**ARTIFICIAL HEART AND CIRCULATORY ASSIST DEVICE**

**ENGINEERING DESIGN-**

1. **Define the problem**—clarification of the task. At first it may appear that defining the problem or clarifying the task to be accomplished is an easy matter. In general, this is not the case. Great care should be taken in defining the problem, being very specific about the requirements and specifications of the system to be designed. Very often, a complex system can be reduced to the solution of one core problem. An excellent way to begin defining the problem or clarifying the task to be accomplished is to begin by writing a careful design specification or design requirement. This is a document that lists all the requirements for the device. Further, this design requirement may elucidate one or two specific problems which, when solved, will yield a satisfactory design.
2. **Conceptual design**—plan treatment. After the problem has been defined, the designer must plan the treatment of the problem and begin conceptual design. In this phase possible solutions to the problem at hand are examined. Various methods of determining possible solutions include brainstorming, focus groups, Delphi method. This is the phase of the design process where a thorough review of the literature and examination of similar problems is valuable. In this phase of design each of the proposed solutions to the problem should be examined in terms of a hazard analysis or failure modes and effects analysis to determine which solution appears the most feasible. Economic considerations should also be examined in this phase.
3. **Detailed design**—Execute the plan. In this phase of engineering design, a detailed design is formulated. Perhaps two designs may be evaluated in the initial detailed design phase. As the detailed design or designs near completion, they must be examined with reference to the design specifications. Here, each of the proposed designs may be evaluated with regard to its ability to perform. Such aspects as system performance, reliability, manufacturability, cost, and user acceptance are all issues which must be considered before a final design is chosen.
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.

**TOTAL ARTIFICIAL HEARTS (TAH) OR VENTRICULAR ASSIST DEVICES (VAD)**

- Artificial circulatory support can be broadly classified into two categories.
- The first category is for those patients who undergo open heart surgery to correct valvular disorders, ventricular aneurysm, or coronary artery disease.
- In several cases, the heart may not recover sufficiently after surgery to take over the pumping action. In such patients ventricular assist devices are used as extracorporeal devices to maintain circulation until the heart recovers.

- Other ventricular assist devices include intra-aortic balloon pumps as well as cardiopulmonary bypass.
- Within several days or weeks, when the natural heart recovers, these devices will be removed.
- In the second category are patients with advanced stages of cardiomyopathy and are subjects for heart transplantation.
- Due to problems in the availability of suitable donor hearts, not all patients with a failed heart are candidates for heart transplantation.
- Electrically driven blood pumps, which can afford tether-free operation within the body, unlike those of the pneumatically powered pumps, are currently at various stages of development for long-term use (of more than two years).
- The components of such devices include the blood pump in direct contact with blood, energy converter (from electrical to mechanical energy), variable column compensator, implantable batteries, transcutaneous energy transmission system, and external batteries.
- The blood pump configuration in these devices includes sac, diaphragm, and pusher plate devices.
- Materials used in blood contacting surfaces in these devices are synthetic polymers (polyurethanes, segmented polyurethanes, Biomer®, and others).
- Segmented polyurethane elastomer used in prosthetic ventricles with a thromboresistant additive modifying the polymeric surface have resulted in improved blood compatibility and reduced thrombo-embolic risk in animal trials
- Design considerations include reduction of regions of stagnation of blood within the blood chamber and minimizing the mechanical stresses induced on the formed elements in blood.

**VASCULAR PROSTHESES**

- In advanced stages of vascular diseases such as obstructive atherosclerosis and aneurysmal dilatation, when other treatment modalities fail, replacement of diseased segments with vascular prostheses is a common practice.
- Refer TABLE 43.4 Classification of Vascular Prostheses(page 776)
- Arterial homografts, even though initially used in large scale, resulted in aneurysm formation especially in the proximal suture line.
- Still, a viable alternative is to use the saphenous vein graft from the same patient.
- Vein grafts have a failure rate of about 20% in one year and up to 30% in five years after implantation.
- Vein grafts from the same patients are also unavailable or unsuitable in about 10 to 30% of the patients.
- Modified bovine heterograft and gluteraldehyde treated umbilical cord vein grafts have also been employed as vascular prostheses with less success compared to autologous vein grafts.

