20.1 INTRODUCTION

Cardiovascular disease remains the leading cause of mortality among men and women in Western countries. Many biomedical engineers have focused their careers on the study of cardiovascular disease and the development of devices to augment or replace function lost to the disease process. The application of engineering principles to device design has improved device function, while minimizing some of the detrimental side effects. Progress to date has allowed complex, challenging cardiovascular surgical procedures (e.g., open-heart surgery) and medical therapies (e.g., dialysis) to become routine, although limitations remain. In this chapter, eight major categories of cardiovascular devices are addressed, including cardiac valves, stents and stent grafts, pacemakers and implantable defibrillators, vascular grafts, hemodialyzers, indwelling catheters, circulatory support devices, and blood oxygenators. For each topic, the market size, indications for device use, device design, complications and patient management, and future trends are covered. The intent is to provide a brief introduction to the current status of cardiovascular device development and application and to identify challenges that remain in the field.

20.2 ARTIFICIAL HEART VALVES

20.2.1 Market Size

There were at least 60,000 valve replacement operations performed in the United States during 1996 (Vongpatanasin et al., 1996). About two-thirds of the artificial heart valve market in the United States
consists of various mechanical valves, with the remaining one-third being distributed among the bioprosthetic, or tissue-based, models. Worldwide, the mechanical valve market is slightly less, approximately 60% of market share (Akins, 1995).

20.2.2 Indications

The medical indications for valve replacement are thoroughly described in a report from the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, which address the management of patients with valve disease (Bonow et al., 1998). The etiology of valve disease differs, depending on the patient group and the valve location, as does the preferred corrective treatment. In general, the young suffer from congenital valve defects, while older adults exhibit acquired valve disease. Valve replacement can be performed upon all valves of the heart but most cases involve the aortic or mitral valves. Common reasons for native valve replacement are severe stenosis and regurgitation with or without symptoms, which may include chest pain, shortness of breath, and loss of consciousness. The reduction in effective orifice size associated with a stenotic lesion results in a large transvalvular pressure gradient that may exceed 50 mmHg in the aortic position for severe cases (Bonow et al., 1998). In regurgitation, the blood pumped forward into the recipient vessel or ventricle spills back into the adjacent pumping chamber through an incompetent valve, minimizing forward movement. The end effects of chronic stenosis or regurgitation are compensatory anatomic changes that accommodate, for a limited time, the reduced pumping efficiency due to restricted blood movement. In general, heart valve replacement is performed when repair is not possible, as the implantation of an artificial heart valve brings with it another set of problems. Total replacement and removal of native valve components in the mitral position is particularly limited, as the mitral valve is anatomically and functionally integral to the left ventricle (David et al., 1983; Yun et al., 1999). Concomitant illnesses such as congestive heart failure, atrial fibrillation, and coronary artery disease can alter the indication for valve replacement, as can the surgical need to correct other cardiac disease.

20.2.3 Current and Historical Device Design

Artificial heart valve design has a long and colorful history, with more than 80 different versions of valves being introduced since the 1950s (Vongpatanasin et al., 1996). The two general types of replacement valves, mechanical and biologic, each have their own set of indications, complications, and performance factors. The mechanical valve can be further categorized into three major design lines: caged ball, single tilting disk, and bileaflet (Vongpatanasin et al., 1996). Caged-ball valves have been largely supplanted by the more modern single-tilting-disk and bileaflet valves. Biologic valves are divided according to the source of the tissue material, with the term bioprosthetic reserved for valves constructed from nonliving, animal-source tissue. Homograft biologic valves are preserved human aortic valves or pulmonary valves surgically placed within a recipient patient (Bonow et al., 1998). Heterograft bioprosthetic valves consist of porcine heart valves or bovine pericardial tissue formed into a valve over a support structure (Vongpatanasin et al., 1996). Because mechanical and bioprosthetic valves have different design considerations, the categories are discussed separately.

**Mechanical Valves.** The assorted mechanical valve designs use different approaches to achieve the same functional goal. Caged-ball valves use a free-floating polymeric sphere constrained by a metal cage to periodically occlude the valve orifice. Single-disk valves possess a central disk occluder that is held in place by struts projecting from the housing ring. The disk opens through a combination of tilting and sliding over the struts to reveal primary and secondary orifices. Bileaflet valves feature leaflets that are hinged into the housing ring. The opened valve presents three orifices, two along the housing ring edge and one central orifice between the leaflet mount points. Figure 20.1 shows both orifice and profile views of representative tilting-disk and bileaflet mechanical valves.
Mechanical valves are expected to perform flawlessly for decades with minimal patient burden. Criteria used to evaluate designs during development and clinical use can be divided into structural and hemodynamic groups, although there is considerable overlap. Structural considerations involve fatigue and device integrity, valve profile, rotatability, and occluder interference (Akins, 1995). To accommodate the wear associated with operating hundreds of millions of times, current mechanical valves are manufactured with durable metal and carbon alloys (Vongpatanasin et al., 1996; Helmus and Hubbell, 1993), and include a polymer fabric sewing ring for surgical placement. Rotatability of the valve is desirable, as evidence suggests that optimum orientations minimizing turbulence and microembolic signals exist for mechanical heart valves in vivo (Kleine et al., 2000; Laas et al., 1999).
Concerns regarding valve profile and occluder interference focus on possible negative interactions between the valve, adjacent ventricular structures, native valve remnants, and surgical suture material. The impingement of these structures into the valve could prevent complete closure of the valve or cause binding of the occluder. Although not a structural requirement, devices tend to be radio-opaque to aid in visualization during radiographic procedures.

