ARTIFICIAL ORGAN

Introduction

An **artificial organ** is a human made organ device or tissue that is implanted or integrated into a human — interfacing with living tissue — to replace a natural organ, to duplicate or augment a specific function or functions so the patient may return to a normal life as soon as possible. The replaced function does not have to be related to life support, but it often is. For example, replacement bones and joints, such as those found in hip replacements, could also be considered artificial organs.

Implied by definition, is that the device must not be continuously tethered to a stationary power supply or other stationary resources such as filters or chemical processing units. (Periodic rapid recharging of batteries, refilling of chemicals, and/or cleaning/replacing of filters would exclude a device from being called an artificial organ.) Thus, a dialysis machine, while a very successful and critically important life support device that almost completely replaces the duties of a kidney, is not an artificial organ.

Purpose

Constructing and installing artificial organs, an extremely research-intensive and expensive process initially, may entail many years of ongoing maintenance services not needed by a natural organ:

- providing life support to prevent imminent death while awaiting a transplant (e.g. artificial heart);
- dramatically improving the patient's ability for self care (e.g. artificial limb);
- improving the patient's ability to interact socially (e.g. cochlear implant); or
- improving a patient's quality of life through cosmetic restoration after cancer surgery or an accident.

The use of any artificial organ by humans is almost always preceded by extensive experiments with animals. Initial testing in humans is frequently limited to those either already facing death or who have exhausted every other treatment possibility.

Enhancement

It is also possible to construct and install an artificial organ to give its possessor abilities that are not naturally occurring. Research is proceeding in areas of vision, memory, and information processing. Some current research focuses on restoring short-term memory in accident victims and long-term memory in dementia patients.

One area of success was achieved when Kevin Warwick carried out a series of experiments extending his nervous system over the internet to control a robotic hand and the first direct electronic communication between the nervous systems of two humans.

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Microchips

Organ chips are devices containing hollow micro vessels filled with cells simulating tissue and/or organs as a microfluidic system that can provide key chemical and electrical signal information. This is distinct from an alternative use of the term microchip, which refers to small, electronic chips that are commonly used as an identifier and can also contain a transponder.

This information can create various applications such as creating "human in vitro models" for both healthy and diseased organs, drug advancements in toxicity screening as well as replacing animal testing.

Using 3D cell culture techniques enables scientists to recreate the complex extracellular matrix, ECM, found in in vivo to mimic human response to drugs and human diseases. Organs on chips are used to reduce the failure rate in new drug development; microengineering these allows for a microenvironment to be modeled as an organ.

Examples:

Artificial limbs


A prosthetic arm

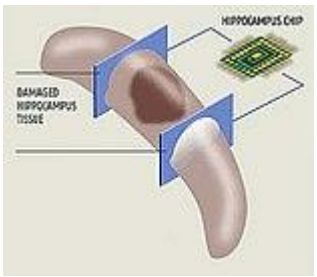
Artificial arms and legs, or prosthetics, are intended to restore a degree of normal function to amputees. Mechanical devices that allow amputees to walk again or continue to use two hands have probably been in use since ancient times,[10] the most notable one being the simple peg leg. Since then, the development of artificial limbs has progressed rapidly. New plastics and other materials, such as carbon fiber have allowed artificial limbs to become stronger and lighter, limiting the amount of extra energy necessary to operate the limb. Additional materials have allowed artificial limbs to look much more realistic. Prostheses can roughly be categorized as upper- and lower-extremity and can take many shapes and sizes.

New advances in artificial limbs include additional levels of integration with the human body. Electrodes can be placed into nervous tissue, and the body can be trained to control the prosthesis. This technology has been used in both animals and humans. The prosthetic can be controlled by the brain using a direct implant or implant into various muscles.

Bladder

The two main methods for replacing bladder function involve either redirecting urine flow or replacing the bladder *in situ*. Standard methods for replacing the bladder involve fashioning a bladder-like pouch from intestinal tissue. As of 2017 methods to grow bladders using stem cells had been attempted in clinical research but this procedure was not part of medicine.

Brain



A diagram of a hippocampal prosthesis

Neural prostheses are a series of devices that can substitute a motor, sensory or cognitive modality that might have been damaged as a result of an injury or a disease.

Neurostimulators, including deep brain stimulators, send electrical impulses to the brain in order to treat neurological and movement disorders, including Parkinson's disease, epilepsy, treatment resistant depression, and other conditions such as urinary incontinence. Rather than replacing existing neural networks to restore function, these devices often serve by disrupting the output of existing malfunctioning nerve centers to eliminate symptoms.