- Prostheses made of synthetic material for vascular replacement have been used for over 40 years. Polymeric material currently used as implants include nylon, polyester, polytetrafluoroethylene (PTFE), polypropylene, polyacrylonitrile, and silicone rubber.
- However, Dacron® (polyethylene terephthalate) and PTFE are the more common vascular prostheses materials currently available.
- These materials exhibit the essential qualities for implants—they are biocompatible, resilient, flexible, durable, and resistant to sterilization and biodegradation.

**SUTURES AND ALLIED AUGUMENTATION DEVICES**

- Sutures and Suture Anchors Sutures are usually packaged as a thread attached to a metallic needle.
- Although most needles are made of stainless steel alloys, the thread component can be made of various materials, and the type used determines the class of the entire suture.
- In fact, it is common to refer to the thread as the suture. Presently, most needles are drilled (mechanically or by laser) at one end for thread insertion.
- Securing the thread in the needle hole can be achieved by crimping or adhesive attachment.
- Among the critical physical properties of sutures are their diameter, in vitro knot strength, needle-holding strength, needle penetration force, ease of knotting, knot security, and in vitro strength retention profile.
- **Two types of threads are used in suture manufacturing and are distinguished according to the retention of their properties in the biologic environment, namely, absorbable and nonabsorbable.**
- These may also be classified according to their source of raw materials, that is, natural (catgut, silk, and cotton), synthetic (nylon, polypropylene, polyethylene terephthalate, and polyglycolide and its copolymers), and metallic sutures (stainless steel and tantalum).
- Sutures may also be classified according to their physical form, that is, monofilament and twisted or braided multifilament (or simply braids).
- The first known suture, the absorbable catgut, is made primarily of collagen derived from sheep intestinal submucosa.
- It is usually treated with a chromic salt to increase its in vivo strength retention and through imparted crosslinking that retards absorption.
- Such treatment extends the functional performance of catgut suture from 1 to 2 weeks up to about 3 weeks. The catgut sutures are packaged in a specially formulated fluid to prevent drying and maintain necessary compliance for surgical handling and knot formation.

- Because of the high modulus of oriented fibers, PG is made mostly in the braided form. A typical PG suture braid absorbs in about 4 months and retains partial in vivo strength after 3 weeks.
- However, braids made of the 90/10 glycolide/l-lactide copolymer have a comparable or improved strength retention profile and faster absorption rate relative to PG. The copolymeric sutures absorb in about 3 months and have gained wide acceptance by the surgical community.
- The use of synthetic absorbable sutures exceeded that of catgut over the past two decades. This is attributed to many factors including
- (1) higher initial breaking strength and superior handling characteristics;
- (2) availability of sutures with a broad range of in vivo strength retention profiles;
- (3) considerably milder tissue reactions and no immunogenic response; and
- (4) reproducible properties and highly predictable in vivo performance. Polyglycolide (PG) was the first synthetic absorbable suture to be introduced, about three decades ago.
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**PERCUTANEOUS AND SKIN IMPLANT**

- The need for percutaneous (trans or through the skin) implants has been accelerated by the advent of artificial kidneys and hearts and the need for prolonged injection of drugs and nutrients.
- Artificial skin is urgently needed to maintain the body temperature and prevent infection in severely burned patients.
- Actual permanent replacement of skin by biomaterials is still a great clinical challenge.
- Several factors are involved in the development of percutaneous devices: 1. Type of end use—this may deal with transmission of information (biopotentials, temperature, pressure, blood flow rate), energy (electrical stimulation, power for heart-assist devices), transfer of matter (cannula for blood), and load (attachment of a prosthesis);
- 2. Engineering factors—these may address materials selection (polymers, ceramics, metals, and composites), design variation (button, tube with and without skirt, porous or smooth surface), and mechanical stresses (soft and hard interface, porous or smooth interface);
- 3. Biologic factors—these are determined by the implant host (human, dog, hog, rabbit, sheep), and implant location (abdominal, dorsal, forearm);
- 4. Human factors—these can pertain to postsurgical care, implantation technique, and esthetic look.

- No percutaneous devices are completely satisfactory. Nevertheless, some researchers believe that hydroxyapatite may be part of a successful approach.
- In one experimental trial, a hydroxyapatite-based percutaneous device was associated with less epidermal downgrowth (1 mm after 17 months vs. 4.6 mm after 3 months) when compared with a silicone rubber control specimen in the dorsal skin of canines.