Hemodynamic performance factors that should be considered during functional evaluation of a valve design are the transvalvular pressure gradient, rate and duration of valve opening, dynamic regurgitant fraction, and static leak rate (Akins, 1995). The transvalvular pressure gradient is a function of the effective orifice area of the valve and the flow regime (turbulent or laminar) encountered. The mass of the occluder and mechanism of action play a significant role in the rate and duration of valve actuation, and similarly in the dynamic regurgitant fraction, which represents the percentage of blood that flows back into the originating chamber prior to valve closure. Finally, some leak is expected in the closed valve position. Consistent convective flow over these surfaces is believed to aid in the minimization of thrombotic deposition.

**Bioprosthetic Valves.** Engineering design concerns have little influence on homograft valves because of their anatomic origin, thereby limiting the focus to heterograft bioprostheses. The bioprosthetic tissue found in heterografts is treated with glutaraldehyde to cross-link the proteins that make up the tissue structure. The treatment is cytotoxic, disrupts the antigenic proteins that can cause an immune response, and improves the toughness of the tissue by cross-linking the structural collagen (Bonow et al., 1998). Some bioprosthetic valves are further treated with surfactants, diphosphonates, ethanol, or trivalent metal cations to limit the rate of calcification and associated structural deterioration (Schoen and Levy, 1999).

Porcine heterograft valves can be mounted on a support scaffold with a sewing ring, although unmounted designs have been introduced to improve flow characteristics and structural endurance. Heterograft valves constructed of bovine pericardium are formed over a scaffold with a sewing ring to mimic an anatomic valve shape. Because the pericardial valves are constructed to design criteria rather than harvested, the orifice size can be made larger to improve flow characteristics, while the higher collagen content may allow improved graft resilience when cross-linked (Bonow, 1998). Figure 20.2 shows representative porcine and bovine pericardial heterograft valves.

**Design Performance Evaluation.** The design of artificial heart valves has benefited from the advent of computational fluid dynamics and other computationally intensive modeling techniques. Simulations have been used to predict the performance of both bioprosthetic (Makhijani et al., 1997) and mechanical (Krafczyk et al., 1998) valve designs. Results from computer modeling can be

![FIGURE 20.2 Two tissue-based artificial heart valves are shown above with a U.S. quarter dollar for size comparison. The valve on the far left is a porcine heart valve, while the other valve is constructed of bovine pericardium. Both valves are intended for aortic placement.](image-url)
compared with findings from experimental studies using such methods as particle image velocimetry (PIV) (Lim et al., 1998) and high-speed photography of valve structure motion (De Hart et al., 1998). Such comparisons provide necessary model validation, revealing inadequacies in the numerical model and capturing phenomena not predicted using existing model assumptions.

### 20.2.4 Complications and Patient Management

Mechanical and bioprosthetic valves suffer from complications that dictate follow-up care and preventive measures. Possible complications facing heart valve recipients include thromboembolism, hemolysis, paravalvular regurgitation, endocarditis, and structural failure of the valve (Vongpatanasin et al., 1996). Some preventive measures are indicated for both mechanical and biologic valve recipients, such as the use of antibiotics during dental surgery and invasive procedures to avoid infective endocarditis (Dajani et al., 1997). Other preventive treatments, such as long-term anticoagulation, are administered differently, depending on the type of valve implanted.

Because of the high incidence of thromboembolic complications associated with mechanical artificial heart valves, chronic anticoagulation is required. Anticoagulation with warfarin and an antiplatelet agent such as aspirin is indicated for both mechanical and heterograft bioprosthetic valves for the first 3 months after implantation (Stein et al., 2001; Bonow et al., 1998; Heras et al., 1995). After that time warfarin is discontinued for heterograft bioprosthetic valves unless the patient possesses a risk factor that increases susceptibility to thromboembolic complications (Bonow et al., 1998). Despite the use of chronic anticoagulant therapy, a recent review reported that between 0.4 and 6.5 percent of mechanical heart valve recipients will experience a thromboembolic event per year, a range that is dependent upon valve type, number, placement, and other risk factors, as well as the level of anticoagulation (Stein et al., 2001). The long-term risk of thromboembolism in bioprosthetic heart valve recipients is comparatively low, ranging from 0.2 to 2.6 percent per year (Stein et al., 2001).

In contrast to the anticoagulation requirement associated with mechanical valves, the largest problem facing patients with bioprosthetic valves is progressive structural deterioration due to calcification, which can eventually require valve replacement and the risks of a reoperation (Hammermeister et al., 2000; Schoen and Levy, 1999). Heterograft bioprosthetic valves exhibit accelerated deterioration in younger patients, which promotes the use of mechanical valves in this age group when homograft valves are unavailable (Bonow et al., 1998).

Although the literature is rife with comparisons between valve designs in regard to their complication rates, the general lack of large randomized trials using standardized methods makes valid comparisons problematic (Horstkotte, 1996). To reduce some of the confusion surrounding outcome reporting in heart valve studies, the Society of Thoracic Surgeons and the American Association of Thoracic Surgery have updated guidelines for reporting common surgical and nonsurgical artificial valve complications (Edmunds et al., 1996). The guidelines distinguish between structural and non-structural valve dysfunction, thrombosis, embolism, bleeding events, and infection. In addition, various types of neurologic events are graded, and methods of statistical data analysis are suggested on the basis of the type of data being collected and analyzed. Adherence to such guidelines should allow valid comparisons to be made between manuscripts reporting on outcomes with different valve types and clinical approaches (Edmunds et al., 1996).