Scientists in 2013 created a mini brain that developed key neurological components until the early gestational stages of fetal maturation.

Corpora cavernosa

To treat erectile dysfunction, both corpora cavernosa can be irreversibly surgically replaced with manually inflatable penile implants. This is a drastic therapeutic surgery meant only for men who have complete impotence who have resisted all other treatment approaches. An implanted pump in the (groin) or (scrotum) can be manipulated by hand to fill these artificial cylinders, normally sized to be direct replacements for the natural corpora cavernosa, from an implanted reservoir in order to achieve an erection.[21]

Ear

An illustration of a cochlear implant

In cases when a person is profoundly deaf or severely hard of hearing in both ears, a **cochlear implant** may be surgically implanted. Cochlear implants bypass most of the peripheral auditory system to provide a sense of sound via a microphone and some electronics that reside outside the skin, generally behind the ear. The external components transmit a signal to an array of electrodes placed in the cochlea, which in turn stimulates the cochlear nerve.[22]

In the case of an outer ear trauma, a craniofacial prosthesis may be necessary.

Thomas Cervantes and his colleagues, who are from Massachusetts General Hospital, built an artificial ear from sheep cartilage by a 3D printer. With a lot of calculations and models, they managed to build an ear shaped like a typical human one. Modeled by a plastic surgeon, they had to adjust several times so the artificial ear can have curves and lines just like a human ear. The researchers said "The technology is now under development for clinical trials, and thus we have scaled up and redesigned the prominent features of the scaffold to match the size of an adult human ear and to preserve the aesthetic appearance after implantation." Their artificial ears have not been announced as successful, but they are still currently developing the project. Each year, thousands of children were born with a congenital deformity called microtia, where the external ear does not fully develop. This could be a major step forward in medical and surgical microtia treatment.

Eye


A bionic eye

The most successful function-replacing artificial eye so far is actually an external miniature digital camera with a remote unidirectional electronic interface implanted on the retina, optic nerve, or other related locations inside the brain. The present state of the art yields only partial functionality, such as recognizing levels of brightness, swatches of color, and/or basic geometric shapes, proving the concept's potential.[23]

Various researchers have demonstrated that the retina performs strategic image preprocessing for the brain. The problem of creating a completely functional artificial electronic eye is even more complex. Advances towards tackling the complexity of the artificial connection to the retina, optic nerve, or related brain areas, combined with ongoing advances in computer science, are expected to dramatically improve the performance of this technology.

Heart


A Ventricular Assist Device

Cardiovascular-related artificial organs are implanted in cases where the heart, its valves, or another part of the circulatory system is in disorder. The artificial heart is typically used to bridge the time to heart transplantation, or to permanently replace the heart in case heart transplantation is impossible. Artificial pacemakers represent another cardiovascular device that can be implanted to either intermittently augment (defibrillator mode), continuously augment, or completely bypass the natural living cardiac pacemaker as needed. Ventricular assist devices are another alternative, acting as mechanical circulatory devices that partially or completely replace the function of a failing heart, without the removal of the heart itself.

Besides these, lab-grown hearts and 3D bioprinted hearts are also being researched. Currently, scientists are limited in their ability to grow and print hearts due to difficulties in getting blood vessels and lab-made tissues to function cohesively.

Liver

HepaLife is developing a bioartificial liver device intended for the treatment of liver failure using stem cells. The artificial liver is designed to serve as a supportive device, either allowing the liver to regenerate upon failure, or to bridge the patient's liver functions until transplant is available. It is only made possible by the fact that it uses real liver cells (hepatocytes), and even then, it is not a permanent substitute.

Lungs

 An artificial lung by MC3

With some almost fully functional, artificial lungs promise to be a great success in the near future. An Ann Arbor company MC3 is currently working on this type of medical device.

Extracorporeal membrane oxygenation (ECMO) can be used to take significant load off of the native lung tissue and heart. In ECMO, one or more catheters are placed into the patient and a pump is used to flow blood over hollow membrane fibers, which exchange oxygen and carbon dioxide with the blood. Similar to ECMO, Extracorporeal CO_2 Removal (ECCO2R) has a similar set-up, but mainly benefits the patient through carbon dioxide removal, rather than oxygenation, with the goal of allowing the lungs to relax and heal.