**EYE AND EAR IMPLANT**

- Implants can be used to restore conductive hearing loss from otosclerosis (a hereditary defect which involves a change in the bony tissue of the ear) and chronic otitis media (the inflammation of the middle ear which can cause partial or complete impairment of the ossicular chain).
- A number of prostheses are available for correcting these defects. The porous polyethylene total ossicular implant is used to achieve a firm fixation by tissue ingrowth.
- The tilt-top implant is designed to retard tissue ingrowth into the section of the shaft which may diminish sound conduction. Materials used in fabricating these implants include polymethyl methacrylate, polytetrafluoroethylene, polyethylene, silicone rubber, stainless steel, and tantalum.
- More recently, polytetrafluoroethylene-carbon composites, porous polyethylene, and pyrolytic carbon have been described as suitable materials for cochlear (inner ear) implants.
- Artificial ear implants capable of processing speech have been developed with electrodes to stimulate cochlear nerve cells.
- Cochlear implants also have a speech processor that transforms sound waves into electrical impulses that can be conducted through coupled external and internal coils.
- The electrical impulses can be transmitted directly by means of a percutaneous device.
- Eye implants are used to restore the functionality of damaged or diseased corneas and lenses.
- Usually the cornea is transplanted from a suitable donor. In cataracts, eye lenses become cloudy and can be removed surgically.
- Intraocular lenses (IOL) are implanted surgically to replace the original eye lens and to restore function.
- IOL are made from transparent acrylics, particularly polymethyl methacrylate, which has excellent optical properties.
- Infection and fixation of the lens to the tissues are frequent concerns, and a number of measures are being used to address them.

# CARDIAC VALVE PROSTHESIS

## MECHANICAL VALVES

- The use of the caged-ball valve in the descending aorta became obsolete with the development in 1960 of what today is referred to as the Starr-Edwards ball-and-cage valve. Similar in concept to the original Hufnagel valve, it was designed to be inserted in place of the excised diseased natural valve.
- This form of intracardiac valve replacement was used in the mitral position and for aortic and multiple replacements. Since 1962 the Starr-Edwards valve has undergone many modifications to improve its performance in terms of reduced hemolysis and thromboembolic complications. However, the changes have involved materials and techniques of construction and have not altered the overall concept of the valve design in any way.
- Other manufacturers have produced variations of the ball and cage valve, notably the Smeloff-Cutter valve and the Magovern Prosthesis. In the case of the former, the ball is slightly smaller than the orifice.
- A subcage on the proximal side of the valve retains the ball in the closed position with its equator in the plane of the sewing ring.
- A small clearance around the ball ensures easy passage of the ball into the orifice.
- This clearance also gave rise to a mild regurgitation which was felt, but not proven, to be beneficial in preventing thrombus formation.

## TISSUE VALVES

- Tissue Valves Two major disadvantages with the use of mechanical valves is the need for life-long anticoagulation therapy and the accompanying problems of bleeding.
- Furthermore, the hemodynamic function of even the best designed valves differs significantly from that of the natural healthy heart valve. An obvious step in the development of heart valve substitutes was the use of naturally occurring heart valves.
- his was the basis of the approach to the use of antibiotic or cryotreated human aortic valves (homografts: from another member of the same species) removed from cadavers for implantation in place of a patient's own diseased valve.
- The first of these homograft procedures was performed by Ross in 1962, and the overall results so far have been satisfactory. This is, perhaps, not surprising since the homograft replacement valve is optimum both from the point of view of structure and function.
- In the open position these valves provide unobstructed central orifice flow and have the ability to respond to deformations induced by the surrounding anatomical structure.

- An alternative approach is to transplant the patient's own pulmonary valve into the aortic position.
- This operation was also the first carried out by Ross in 1967, and his study of 176 patients followed up over 13 years showed that such transplants continued to be viable in their new position with no apparent degeneration .