### 20.2.5 Future Trends

Increasing efforts in the area of tissue engineering hold great promise for the development of replacement valves with improved biocompatibility. As reviewed in a recent article (Jankowski and Wagner, 1999), researchers have attempted to stimulate the growth of endothelial cells on existing bioprosthetic valves to limit valve degradation and thromboembolic complications, while others have endeavored to grow valves and individual leaflets de novo using cell-seeded polymeric scaffolds. Endothelialization of commercial bioprosthetic valve tissue is hampered by the cytotoxic aftereffects.
of glutaraldehyde fixation (Eybl et al., 1992), directing efforts toward alternative fixation techniques and coatings to improve cell adhesion and growth. Although these efforts have reached in vivo experimentation, results for endothelialized bioprosthetic valves have been mixed (Lehner et al., 1997). Efforts to produce artificial valves de novo using harvested endothelial cells and fibroblasts grown on a biodegradable scaffold have resulted in functional pulmonary valve leaflets in a lamb model (Shinoka et al., 1996). More recently, a biohybrid trileaflet pulmonary valve has been successfully tested in lambs for a limited period (Sodian et al., 2000a). In vitro (Sodian et al., 2000b) and recent in vivo (Sodian et al., 2000a) work has shown much promise although challenges in creating valves with ideal performance characteristics remain. Successful development of a viable autologous biologic valve capable of long-term stability and growth would likely revolutionize the management of heart valve disease through a reduction of implant-related morbidity and mortality, with particular applicability to pediatric patients.

20.3 STENTS AND STENT-GRAFTS: PERCUTANEOUS VASCULAR THERAPIES

20.3.1 Market Size

According to Taber’s Cyclopedic Medical Dictionary, the term stent refers to “any material used to hold tissue in place or to provide a support for a graft or anastomosis while healing is taking place” (Thomas, 1989). As this broad definition would suggest, stents are indicated for a wide range of disease states in the genitourinary, hepatobiliary, gastrointestinal, reconstructive, and vascular fields. The focus of the current section is limited to those devices used in the vasculature, primarily the peripheral and coronary arteries. It is worth noting that stents approved by the FDA for use in a particular intervention are often used for other tasks, such as the use of biliary stents in coronary bypass grafts (Holmes et al., 1998).

Stents and stent-grafts are widely used to treat vascular lesions and are being employed in a growing number of cases. Many patients suffering from atherosclerotic vascular disease possess focal narrowings inside their blood vessels. These narrowed regions, termed stenoses, are made up of fatty plaques and can reach a size where they restrict the movement of blood to the tissue, resulting in sequelae ranging from pain upon physical exertion to tissue breakdown in severe cases. One dangerous scenario is thrombus formation at the lesion site with the potential for embolization distally. Thrombosis and thromboembolization can directly lead to tissue ischemia (oxygen starvation) and possible tissue death. Percutaneous transluminal coronary angioplasty (PTCA), otherwise known as balloon angioplasty, is a procedure wherein a catheter-mounted balloon is moved to the lesion site and inflated, displacing the tissue and creating a wider lumen in the vessel. Stents are designed to keep the treated lesion open through forceful opposition with the vessel wall; in essence, the stent braces the disrupted lesion in an expanded position. In 1998 it was estimated that each year more than a million patients worldwide received some type of nonsurgical cardiac revascularization procedure (Holmes et al., 1998). Stents are placed during most of these coronary interventions either as a primary or adjunct therapy (Al Suwaidi et al., 2000), and recent guidelines report that less than 30 percent of interventions are composed of PTCA alone (Smith et al., 2001). Estimates for the number of interventional procedures in the peripheral vasculature exceeded 200,000 per year in 1997, with the expectation that up to 50 percent of traditional vascular procedures would be replaced with an endovascular analogue in the near future (Krajcer and Howell, 2000). One such endovascular intervention is the abdominal aortic stent-graft and its use in abdominal aortic aneurysm repair, which is traditionally a high-risk surgical procedure with perioperative mortalities ranging from 3 to 60 percent, depending upon patient characteristics (Krajcer and Howell, 2000). Stent-grafts consist of a polymer fabric or sheet coating mounted on a stenting device that excludes the vessel wall from the flowing blood, thus reducing its exposure to the pulse pressure wave. More than 4000 abdominal aortic stent-grafts were placed in 1999 (Krajcer and Howell, 2000).
20.3.2 Indications

Consensus documents from the American College of Cardiology and the American Heart Association detail coronary stenting indications currently supported by literature findings (Holmes et al., 1998; Smith et al., 2001). It is worth noting that few patients qualify for stent placement under the FDA guidelines associated with device approval (Holmes et al., 1998), yet stent utilization has increased to encompass pathologies not within the approved sphere of use despite the lack of strong supporting clinical evidence (Smith et al., 2001). Stents are most often placed in nonemergent settings to optimize outcome and improve patency of vessels that have undergone balloon angioplasty (Al Suwaidi et al., 2000). An ideal acute PTCA outcome is variously defined, but a residual vessel diameter stenosis of <35 percent along with a ratiometric increase in coronary blood flow of 2.5 under adenosine stimulation has been predictive of improved patient outcomes (Serruys et al., 1997). Unfortunately, an ideal PTCA result occurs in only 25–50 percent of patients, thus stenting is an important adjunctive therapy (Holmes et al., 1998). Stents are also placed emergently to treat or prevent acute closure of an artery following balloon angioplasty. Other less well-established indications include stent placement for the treatment of chronic total vessel occlusion, saphenous vein bypass graft lesions, acute myocardial infarction, gradual tissue overgrowth in an existing stent, and lesions with difficult morphology, such as long, diffuse stenoses, stenoses in small vessels, and lesions at a bifurcation or vessel opening (Holmes et al., 1998). Randomized trials currently underway or in the planning stages are expected to clarify these and other potential indications.

A recent review article listed the current indications for peripheral, noncoronary vascular stent placement (Mattos et al., 1999). The reported indications include immediate treatment of balloon angioplasty complications such as intimal dissection and flap formation; the correction of unsatisfactory angioplasty outcomes such as residual stenosis, spasm, recoil or occlusion; treatment of complicated, chronic lesions or occlusions; and as a routine combination treatment with angioplasty. The most common reason for placement of a stent in the peripheral vasculature is an unsatisfactory result from angioplasty.

