UNIT I – INTRODUCTION

An **artificial organ** is a man-made device that is implanted or integrated into a human — interfacing with living tissue — to replace a natural organ, for the purpose of duplicating or augmenting a specific function or a group of related functions so the patient may return to a normal life as soon as possible. For example, replacement bones and joints, such as those found in hip replacements, could also be considered artificial organs.

PURPOSE

Reasons to construct and install an artificial organ, an extremely research-intensive and expensive process initially, which may entail many years of ongoing maintenance services not needed by a natural organ, might include:

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.

EXAMPLES

Artificial limbs - 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, 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.

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. An alternative emerging method involves growing a bladder from cells taken from the patient and allowed to grow on a bladder-shaped scaffold.

BRAIN - 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

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

HEART - 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 which 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.

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

ENHANCEMENT

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.

This might also include the existing practice of implanting subcutaneous chips for identification and location purposes (ex. RFID tags).

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.

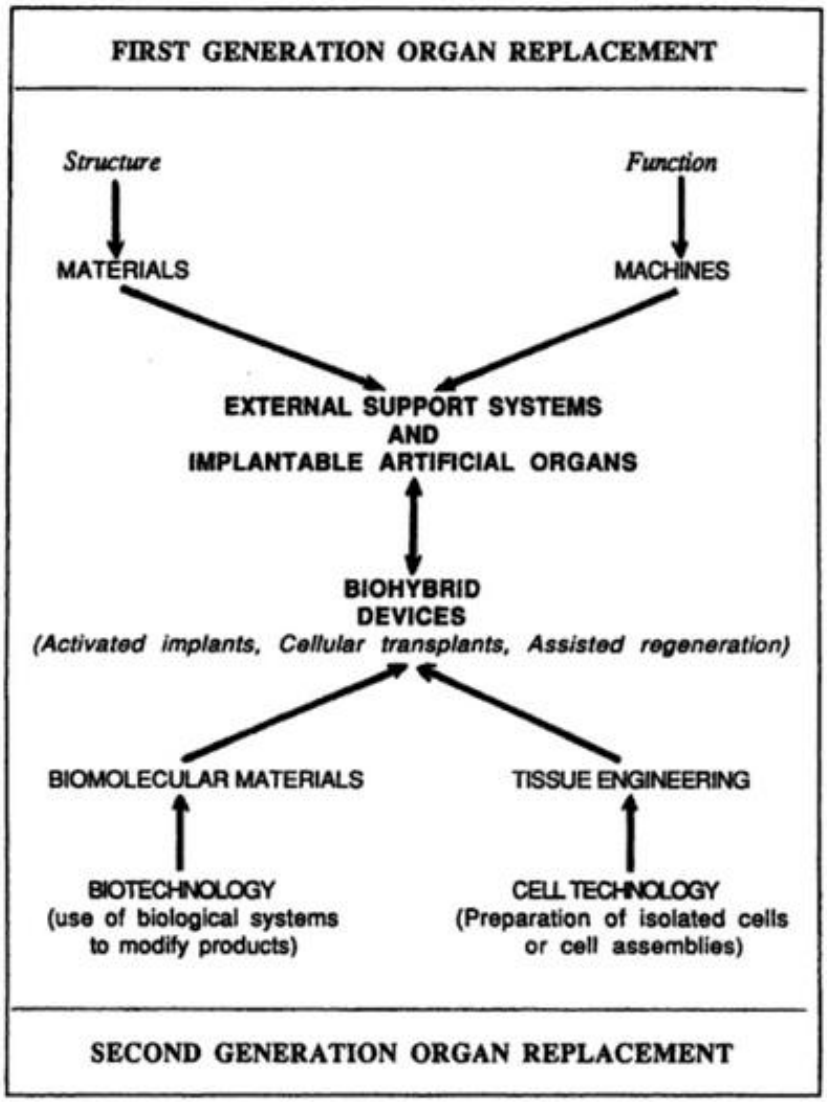
FIRST GENERATION ORGAN REPLACEMENT
Structure
Function
MATERIALS
MACHINES
EXTERNAL SUPPORT SYSTEMS
AND
IMPLANTABLE ARTIFICIAL ORGANS
BIOHYBRID
DEVICES
(Activated implants, Cellular transplants, Assisted regeneration)
BIOMOLECULAR MATERIALS
TISSUE ENGINEERING
BIOTECHNOLOGY
(use of biological systems
to modify products)
CELL TECHNOLOGY
(Preparation of isolated cells
or cell assemblies)
SECOND GENERATION 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

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. This may be reflected by a temporarily impaired function in the postoperative period or by permanent necrosis of the most delicate components of the transplant, resulting in some degree of functional limitation. 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 immunosuppression 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.

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 (modeling is often useful at that stage), 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 misjudgment 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*, if the specifications were well defined from the outset, or *reevaluation*, if they were not. More commonly it is the reconciliation of competition and at times contradictory design criteria which leads to a second prototype.

At this point, new experiments are needed to establish the reliability and effectiveness of the device in animal models of the target disease (if such exist) or at least in animals in which the natural organ can be removed or bypassed. 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. These criteria, however, cannot always be met for long-term implants, since the life expectancy of most animals is shorter than that of humans. By this point, the diverse vantage points of the theoretician, the manufacturer, the performance evaluator, and the clinical user have been articulated for some specific devices and generalized in terms of quality control for classes of devices.