**CURRENT TYPES OF PROSTHESES**

- The ideal heart valve should:

• Be fully sterile at the time of implantation and be nontoxic

• Be surgically convenient to insert at or near the normal location of the heart

• Conform to the heart structure rather than the heart structure conforming to the valve (i.e., the size and shape of the prosthesis should not interfere with cardiac function)

• Show a minimum resistance to flow so as to prevent a significant pressure drop across the valve

• Have a minimal reverse flow necessary for valve closure, so as to keep the incompetence of the valve at a low level

• Show long resistance to mechanical and structural wear

• Be long-lasting (25 years) and maintain its normal functional performance (i.e., must not deteriorate over time)

• Cause minimal trauma to blood elements and the endothelial tissue of the cardiovascular structure surrounding the valve

• Show a low probability for thromboembolic complications without the use of anticoagulants

• Be sufficiently quiet so as not to disturb the patient

• Be radiographically visible

• Have an acceptable cost

**TISSUE VERSUS MECHANICAL**

- Tissue prostheses gained widespread use during the mid-1970s. The major advantage of tissue valves compared to mechanical valves is that tissue valves have a lower incidence of thromboembolic complications.
- Therefore, most patients receiving tissue valves do not have to take anticoagulants long-term.
- The major disadvantages to tissue valves are large pressure drops compared to some mechanical valves (particularly in the smaller valve sizes), jetlike flow through the valve leaflets, material fatigue and/or wear of valve leaflets, and calcification of value leaflets, especially in children and young adults. Valve deterioration, however, usually takes place slowly with tissue valves, and patients can be monitored by echocardiography and other noninvasive techniques.
- The clear advantage of mechanical valves is their long-term durability.
- Current mechanical valves are manufactured from a variety of materials, such as pyrolitic carbon and titanium. Structural failure of mechanical valves is rare, but, when it occurs, is usually catastrophic.
- One major disadvantage of the use of mechanical valves is the need for continuous, life-long anticoagulation therapy to minimize the risk of thrombosis and thromboembolic complications.

**HEAMODYNAMIC ASSESSMENT OF PROSTHETIC VALVE**

- In terms of considerations related to heart valve design, the basic engineering concerns are

• Hydrodynamics/hemodynamics

• Durability (structural mechanics and materials)

• Biologic response to the prosthetic implant

- The ideal heart valve design from the hemodynamic point of view should

• Produce minimal pressure gradient

• Yield relatively small regurgitation

• Minimize production of turbulence

• Not induce regions of high shear stress

• Contain no stagnation or separation regions in its flow field, especially adjacent to the valve superstructure

**IMPLICATIONS FOR THROMBUS DEPOSITION**

- In the vicinity of mechanical aortic heart valves, where peak shear stresses can easily exceed 1500 dynes/cm2 and mean shear stresses are frequently in the range of 200–600 dynes/cm2 platelet activation and aggregation can readily occur. Data indicating that shear-induced platelet damage is cumulative are particularly relevant to heart valves.
- During an individual excursion through the replacement valve, the combination of shear magnitude and exposure time may not induce platelet aggregation.
- However, as a result of multiple journeys through the artificial valve, shear-induced damage may accumulate to a degree sufficient to promote thrombosis and subsequent embolization.

**DURABILITY**

- The performance of prosthetic valves is in several ways related to structural mechanics.
- The design configuration affects the load distribution and dynamics of the valve components, which, in conjunction with the material properties, determine durability—notably wear and fatigue life.
- Valve configuration, in concert with the flow engendered by the geometry, also dictates the extent of low-wear (e.g., flow separation) and high-shear (e.g., gap leakage) regions.
- The hinges of bileaflet and tilting disc valves are vulnerable—their design can produce sites of stagnant flow, which may cause localized thrombosis, which may in turn restrict occluder motion.
- In addition, as discussed earlier, the rigid circular orifice ring is an unnatural configuration for a heart valve, since the elliptically shaped natural valve annulus changes in size and shape during the cardiac cycle.
- The choice of valve materials is closely related to structural factors, since the fatigue and wear performance of a valve depends not only on its configuration and loading but on the material properties as well.
- In addition, the issue of biocompatibility is crucial to prosthetic valve design—and biocompatibility depends not only upon the material itself but also on its in vivo environment.

**VASCULAR GRAFTS**

- Vascular surgery was first defined as a field with the initial publication of Alexis Carrel's work in 1902.
- Goyanes performed the first arterial graft in 1906 by using the popliteal vein in situ to replace an excised popliteal artery aneurysm.