20.3.3 Vascular Stent Design

The ideal stent would possess a number of characteristics designed to ease handling and permit stable, long-term function. Desired handling characteristics include a simple, effective deployment method, high radiopacity for visualization under fluoroscopy, flexibility to ease passage through tortuous vessels, limited shortening during expansion so placement is optimal, high expansion ratio to allow smaller profiles, and ease of retrievability or removal if misplaced (Henry et al., 2000; Mattos et al., 1999). Preferred functional characteristics include a high hoop strength to counteract arterial spasm, biocompatibility that minimizes short-term and long-term complications, plus durability in the stressful, corrosive environment of the human body (Henry et al., 2000; Mattos et al., 1999). Despite the large number of stent designs, with additional models under development, no one stent possesses all these particular characteristics (Henry et al., 2000).

Stents can be divided into two main groups on the basis of the method of expansion. Balloon-expandable stents either arrive premounted on a balloon angioplasty catheter or are mounted by the doctor prior to the procedure. A balloon catheter with inflation apparatus is shown in Fig. 20.3. While mounted, the stent is moved into place and the balloon inflated to expand the stent to the desired diameter. Figure 20.4 illustrates the placement and inflation procedure for balloon-expandable stents. In contrast, self-expanding stents come premounted or sheathed. Once deployed to the treatment area, the sheath is pulled back, allowing the stent to expand to its predetermined diameter. Balloon-expandable stents can be further subdivided into slotted-tube and coil-based designs (Oesterle et al., 1998).

Each stent type possesses particular advantages and disadvantages. Self-expanding stents can experience shortening during deployment, which may complicate placement, although more recent stent designs are able to mitigate this effect to a significant degree (Oesterle et al., 1998). Balloon-expandable stents exhibit a greater stiffness than the self-expanding models, which can cause
FIGURE 20.3 A balloon catheter and inflation pump are shown. Balloon catheters are used to widen stenosed or narrowed vessels and to expand stents. The balloon is often inflated with a mixture of saline and contrast agent to aide radiographic visualization.

FIGURE 20.4 The stent implantation procedure for a balloon-expandable stent is demonstrated in the above figure. The balloon-mounted stent is first guided into place inside a damaged vessel under fluoroscopy. The balloon is then inflated, expanding the stent to lie in opposition to the vessel wall. The balloon is then deflated and withdrawn, leaving the stent in place to prevent constriction of the vessel. (Cordis Corporation, Miami Lakes, Florida.)
difficulty navigating long or tortuous lesions and anatomy (Mattos et al., 1999). In general, coil
design stents have greater flexibility than the slotted tube models, making them attractive for more
complex and difficult to reach lesions such as those found at bifurcations and in side branches
(Oesterle et al., 1998). Some more recent stent designs combine features of slotted tube and coil
models. Both stent types usually undergo further balloon expansion to optimize the resulting
placement (Oesterle et al., 1998). Figure 20.5 illustrates the flexibility that can be achieved by a
modern stent.

Most stent designs use metal as a construction material. Traditional alloys include tantalum and
certain stainless steels (304 and 316L) (Mattos et al., 1999). Nitinol, a nickel-titanium alloy, has been
used in self-expanding stent designs for its shape memory properties (Mattos et al., 1999). Both
biodegradable and nondegradable polymeric stents have been developed, but the positive results of
metallic stents over the long term, coupled with the technical challenges of producing a mechanically
viable polymeric stent, have limited efforts in this area (Bertrand et al., 1998).

To accommodate the variety of arterial pathologies encountered, stents come in an ever-increasing
array of sizes. Coronary stent diameters span from 2.5 to 4 mm, with lengths ranging from 8 to 38
mm (Al Suwaidi et al., 2000). Stents for the peripheral vasculature are of a considerably greater size
because of the much larger vessels in the thorax, abdomen, and proximal extremities. The various
stent designs appear to differ in their ability to maintain postexpansion lumen size (Okabe et al.,
1999), which could affect clinical outcomes such as long-term patency (Fischman et al., 1994).

20.3.4 Management and Complications

As of 1997, incidence rates for complications following coronary stenting were under 1 percent for
thrombosis when the patient was treated with antiplatelet agents, less than 25 percent for repeated
arterial narrowing, and less than 15 percent of patients required an additional procedure on the
stented lesion during the follow-up period (Oesterle et al., 1998). Restenosis is a term referring to the
repeated narrowing or closure experienced in stented lesions typically due to an overgrowth of
smooth muscle cells. Affecting up to a full quarter of patients, restenosis is a common complication

FIGURE 20.5 The flexibility of a modern stent design (Cordis Corporation 7-cell BX Velocity) is demonstrated.
(Cordis Corporation, Miami Lakes, Florida.)
following coronary stent placement and remains the major stumbling block in the long-term success of stenting (Virmani et al., 1999). Evidence from animal studies suggest that the amount of restenosis is related to the amount of damage incurred at stent implantation (Schwartz et al., 1992), while other evidence implicates the stent design as affecting the rate of restenosis and thrombosis (Rogers and Edelman, 1995). Additional causes implicated in restenosis include excessive thrombosis, inflammation, poor stent apposition, and the presence of large amounts of necrotic tissue or ruptured plaque (Oesterle et al., 1998). Restenosis is not limited to stented lesions, but actually occurs at a higher rate in lesions receiving PTCA only (Serruys et al., 1994) and is a significant contributor to stent placement in previously treated lesions.

