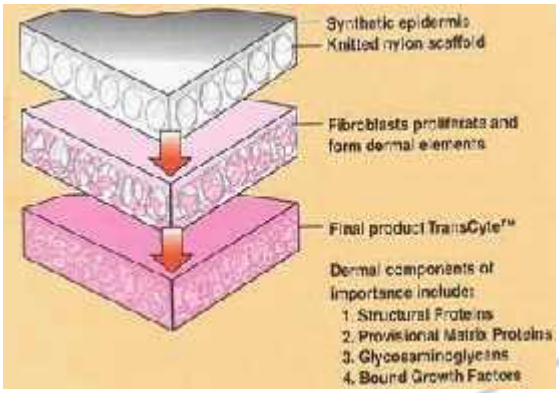
In extracapillary space, pancreatic cells are being cultured. The pancreatic cells are islet of Langerhans, which secrets hormone insulin and assimilate glucose. Glucose rich blood in diabetes patient are passed through the capillaries (made of silicone rubber, Teflon, Dacron, etc.). Glucose from the blood diffuses through the membrane to the extracapillary site and insulin is released from pancreatic cells and also passes through the membrane into the intracapillary site. Insulin converts the glucose into glucagons and ultimately, glucose level in blood decreases by a significant level. The blood is circulated through capillary till the desired level of glucose in blood is achieved.

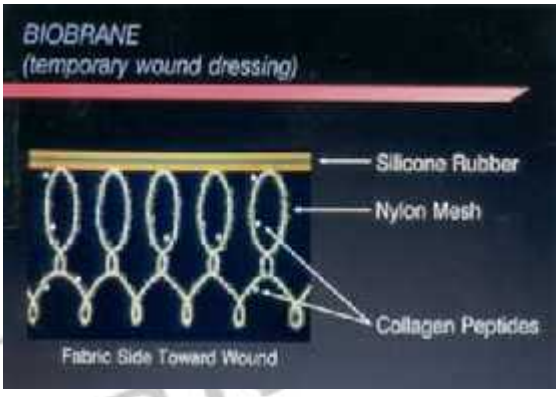


Capillary Artificial Pancreas

Artificial skin

Artificial skin is a synthetic covering with two layers for regeneration of skin and is used to treat burn victims. The material contains microcapsules filled with a special healing agent. Like human skin, it bleeds and heals itself, offering a potential breakthrough in vital materials used in surgical implants.





Trancyte is a bilayer skin substitute. Outer epidermal analog is a thin nonporous silicone film with barrier functions. Inner dermal analog is layered human fibroblast products mainly collagen type 1,fibronectin and Glycosaminoglycan. Subsequent cryo-preservation destroys fibroblasts but preserves activity of fibroblast-derived products. Thin water layer at surface is maintained for epidermal cell migration. It is removed after re-epithelialization (or prior to skin graft or excised wound). Silicone provides flexibility. It must be kept frozen until use.

Biobrane is a bilayer synthetic skin substitute. Outer epidermal analog constructed of a thin silicone film with barrier functions comparable to skin . Small pores present in silicone to allow for exudates removal, permeability to topical antibiotics. Inner dermal analog composed of a three dimensional irregular nylon filament weave upon which is bonded type I collagen peptides .

Surface binding of inner membrane potentiated by collagen-fibrin bonds as well as fibrin deposition between nylon weave . Subsequently fibronectin, produced by migrated fibroblasts, enhances binding to the fibrin entrapped in mesh .New epithelial cells growing along mesh measures adherence . Thin water layer at surface maintained for epidermal cell migration . Removed after re-epithelialization (or prior to skin graft on excised wound) .Silicone and nylon weave provides flexibility.

Personal grooming

Personal grooming (**also called titivating and preening**) is the art of cleaning, grooming, and maintaining parts of the body. It is a species-typical behavior that is controlled by neural circuits in the brain.

Evaluation process: Detail

In vivo bench testing:

In vivo bench testing of a completed prototype has three major purposes:

1. To observe the mode of operation of the device and assess its performance under tightly controlled circumstances
2. To define performance in quantitative terms over a wide range of environmental or input conditions
3. To assess the device's reliability and durability in a manner which can be extrapolated to the intended clinical use

For all its value, there are limitations to the in vitro testing of device. Devices are made to work while in contact with body fluids or body tissues. This complex environment modifies materials in ways which are not always predictable. To duplicate this effect as closely as possible a laboratory bench system can be made to match the body's environment in terms of temperature and humidity. Operating pressures and external forces can also be imitated but not perfectly reproduced (eg. complex pulsatile mature of cardiovascular events.). Other fluid dynamic conditions such as viscosity, wall shear stress and compliances of device surrounding structures call for sophisticated laboratory system and can only be approximated. The chemical environment is the most difficult to reproduce in view of the complexity of body fluids and tissue structures. Some in vitro testing systems make use of body fluids such as plasma or blood. This in turn brings in additional intricacies because these fluids are not stable outside of the body without preservatives and must be kept sterile if the experiment is to last more than a few hours.