- Lexer, in 1907, performed the first free autogenous vein graft by replacing an axillary artery defect with a segment of greater saphenous vein from the same patient.
- It was not until 1949, however, that Kunlin performed the first successful femoropopliteal bypass with reversed saphenous vein.
- The Korean War was the true advent of reconstructive surgery for arterial injuries as initiated by Shumacker and reported by Hughes and Bowers in 1952.

**SYNTHETIC GRAFTS**

- Synthetic prostheses are the preferred conduit for large-vessel reconstruction and the primary alternative to saphenous vein in small-vessel repair. Thankfully, the saphenous vein is of adequate quality and length in 70–75% of patients requiring small-vessel grafting.
- The two major choices available for prosthetic reconstruction are Dacron (polyethylene terephthalate) and PTFE (polytetrafluoroethylene).
- The tensile strength of these grafts remains unchanged even after years of implantation, whereas Nylon (Polyamide), Ivalon, and Orlon lose significant tensile strength over a period of months.
- Dacron grafts are constructed from multifilamentous yarn and fabricated by weaving or knitting.
- Woven fabric is interlaced in an over-and-under pattern resulting in a nonporous graft with no stretch. Knitted fabrics have looped threads forming a continuous interconnecting chain with variable stretch and porosity.
- Knitted velour is a variant in which the loops of yarn extend upward at right angles to the fabric surface resulting in a velvety texture.
- The velour finish may be created on the internal, the external, or both surfaces to enhance preclotting and tissue incorporation.
- Porous knitted Dacron prostheses may be made impervious by impregnation or coating with albumin/collagen to obviate preclotting and minimize blood loss while maintaining the superior handling characteristics of knitted Dacron grafts.
- Dacron prostheses are often crimped to impart elasticity, maintain shape during bending, and facilitate vascular anastomosis formation.
- The use of external support for vascular grafts is an alternative to crimping which uses externally attached polyprophylene rings to avoid kinking with angulation and to create dimensional stability.

- Woven Dacron grafts possess poor handling characteristics and poor compliance and elicit a poor healing response and, therefore, are used predominantly in the repair of the thoracic aorta, ruptured abdominal aortic aneurysms, and patients with coagulation defects.

**REGIONAL PATENCY**

- Patency data for any vascular graft depend on multiple factors including the conduit and vessel size.
- Large-diameter vessels have a high rate of patency, and therefore, synthetic grafts are the conduit of choice and display high short- and long-term patencies.
- Saphenous vein is the primary graft for small-caliber vessel reconstruction with good patency rates, and prosthetic grafts demonstrate acceptable short-term patencies but poor long-term results.
- Extra-anatomic bypasses utilize synthetic conduits with external support to reduce kinking**.**
- Graft failures are typically caused by:
- (1) thrombosis in the early postoperative period of 1 month,
- (2) tissue ingrowth or neointimal hyperplasia at the anastomoses after several years
- (3) graft infections

**THROMBOSIS**

- When an artificial vascular graft is first exposed to blood, a clot will typically form at the surface.
- The clot is formed initially of platelet aggregates, and then the coagulation cascade is activated to lay down fibrin and thrombin.
- The tissue which forms this inner lining of the graft is often called pseudointimal hyperplasia.
- Pseudointimal hyperplasia is devoid of cellular ingrowth and is composed mainly of fibrin, platelet debris, and trapped red blood cells .
- The blood clots immediately on contract and will occlude the vessel if the blood is stagnant or very sluggish.
- Platelet activity is generally most intense during the first 24 hours and subsidies to a very low level after 1 week.
- Various artificial surfaces are more or less thrombogenic. Many approaches have been developed in an attempt to make the grafts less thrombogenic .

- Typically, the surface characteristics have been modified to prevent adherence or activation of platelets. The surfaces have been modified by seeding with endothelial cells and other exotic treatments such as photopolymerization, plasma-gas coatings, and antisense genetics.