A large assortment of potential stent coatings and materials have been evaluated in an effort to reduce the number of complications associated with stent implantation. Approaches have included both degradable and nondegradable polymeric coatings for surface passivation and drug elution, coating with the anticoagulant heparin to limit platelet activation, endothelial cell seeding to create a “natural” surface, and the use of radioactive sources to inhibit cellular proliferation (Bertrand et al., 1998). As detailed in a recent review, some nondegradable polymers under investigation include polyethylene terephthalate, poly(dimethyl)siloxane (van der Giessen et al., 1996), poly(organo) phosphazene (De Scheerder et al., 1995), methacrylphosphorylcholine/laurylmethacrylate copolymer (Chronos et al., 1995), and polyurethane (Bertrand et al., 1998). Degradable polymer systems have included polyhydroxybutyrate valerate, polyorthoester, polyethylene oxide/polybutylene terephthalate (van der Giessen et al., 1996), polyglycolic/polyactic acid, and polycaprolactone (Bertrand et al., 1998). Nonpolymeric coatings such as silicon carbide (Ozbek et al., 1997) and the hemostatic protein fibrin have also been investigated (Bertrand et al., 1998). The spectrum of results reported in humans and various animal models suggests that the overall direct effect of polymer coatings on stent biocompatibility is unclear at this time (Bertrand et al., 1998).

Inclusion of various drugs into the polymeric coatings further complicates analysis, but recent animal studies have shown a reduction of neointimal proliferation using such an approach with polylactic acid and related copolymer coated stents containing a common steroid (Strecker et al., 1998). Promising results from studies using other drugs with polylactic acid acting as a degradable stabilizer (Alt et al., 2000) indicate that the polymer-based delivery system shows future potential. Heparin coating of stents has been shown to limit thrombosis without an apparent long-term effect on neointimal growth (Serruys et al., 1998), but it is speculated that improvements in deployment technique and antithrombotic drug regimens might have contributed to improved outcomes (Bertrand et al., 1998). Radiation treatment of the stented area has been attempted with both gamma- and beta-type radiation sources being delivered via catheter or radioactive stent to reduce cell proliferation (Waksman, 1999). Recent results with a gamma radiation source have shown improved rates of clinical and angiographic restenosis in patients treated for instant restenosis; unfortunately, the treatment was associated with a higher rate of late thrombosis and subsequent heart attack (Leon et al., 2001). Beta irradiation of lesions treated with PTCA without concomitant stent placement has been shown to reduce restenosis in a dose-dependent manner (Verin et al., 2001), and could eliminate the need for eventual stenting in some patients.

20.3.5 Future Developments

Progress in stent technology will undoubtedly focus on reducing the incidence of restenosis and on the improvement of stent outcomes in challenging vascular lesions. Recent developments include PTFE-coated coronary stents designed primarily for placement in saphenous vein grafts (Baldus et al., 2000), which usually exhibit diffuse atherosclerotic disease and high complication rates when stented (Oesterle et al., 1998). Stents coated with native arterial and venous tissue are also under testing (Stefanadis et al., 2000a; 2000b). Drug-eluting stents show promise for mitigating neointimal formation and late-phase restenosis, as high local concentrations of therapeutic and preventative agents may be achieved. It is not difficult to envision a stent capable of minimizing vessel injury during deployment, sealing the injured site when expanded, and releasing radiation, drugs, or other factors in a manner responsive to the particular characteristics of the lesion involved. Wound-responsive “smart” stents could result in improved patency rates even in difficult lesions where...
enhanced thrombotic deposition or neointimal proliferation is likely to occur. Improved knowledge regarding the pathobiologic causes of stent complications is required, as is additional insight into technical details such as elution rates, radiation dosing, and other responsive features.

20.4 PACEMAKERS AND IMPLANTABLE DEFIBRILLATORS

20.4.1 Market Size

The market for pacemakers has grown over the past 4 decades as a result of improved device function and an expanding set of clinical indications. Approximately 1 million patients in the United States had permanent pacemakers in 1996 (Kusumoto and Goldschlager, 1996), many of whom will need either a lead or generator replacement sometime in the future. Recent incidence data from nonfederal, short-stay hospitals suggests at least 135,000 permanent cardiac pacemakers were implanted in the United States in 1997, with a minimal estimate of 26,000 automatic implantable cardioverter-defibrillator (AICD) units being placed during the same year (Owings and Lawrence, 1999).

20.4.2 Indications

The American College of Cardiology and American Heart Association consensus practice guideline lists current indications for artificial pacemaker and implanted cardioverter-defibrillator use (Gregaratos et al., 1998). The purpose of a pacemaker is to deliver an electrical impulse of sufficient magnitude to depolarize the heart chamber in a spreading, coordinated fashion, as occurs in a normal heart beat. In contrast, defibrillators are used to depolarize the entire heart at once in an effort to terminate uncoordinated contractions. The natural refractory period of the myocardial tissue usually prevents erratic residual electrical activity from propagating for a short period of time, restoring coordinated muscular contraction.

In general, a pacemaker is warranted in certain cases where electric impulse conduction or initiation in the heart is blocked, slowed, or triggered in an irregular, variable fashion. Specific diseases for which pacemaker therapy is employed include certain forms of atrioventricular and fascicular conduction block, sinus node dysfunction, and some forms of neurocardiogenic syncope (Gregaratos et al., 1998). The most popular indications for first-time implantation of cardiac pacemakers have changed over time. In 1993, over half of all new pacemakers were placed to treat sinus node dysfunction, the most common indication for pacemaker implantation (Bernstein and Parsonnet, 1996a). Congenital or acquired atrioventricular (AV) conduction block was second, accounting for approximately 31 percent of primary implantations, followed by drug-induced bradycardia, AV block secondary to ablation, and tachyarrhythmia (Bernstein and Parsonnet, 1996a). Emerging indications, particularly pacemaker treatment of congestive heart failure, could significantly alter the percentages indicated above (Cazeau et al., 2001; Gerber et al., 2001).