The final stage of design, for many artificial organs, is *individualization*, i.e., the ability to fit the needs of diverse individuals. Humans come in a wide range of body sizes. In some cases, the prostheses must fit very strict dimensional criteria, which implies that they must be fabricated over an extended range of sizes (e.g., cardiac valves). In other cases, there is enough reserve function in the device that one pediatric model and one adult size model may suffice (e.g., blood oxygenator for cardiac surgery).

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:

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 in vitro testing of devices. 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 (e.g., the complex pulsatile nature of cardiovascular events). Other fluid dynamic conditions such as viscosity, wall shear stress, and compliance of device-surrounding structures call for sophisticated laboratory systems 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 machines. 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 example, the human heart beats about 40 million times per year. Manufacturers and regulatory agencies conduct testing of prosthetic cardiac valves 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, i.e., to about a year.

EXVIVO 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 is 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 hemorrhage. 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 anesthesia. It is also possible in some cases to evaluate several devices in parallel or sequentially under quite realistic conditions and therefore to conduct comparative experiments under reasonably standardized conditions.

In Vivo Evaluation with Healthy Experimental Animals

There comes a stage in the development of most devices where they must be assessed in their target 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 calves 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 the 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 in animals which can be fitted with a device, useful information is obtained which helps to refine the final prototypes.

Controlled Clinical Trials

Although some devices can be evaluated with little risk in normal volunteers who derive no health benefit from the experiment, 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 postmarket surveillance, i.e., a system of clinical outcomes analysis under conditions of general availability of the device to a wide range of doctors and patients.

Postmarket 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 and statistical analysis, a device-tracking system aimed at early identification of unforseen 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 a 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 postmarket surveillance requires a constructive collaboration between patients, doctors, device manufacturers, government regulatory agencies, and study groups assessing health care policy issues in the public and private sectors.

Defining Terms

Artificial organs: Human-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 nonbiologic material interface with living tissue.

Assist device: An apparatus used to support or partially replace the function of a failing organ.

Bioartificial organ: Device combining living elements (organelles, cells, or tissues) with synthetic materials in a therapeutic system.

Bicompatibility: The ability of a material to perform with an appropriate host tissue response when incorporated for a specific application in a device, prosthesis, or implant.

Biomaterial: Any material or substance (other than a drug) or combination of materials, synthetic or natural in origin, which can be used as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body.

Compatibility: A material property which encompasses a set of specifications and constraints relative to material-tissue interactions.

Device: Defined by Congress as "...an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is...intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals,...and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes."

Hemocompatibility: The ability of a biomaterial to stay in contact with blood for a clinically relevant period of time without causing alterations of the blood constituents.

Hybrid artificial organs: Synonym of *bioartificial organs*, stressing the combination of cell transplantation and artificial organ technology.

Implant: Any biomaterial or device which is actually embedded within the tissues of a living organism.

Organs: Differentiated structures or parts of a body adapted for the performance of a specific operation or function.

Organoid: An organlike aggregate of living cells and synthetic polymer scaffolds or envelopes, designed to provide replacement or support function.

Organ transplant: An isolated body part obtained from the patient, a living relative, a compatible cadaveric donor, or an animal and inserted in a recipient to replace a missing function.

Prosthesis: An artificial device to replace a missing part of the body.

Substitutive medicine: A form of medicine which relies on the replacement of failing organs or body parts by natural or human-made counterparts.

Tissue-material interface: The locus of contact and interactions between a biomaterial, implant, or device and the tissue or tissues immediately adjacent.

TYPES OF TISSUE GRAFTS

Transplantation involves the removal of cells, tissues or organs from one individual and then placing them into another individual. If the graft is returned to the same patient it is termed an **autograft**, while if it is placed in another individual of the same species it is termed an **allograft**. Tissue transferred to another species is termed a **xenograft**. If it is placed in the same anatomic location from which it was derived the transplantation procedure is termed **orthotopic**, while if the location to which it is moved is different from the original anatomic site, it is termed **heterotopic**. If tissue is transplanted from one individual to another unrelated individual there is high probability that the vascular supply to the graft will be destroyed and that it will be **rejected**.

First set rejection occurs seven to ten days after a graft is transferred between unrelated individuals. A subsequent skin graft transplanted from the same

Both **acute and chronic rejection** are processes that can occur simultaneously and are characterized by the cell types present. **Hyperacute rejection** is characterized by occlusion of vascular channels, by deposition of platelets and fibrin networks and begins within minutes of surgical completion of the suturing of donor and host vessels (Table 1.21). **Blood clotting** and **platelet aggregation** (thrombosis) occurs prior to the development of inflammation and is mediated by pre-existing antibodies that attach to endothelial cells, which subsequently activate complement. Endothelial cells secrete a form of von Willebrand factor which mediates platelet adhesion and aggregation and activates blood clotting. In early experimental transplantation procedures, hyperacute rejection occurred as a result of mismatching of blood types.

Table 1.21 Differences between hyperacute, acute and chronic rejection†

Type of rejection	Characterization
Hyperacute	Occlusion of vascular channels blood clotting and platelet aggregation mediated by circulating antibodies that activate complement
Acute humoral	Mediated by IgG antibodies to endothelial cell antigens and involves complement
Acute cellular	Necrosis of parenchymal cells in presence of lymphocytes and macrophages
Chronic	Deposition of collagen and loss of normal tissue