Ovaries

The ground work for the development of the artificial ovary was laid in the early 1990s.[31]

Reproductive age patients who develop cancer often receive chemotherapy or radiation therapy, which damages oocytes and leads to early menopause. An artificial human ovary has been developed at Brown University with self-assembled microtissues created using novel 3-D petri dish technology. In a study funded and conducted by the NIH in 2017, scientists were successful in printing 3-D ovaries and implanting them in sterile mice. In the future, scientists hope to replicate this in larger animals as well as humans. The artificial ovary will be used for the purpose of in vitro maturation of immature oocytes and the development of a system to study the effect of environmental toxins on folliculogenesis.

Pancreas

An artificial pancreas is used to substitute endocrine functionality of a healthy pancreas for diabetic and other patients who require it. It can be used to improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of the complications of hyperglycemia, and it can also ease the burden of therapy for the insulin-dependent. Approaches include using an insulin pump under closed loop control, developing a bio-artificial pancreas consisting of a biocompatible sheet of encapsulated beta cells, or using gene therapy.[34][35]

Red blood cells

Artificial red blood cells (RBC) have already been in projects for about 60 years, but they started getting interest when the HIV-contaminated-donor blood crisis. Artificial RBCs will be dependent 100% on nanotechnology. A successful artificial RBC should be able to totally replace human RBC, which means it can carry on all the functions that a human RBC does.

The first artificial RBC, made by Chang and Poznanski in 1968, was made to transport Oxygen and Carbon Dioxide, also fulfilled antioxidant functions.

Scientists are working on a new kind of artificial RBC, which is one-fiftieth the size of a human RBC. They are made from purified human hemoglobin proteins that have been coated with a synthetic polymer. Thanks to the special materials of the artificial RBC, they can capture oxygen when blood pH is high, and release oxygen when blood pH is low. The polymer coating also keeps the hemoglobin from reacting with nitric oxide in the bloodstream, thus preventing dangerous constriction of the blood

vessels. Allan Doctor, MD, stated that the artificial RBC can be used by anyone, with any blood type because the coating is immune silent.

ENHANCEMENT

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EVOLUTION OF ORGAN REPLACEMENT TECHNOLOGY

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. Table provides a current snapshot in the continuing evolution of substitutive medicine.

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, that is, 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).

Biomaterials

The materials of the first generation of artificial organs — those which are widely available at the moment — are for the most part standard commodity plastics and metals developed for industrial purposes. Engineers have long recognized the limitations of construction materials in the design and performance of machines. However, a new awareness arose when they started interacting with surgeons and biologic scientists in the emerging field of medical devices. In many cases the intrinsic and well established physical properties of synthetic materials such as mechanical strength, hardness, flexibility, or permeability to fluids and gases were not as immediately limiting as the detrimental effects deriving from the material's contact with living tissues. As a result, fewer than 20 chemical compounds among the 1.5 million candidates have been successfully incorporated into clinical devices. Yet some functional implants require material properties which exceed the limits of current polymer, ceramic, or metal alloy technology. This is an indirect tribute to the power of evolution, as well as a challenge to scientists to emulate natural materials with synthetic compounds, blends, or composites.