The indications for implantation of a cardioverter-defibrillator are based primarily on the past presence of a potentially fatal ventricular arrhythmia due to nontransient causes, regardless of the specific illness (Gregaratos et al., 1998). Recent evidence has suggested that the contributing illness might alter therapy effectiveness, leading to changes in the recommendations in the near future (Gregaratos et al., 1998). Two indications, ventricular tachycardia or fibrillation and aborted sudden death, dominated the list of indications for implantable cardioverter-defibrillator (ICD) placement in a 1993 survey, accounting for 97 percent of the devices implanted for which an indication was reported (Bernstein and Parsonnet, 1996a).

20.4.3 Device Design

The wide range of electrophysiologic disorders treated with pacemakers and defibrillators requires devices with various capabilities and settings. Generic classification codes have been developed to
ease the identification of the different pacemakers, defibrillators, and associated leads presented both in the literature and medical practice. One such code is the North American Society for Pacing and Electrophysiology/British Pacing and Electrophysiology Group Generic Pacemaker Code, which contains five positions and defines the chambers that are paced and sensed, the potential electrical response to sensed rhythms, rate modulation functions and the degree of programmability, and antitachyarrhythmia functions, if present (Bernstein et al., 1987). The code represents an expansion of previous generic classification schemes to incorporate rate-adaptive functions and cardioversion-defibrillation tasks (Bernstein et al., 1987). Table 20.1 summarizes the possible features for each location. More than 60 percent of pacemakers implanted in 1993 were of the DDD type, possessing dual chamber sensing and pacing with both excitatory and inhibitory functions, with half of that number having additional rate adaptive features (DDDR) (Bernstein and Parsonnet, 1996a). Similar classification codes exist for defibrillators (Bernstein et al., 1993) and pacing leads (Bernstein and Parsonnet 1996b).

Pacemaker and defibrillator systems consist of two implanted and one external component: the generator, cardiac leads, and programmer, respectively (Morley-Davies and Cobbe, 1997). Although the clinical functions of pacemakers and defibrillators differ, the desired component characteristics are similar and include low complication rates coupled with small size, durability, and longevity.

**Generators.** Despite enhanced functional performance and an ever-increasing array of features, current ICD generators displace less than half the volume of those devices implanted a short time ago as a result of improved circuit, packaging, and power storage technology (Morris et al., 1999). Similarly, modern pacemaker generators are small, thin, and weigh only 20–30 g (Kusumoto and Goldschlager, 1996). Generator and battery technology allows pacemakers to last approximately 5 to 9 years in the body (Morley-Davies and Cobbe, 1997), with the more complex dual-chamber designs having a shorter lifespan than the simpler, single-chamber units (Kusumoto and Goldschlager, 1996). An example of state-of-the-art pacemaker and implantable defibrillator generators is shown in Fig. 20.6.

Power technology has steadily improved since the first mercury-zinc batteries of the 1960s, with modifications in other generator components and usage algorithms further increasing battery endurance (Jeffrey and Parsonnet, 1998). Novel power supplies have included the nuclear slug and biokinetic sources, but the advent of the lithium-based power source allowed for increased generator longevity over mercury-zinc types and was amenable to being hermetically sealed (Jeffrey and Parsonnet, 1998). The current batteries used in pacemakers and defibrillators differ in formulation. Pacemakers utilize lithium-iodine batteries (Kusumoto and Goldschlager, 1996), while ICDs utilize lithium-silver-vanadium batteries and a capacitor network for discharges (Morris et al., 1999).

**Electrical Leads.** The pacing lead consists of five components: the connector, conductor, insulating material, electrode(s), and fixation mechanism (Crossley, 2000). Electrical leads have to fulfill a number of conflicting requirements, although reliable performance remains the dominant criterion.

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**TABLE 20.1** The five-position NASPE/BPEG Generic Pacemaker Code. The purpose of the code is to allow medical practitioners to recognize the basic features and capabilities of a given pacemaker. The code alone does not provide a complete description of device features, but is clear and simple to use.

<table>
<thead>
<tr>
<th>Positions and description</th>
<th>I. Chamber(s) paced</th>
<th>II. Chamber(s) sensed</th>
<th>III. Pacemaker response</th>
<th>IV. Rate adaptive and programming features</th>
<th>V. Antiarrhythmic pacing, cardioversion, and defibrillator functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrium</td>
<td>Atrium</td>
<td>Triggered</td>
<td>Rate Adaptive</td>
<td>Pacing</td>
<td></td>
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<tr>
<td>Ventricile</td>
<td>Ventricile</td>
<td>Inhibited</td>
<td>Simple Programmability</td>
<td>Shock</td>
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<td>Dual</td>
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<td>Multiple Programmability</td>
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<td>NOOne</td>
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<td>NOOne</td>
<td>Communicating</td>
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Source: Adapted from Bernstein et al., (1987.)
FIGURE 20.6 The generators of a modern cardioverter-defibrillator (Ventak Prizm DR, Guidant Corporation, Minneapolis) and pacemaker (Discovery II DR, Guidant Corporation, Minneapolis) are shown. Both are dual-chamber devices, with the cardioverter-defibrillator possessing pacing features in addition to the core cardioversion hardware. The added hardware and power requirements demand a larger housing for this device in comparison to the pacemaker.

(de Voogt, 1999). Leads should possess a small diameter, be flexible enough to place but durable enough to resist wear, possess favorable power consumption characteristics, anchor in place to prevent migration, and enjoy good biocompatibility.