**NEOINTIMAL HYPERPLASIA**

- Tissue ingrowth onto the artificial surface of a PTFE graft occurs at the anastomoses and is called neointimal hyperplasia. Initially, platelets and thrombin/fibrin cover the entire graft surface within the first 24 hours.
- After this initial phase, smooth-muscle cells migrate from the native artery into the graft, variously referred to as pannus ingrowth, neointimal hyperplasia, and fibromuscular hyperplasia.
- The advances from the edge of the graft at a rate of approximately 0.1 mm per week but does not cover the entire surface in humans.
- Typically, the maximum extent of ingrowth in humans is 1-2 cm.
- In the first few hours, a thrombotic stage of platelet, fibrin, and red blood cell accumulation occurs (stage I).
- Days 3-4 consist of cellular recruitment in which the thrombus is coated with an endothelial layer (stage II).
- Cell proliferation of actin-positive cells which resorb and replace the residual thrombus are the major events in stage III, at approximately 7–9 days.(stage III)
- This description leads to a conclusion that thrombosis and cell proliferation are the two controlling events affecting graft patency.
- However, this process is one of normal healing which creates no significant stenosis in most cases.
- Recent findings indicate that a fourth stage should be added in which the tissue growths in volume primarily by synthesis and deposition of large amounts of extracellular substance over the following months.
- This stage IV leads to a hemodynamically significant stenosis.

**GRAFT INFECTIONS**

- Vascular graft infections are catastrophic and challenging problems that threaten life and limb.

- The incidence of synthetic graft infection is approximately 2% and has remained stable despite advances in aseptic surgical technique, vascular graft production, and immunology.
- Prosthetic grafts are involved in infections four times as often as autogenous vein. The infection rates for PTFE and Dacron prostheses are about the same.
- The mechanism of infectious complications may involve direct inoculation during surgery or hematogenous seeding, but most occur due to contamination at the time of surgery.
- Contact of the prosthesis with the skin of the patient is felt to be a key event. The highest incidence anatomically occurs in the inguinal areas due to perineal proximity, lymphatic disruption, and poor wound healing.
- Antibiotic prophylaxis, both systemically and locally, decreases the incidence of graft infection.
- The bonding of antibiotics to the prosthesis has been attempted in various forms to prevent prosthetic graft infection but to date is not clinically available.

Staphylococcus epidermidis is the most common organism involved in graft infections, which Staphylococcus aureus also a prevalent organism.

## ARTIFICIAL KIDNEY

### FUNCTION OF KIDNEY

- The key separation functions of the kidney are:
- 1. To eliminate the water-soluble nitrogenous end-products of protein metabolism
- 2. To maintain electrolyte balance in body fluids and get rid of the excess electrolytes
- 3. To contribute to obligatory water loss and discharge excess water in the urine
- 4. To maintain acid-base balance in body fluids and tissues
- To fulfill these functions, the kidney processes blood—or more accurately, plasma water—which in turn exchanges water and solutes with the extravascular water compartments: extracellular, intracellular, and transcellular.
- The solute concentrations in body fluids vary from site to site, yet all compartments are maintained remarkably constant in volume and composition despite internal and external stresses.
- The global outcome of normal renal function is a net removal of water, electrolyte, and soluble waste products from the blood stream.

- The kidney provides the major regulatory mechanisms for the control of volume, osmolality, and electrolyte and nonelectrolyte composition as well as pH of the body fluids and tissues.

**RENAL FAILURE**

- There are two types of renal failure: acute (days or weeks) and chronic (months or years). Acute renal failure is typically associated with ischemia (reduction in blood flow), acute glomerulonephritis, tubular necrosis, or poisoning with "nephrotoxins" (e.g., heavy metals, some aminoglycosides, and excessive loads of free hemoglobin).

- Chronic renal failure is usually caused by chronic glomerulonephritis (of infectious or immune origin), pyelonephritis (ascending infection of the urinary tract), hypertension (leading to nephrosclerosis), or vascular disease (most commonly secondary to diabetes). Renal insufficiency elicits the clinical picture of uremia.

- Although the word uremia means that there is too much urea in the blood, urea level in itself is not the cause of the problem. Uremia, often expressed in the United States as blood urea nitrogen concentration or BUN (which is actually half the urea concentration), serves as an indicator of the severity of renal disease.

- Urea is a metabolic end product in the catabolism of proteins that is hardly toxic even in high concentration. However, it mirrors the impaired renal elimination and the resulting accumulation in body fluids of other toxic substances, some of which have been identified (e.g., phenols, guanidine, diverse polypeptides); others remain unknown and are therefore referred to as uremic toxins or, for reasons to be discussed later, middle molecules.

- The attenuation of uremic symptoms by protein restriction in the diet and by various dialytic procedures underscores the combined roles of retention, removal, and metabolism in the constellation of signs of uremia.