Accelerated testing is a standard component in the evaluation of machine. It is critical for permanent implants with moving parts which are subject to the repeated action of external forces. Fatigue testing provides important information on progressive wear or catastrophic failure of device components. For examples, the human heart beats about 40 million time per year. Manufacturers and regulatory agencies conduct testing of prosthetic cardiac valve over

at least 400 million cycles. With a testing apparatus functioning at 1200 cycles per minute, this evaluation can be compressed by a factor of about 15, that is to about a year.

Ex vivo appraisal:
Because of the difficulty of keeping blood in its physiologic state in a container, the evaluation of some blood processing or blood contacting devices in performed by connecting them through the skin to an artery or vein or both if the blood must be returned to the cardiovascular system to avoid excessive haemorrhage. Such experiments retain the advantage of keeping the device under direct observation while allowing longer experiments than are feasible in vitro, particularly if the animal does not require general anaesthesia. It is also possible in some cases to evaluate several devices in parallel or sequentially under quite realistic conditions and therefore to conduct comparative experimental animals prevents studies for periods of service as long as can be expected with permanent implants in man.

In vivo evaluation with health experimental animals:
There comes a stage in the development of most devices where they must be assessed to their target location in a living body. The matching of device size and shape with available experimental sites in the location in a living body. The matching of device size and shape with available experimental sites in the appropriate animal species is a necessary condition. Such experiments typically last weeks, months, or years and provide information about body-device and tissue-material interactions either through non-invasive measurement techniques or through device retrieval at the end of the observation period. Rodents, felines, and dogs raised for research purposes are usually too small for the evaluation of human sized devices. Farm animals such as sheep, goats, pigs and claves are commonly used. Here again the limited life expectancy of experimental animals prevents studies for periods of service as long as can be expected with permanent implants in man.

In vivo evaluation with animal models of disease:
A first approximation of the effectiveness of a device in replacing a physiologic function can be obtained after removing the target organ in a normal animal. However, when the organ failure is only the cardinal sign of a complex systemic disease, the interactions between device and the persisting manifestations of the disease occur spontaneously in some species and in other cases can be obtained by chemical, physical or surgical intervention, where such models of disease exist n animals which can be fitted with a device, useful information is obtained which helps to refine the final prototype.

Controlling clinical trials:
Although some devices can be evaluated with little risk in normal volunteers who derive no health benefit from the experiments, our culture frowns on this approach and legal considerations discourage it. Once reliability and effectiveness have been established through animal experiments and the device appears to meet a recognized clinical need, a study protocol is typically submitted to an appropriate ethics committee or institutional review board and, upon their approval, a series of clinical trials is undertaken. The first step often concentrates on the demonstration of safety of the device with a careful watch for side effects or complications. If the device passes this first hurdle, a controlled clinical trial will be carried out with patients to evaluate effectiveness as well as safety on a scale which allows statistical comparison with a control form of treatment. This protocol may extend from a few months to several years depending upon the expected benefits of the device and the natural history of the disease.

General clinical use:
Once a device is deemed successful by a panel of experts, it may be approved by regulatory agencies for commercial distribution. Increasingly a third stage of clinical evaluation appears necessary, namely post market surveillance, that is a system of clinical outcomes analysis under conditions of general availability of the device to a wide range of doctors and patients.

Post market surveillance is a new concept which is not yet uniformly codified. It may take the form of a data collection and analysis network, a patient registry to allow continuing follow up a statistical of a data analysis, a device-tracking system aimed at early identification of unforeseen types of failure, or ancillary controls such as inspection of facilities and review of patient histories in institutions where devices are used. Protocols of surveillance on al large scale are difficult and costly to implement and their cost-effectiveness is therefore open to question. They are also impaired by the shortage of broadly available and minimally invasive diagnostic methods for assessing the integrity or function of a device prior to catastrophic failure. Worthwhile post market surveillance requires a constructive collaboration between patients, doctors, device manufacturers, government regulatory agencies, and study groups assessing health care policy in the public and private sectors.