Pacing leads can be subdivided into a number of groups based on the area of placement and method of stimulation. Leads can be placed either on the epicardium (external surface) of the heart or, by a transvenous route, onto the endocardium (internal surface) of the right heart atrium or ventricle. Epicardial leads are used for permanent pacing in pediatric cases, where size considerations or congenital defects prevent transvenous placement, and in patients who have undergone tricuspid valve replacement (Mitrani et al., 1999). Transvenous placement of the lead is the preferred route in most patients.

The depolarization shock can be delivered through either a unipolar or bipolar lead. Most older leads utilize the unipolar design (Morley-Davies and Cobbe, et al., 1997), in which a single insulated electrode is placed near the myocardium of the heart and acts as a cathode (Tyers et al., 1997;
Morley-Davies and Cobbe, 1997). The generator shell acts as the anode of the resulting circuit. Modern leads use a bipolar design where the cathode and anode are both in the lead and spaced a short distance apart (Morley-Davies and Cobbe, 1997). Three general approaches have been developed for placing two insulated conducting wires within the lead body for the bipolar design. The original bipolar leads were fabricated with two conducting wires alongside one another, enclosed in a large silicone rubber sheath (Tyers et al., 1997). These designs gave way to coaxial systems where a layered approach was used. Here, a conducting wire at the center is sheathed in an insulator and surrounded by another conducting layer and a final layer of insulation. Coaxial pacing leads tend to be smaller than the side-by-side models (Tyers et al., 1997). The most recent approach to bipolar lead design is described as a coradial pacing lead. The two conducting wires are coated with a thin layer of insulation and wound in a helical manner along the length of the pacing lead (Schmidt and Stotts, 1998). The wound helix is also sheathed in another layer of insulation to improve handling characteristics and provide some insulation redundancy. The compact nature of the coradial inner structure results in a very small lead.

To avoid the incompatibilities in mating technologies that arise from having a large number of electrophysiology (EP) device manufacturers, internationally accepted standards have been developed to define the mating connection between pacemakers and leads, thus allowing leads from one manufacturer to be mated to the generator of another. Originally developed by the British Standards Institution as the IS-1 specification for low-profile connectors for implantable pacemakers, the standard has been revised and rereleased in 2000 as the ISO 5841-3 standard from the International Organization for Standardization as part of its publications governing the design of cardiac pacemakers. A similar standard (DF-1) exists for ICD shock leads (Morris et al., 1999).

A number of materials have been used for insulation in cardiac pacing leads, including polyethylene, polysiloxanes, polyurethanes, and poly(ethylene-co-tetraflouroethylene) (ETFE). Polyethylene was the original lead insulation material, but poor long-term performance has eliminated its use in the pacing lead market (Crossley, 2000). Polysiloxanes are used in modern electrophysiology leads but have undergone an evolution in performance and formulation over the years. A limited resistance to tearing required a relatively thick layer until newer, high-performance polysiloxanes were released (Crossley, 2000). Polyurethanes possess a high tear strength and, in contrast to early polysiloxane formulas, a low coefficient of friction, both of which served to popularize polyurethane use; leads could be made smaller and possessed improved placement characteristics, especially in multiple-lead applications (Crossley, 2000; Schmidt and Stotts, 1998). The newest coradial bipolar leads utilize a thin layer of ETFE as an insulation coating for the interior helically wound leads, with a redundant layer of exterior polyurethane insulation (Crossley, 2000; Schmidt and Stotts, 1998). The coradial leads are small and appear to have a reduced complication rate compared to coaxial designs (Tyers et al., 1997).

To prevent migration, lead tips are fitted with either passive or active fixation mechanisms. Passive devices use hooks or tines to secure the line into place, while active fixation methods rely upon a screwlike tip to burrow the lead into the heart tissue. Although active fixation leads have been considered less likely to dislodge or suffer from complications than passive leads, few major studies have been performed (Crossley, 2000), and some doubt that differences in performance exist in the hands of an experienced implanter (Mitrani et al., 1999). Some situations do warrant active fixation leads, however. Congenital heart disease may require lead placement in an odd area, which can make active fixation useful (Mitrani et al., 1999). Active fixation leads appear to be preferred for atrial placement, while passive fixation leads are the overwhelming choice when leads are placed in the ventricle (Bernstein and Parsonnet, 1996a). Figure 20.7 provides a close-up view of a variety of lead tips, revealing the fixation equipment used for both passive and active methods.

Rate-adaptive pacing requires some method of rate modulation, preferably without patient intervention, that mimics as closely as possible the normal behavior of the intact sinus node during exertion (Leung and Lau, 2000). A very large number of sensors, control techniques, and algorithms have been proposed in an effort to provide optimal rate responses to exercise and activity in those patients unable to generate an adequate heart rate increase (Leung and Lau, 2000). Because no single sensor and associated circuitry can perfectly replace the sinus node, dual sensor systems have been introduced to accommodate for particular deficiencies in either sensor (Mitrani et al., 1999).
FIGURE 20.7 Close-up views of three pacemaker and/or cardioverter-defibrillator leads. The lead on the far left is an active fixation lead with a retractable screw embedded in the lead tip. It can be extended after implantation to attach the lead to the heart wall. The middle lead possesses a soluble cap that dissolves within a few minutes inside the body to reveal a hook or screw for tip fixation. A tined passive fixation lead is shown on the right. The soft tines become lodged in the irregular inside surface of the heart, preventing lead migration.

The most popular sensors are mechanical devices that measure vibration, which roughly indicates that body movement is taking place (Morley-Davies and Cobbe, 1997; Leung and Lau, 2000). These units have the benefit of being compatible with existing lead technology (Leung and Lau, 2000).