**RENAL TRANSPLANTATION**

- The uremic syndrome resembles complex forms of systemic poisoning and is characterized by multiple symptoms and side effects.

- Survival requires that the toxins be removed, and the resulting quality of life depends on the quantity of toxins which are actually eliminated. Ideally, one would like to clean blood and body fluids to the same extent as is achieved by normal renal function.

- This is only possible at the present time with an organ transplant.

- The feasibility of renal transplantation as a therapeutic modality for ESRD was first demonstrated in 1954 by Murray and coworkers in Boston, and Hamburger and coworkers in Paris, in homozygous twins.

- Soon the discovery of the first immunosuppressive drugs led to the extension of transplantation practice to kidneys of live, related donors.
- Kidney donation is thought to be innocuous since removal of one kidney does not lead to renal failure.
- The remaining kidney is capable of hypertrophy, meaning that the glomeruli produce more filtrate, and the tubules become capable of increased reabsorption and secretion.
- Even though under ideal circumstances each cadaver donor allows two kidney transplants, the scarcity of donors is the major limitation to this form of treatment of ESRD.

**MEMBRANES OF HAEMODIALYSIS**

- Hemodialysis membranes vary in chemical composition, transport properties, and, as we will see later, biocompatibility.
- Hemodialysis membranes are fabricated from these classes of materials: regenerated cellulose, modified cellulose, and synthetics.
- Regenerated cellulose is most commonly prepared by the cuproamonium process and are macroscopically homogenous. These extremely hydrophilic structures sorb water, bind it tightly, and form a true hydrogel.
- Solute diffusion occurs through highly water-swollen amorphous regions in which the cellulose polymer chains are in constant random motion and would actually dissolve if they were not tied down by the presence of crystalline regions.
- Their principles advantage is low unit cost, complemented by the strength of the highly crystalline cellulose, which allows polymer films to be made very thin.
- These membranes provided effective small-solute transport in relatively small exchange devices.
- The drawbacks of regenerated cellulose are their limited capacity to transport middle molecules and the presence of labile nucleophilic groups which trigger complement activation and transient leukopenia during the first hour of exposure to blood.
- The advantages appear to outweigh the disadvantages, since over 70% of all hemodialyzers are still prepared from cellulosics, the most common of which is supplied by Akso Faser AG under the trade name Cuprophan.
- A variety of other hydrophilic polymers account for 20% of total hemodialyzer production, including derivatized cellulose, such as cellulose acetate, diacetate, triacetate, and synthetic materials such as polycarbonate (PC), ethylenevinylalcohol (EVAL), and polyacrylonitrile-sodium methallyl sulfonate copolymer (PAN-SO3), which can all be fabricated into homogeneous films.

**PERITONEAL DIALYSIS**

- The process of CAPD is technically simple. Approximately 2 L of a sterile, nonpyrogenic, and hypertonic solution of glucose and electrolyte are instilled via gravity flow into the peritoneal cavity.
- The growth of peritoneal dialysis. Line and points refer to the total estimated worldwide peritoneal dialysis population; the numbers adjacent to the points are PD patients as a percent of total dialysis population. At the end of 1993, 14,000 of the 90,000 peritoneal dialysis patients utilized some version of APD; the remainder were treated with CAPD. Data compiled taken from various patient registries and industrial sources.
- Intraperitoneal fluid partially equilibrates with solutes in the plasma, and plasma water is ultrafiltered due to osmotic gradients.
- After 4–5 hours, except at night where the exchange is lengthened to 9–11 hours to accommodate sleep, the peritoneal fluid is drained and the process repeated.
- **Patients perform the exchanges themselves in 20–30 minutes, at home or in the work environment after a training cycle which lasts only 1–2 weeks. In APD, 10–15 L are automatically exchanged overnight; 2 L remain in the peritoneal cavity during the day for a "long dwell" exchange.**
- Net fluid removal ranges up to 1000 ml per exchange. CAPD generally removes the same quantity of toxins and fluid as HD ( a little thought will show that this is a requirement of steady state, provided that generation is unaltered between the two treatment formats); however, CAPD requires a higher plasma concentration as the driving force for this removal. Steady-state concentrations during CAPD are typically close to the peak, i.e., pretreatment, concentrations of small solutes during HD but much lower than the corresponding peaks for larger species.