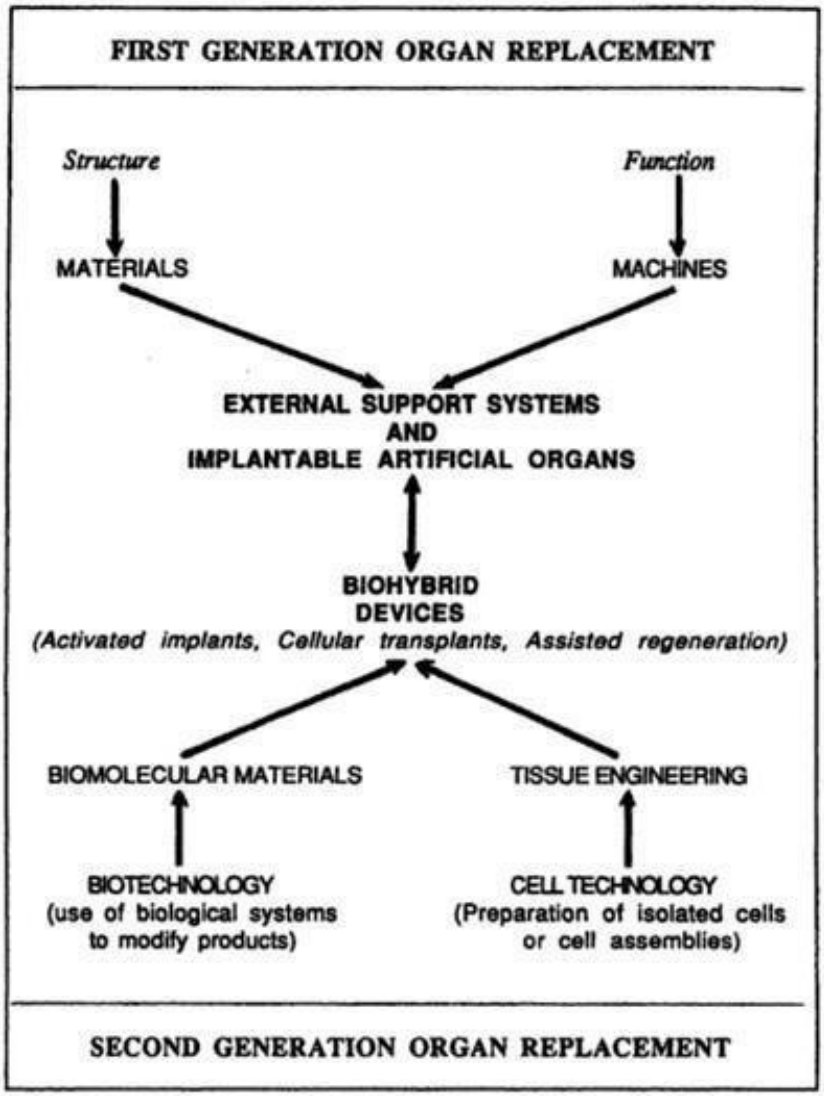

Fig. Outlook of organ replacement

TABLE VI.1 Evolution of Organ Replacement Technology: A 1995 Perspective

Current status	Artificial organs	Transplantation
Broadly accepted clinically	Heart-lung machine	Blood transfusion
	Large-joint prostheses	Corneal transplants
	Bone fixation systems	Banked bone
	Cardiac pacemakers	Bone marrow
	Implantable defibrillators	Kidney — living related donor
	Large vascular grafts	Kidney — cadaveric donor
	Prosthetic cardiac valves	Heart
	Intra-aortic balloon pump	Liver
	Intraocular lenses	
	Middle ear ossicle chain	
	Hydrocephalus shunts	
	Dental implants	
	Skin and tissue expanders	
	Maintenance hemodialysis	
	Chronic ambulatory peritoneal dialysis	
Accepted with reservations	Breast implants	Whole pancreas
	Sexual prostheses	Single and double lung
	Small joint prostheses	Combined heart-lung
	ECMO in children	
Limited clinical application	ECMO in adults	Cardiomyoplasty
	Ventricular assist devices	Pancreatic islets
	Cochlear prostheses	Liver lobe or segment
	Artificial tendons	Small Intestine
	Artificial skin	
	Artificial limbs	
Experimental stage	Artificial pancreas	Bioartificial pancreas
	Artificial blood	Bioartificial liver
	Intravenous oxygenation	CNS implants of secreting tissue
	Artificial esophagus	Gene therapy products
	Total artificial heart	
	Nerve guidance channels	
Conceptual stage	Artificial eye	Striated muscle implants
	Neurostimulator	Smooth muscle implants
	Blood pressure regulator	Cardiac muscle implants
	Implantable lung	Functional brain implants
	Artificial trachea	Bioartificial kidney
	Artificial gut	
	Artificial fallopian tube	

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 andthe 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 artificialorgan. 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 usuallyit exhibitssome 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 stageof 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 theneeds 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 anextended 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.

EVALUATION PROCESS

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 undertightly controlled circumstances
2. To define performance in quantitative terms over a wide range of environmental orinputconditions
3. To assess the device's reliability and durability in a manner which can be extrapolatedtothe 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 intricaciesbecause these fluids are not stable outside of the body without preservatives and must be kept sterile if the experiment isto last more than a few hours.

Accelerated testing is a standard component in the evaluation of machine. It is critical for permanentimplants 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 inparallel 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 targetlocation 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 shapewith 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 techniquesor through device retrieval at the end of the observation period. Rodents, felines, and dogs raised for research purposes are usually too small forthe 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 aslong 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 canbe 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 throughanimal 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 effectsor 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 agenciesfor 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.

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may take theform of a data collection and analysis network, a patient registry to allow continuing follow up a statisticalof 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.

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