The current standard pacemaker lead utilizes many of the innovations described above and possesses a low coil resistance coupled with a high electrode impedance and a steriod-eluting tip (de Voogt, 1999). The steroid reduces the inflammatory reaction to the implanted lead that can increase the stimulation threshold over time (Mitani et al., 1999; Crossley, 2000).

**Programmer.** The programmer allows the physician to adjust pacemaker and defibrillator settings to meet the particular needs of the patient. Modern microcomputer-based systems use radio-frequency waves or magnetic fields to communicate with the EP device noninvasively (Kusumoto and Goldschlager, 1996; Morley-Davies and Cobbe, 1997). The programmer can retrieve device settings and performance data, including failure episodes, electrocardiograms, and battery function, allowing the physician to optimize device performance or analyze an existing problem (Kusumoto and Goldschlager, 1996). A recent review divided the most common programmable features into six categories, including pacing mode selection, energy output and characteristics, electrical sensitivity, rate limits, refractory periods and their duration, and the various rate-adaptive features and functions (Kusumoto and Goldschlager, 1996). The ever-growing range of features and functions on the modern EP device complicates patient management but does allow tailored therapy.

**20.4.4 Complications**

Complications associated with electrophysiology devices can be divided into those that are a consequence of device failure or malfunction and those that are secondary to device implantation, extraction, or patient care. In general, complications are reported to occur at a greater rate with those
physicians who implant pacemakers less frequently (Bernstein and Parsonnet, 1996a). Clinically significant perioperative complications such as hemothorax (blood in the chest cavity), pneumothorax (air in the chest cavity), infection, and hematoma (blood collection around insertion site) are relatively rare at 1 to 2 percent (Morley-Davies and Cobbe, 1997).

**Generators.** Although there are a number of problems that could necessitate generator replacement, the most common reason is a depleted battery at the end of its service life, which indicates that proper generator function and longevity is the norm rather than the exception. However, a relatively common emergent indication for generator replacement is apparent electrical component failure (Bernstein and Parsonnet, 1996a).

**Electrical Leads.** Pacing (de V oogt, 1999) and defibrillator electrical leads are the most problematic components in their respective electrophysiology systems. As a common site of malfunction and a significant factor in device power consumption, the electrical pacemaker lead has been subject to a variety of design and usage improvements (de V oogt, 1999). A recent survey of cardiac pacing revealed that the most common reason for lead replacement was insulation failure, followed by a high stimulation threshold for cardiac depolarization and displacement of the lead electrode itself (Bernstein and Parsonnet, 1996a). Bipolar leads suffered from a higher complication rate in both the atrial and ventricular positions, and ventricular leads secured with passive fixation devices also experienced a higher reported complication rate (Bernstein and Parsonnet, 1996a). Results from the Danish Pacemaker Register (Moller and Arnsbo, 1996) revealed significantly lower reliability in bipolar leads versus unipolar leads, but unipolar leads do have shortcomings. Unipolar sensing units suffer from electrical interference due to extracardiac muscle activity or electromagnetic interference (EMI), which can cause pacemaker malfunction (Morley-Davies and Cobbe, 1997; Mitrani et al., 1999). Furthermore, unipolar pacemaker leads are incompatible with implantable defibrillator devices (Mitrani et al., 1999).

Among common lead insulation materials, polyurethane 80A, a polyetherurethane (PEU), is known to suffer from higher rates of degradation and failure and is responsible for a large proportion of lead malfunctions (Crossley, 2000; Tyers et al., 1997). The PEU 80A degrades via three mechanisms: environmental stress cracking, metal ion catalyzed oxidation, and calcification (Schmidt and Stotts, 1998; Crossley, 2000). Alternative polymers such as ETFE, polycarbonateurethanes, and more durable formulations of PEU are being used to overcome the limitations of PEU 80A (Schmidt and Stotts, 1998). These materials do not suffer from the same mechanisms of failure, or at least exhibit increased resilience to degradation via those pathways (Schmidt and Stotts, 1998).

20.4.5 Future Developments

Up to a fifth of all patients with implanted cardioverter-defibrillators have also demonstrated a pacemaker requirement (Pinski and Trohman, 2000). The dual requirement for pacemakers and ICDs has led to the development of units combining the two technologies on an advanced level, complete with dual chamber activity (Morris et al., 1999; Pinski and Trohman, 2000). The benefit of a combined EP device is the elimination of separate costs for each system and potential harmful interactions between pacemakers and ICDs, including a reduction in the number of leads (Morris et al., 1999; Pinski and Trohman, 2000).

Steady improvements in microelectronics and software will further expand the capabilities of EP devices toward the analysis and treatment of other pathologic heart conditions currently on the fringe of electrophysiology, such as atrial arrhythmias (Morris et al., 1999). These enhanced units will monitor a wide variety of patient and system data to optimize performance to a greater extent than current systems. There is room for improvement in power technology and lead design, as well as improved algorithms able to perform advanced rhythm discrimination (Morris et al., 1999). As suggested in the literature, the development of a universal programmer capable of interfacing with any EP device would be a significant advance both in cost and ease of use for providers now faced
with a multitude of different programming units (Kusumoto and Goldschlager, 1996). Improved and simplified programmer interfaces would also benefit the implanting physicians, who are now overwhelmed with feature-heavy and highly adjustable systems (Morris et al., 1999).

20.5 ARTIFICIAL VASCULAR GRAFTS

20.5.1 Market Size

According to a recent discharge survey of nonfederal short-stay hospitals, at least 66,000 blood vessel resections with graft replacement were performed in 1997, with the majority of those reported involving the abdominal aorta (Owings and Lawrence, 1999). Because of the limited availability of biologic tissues with the proper size and length for the replacement of large vessels, artificial vascular prostheses are often used in the clinical setting (Brewster, 2000; Greisler, 1991). The placement of vascular access grafts for dialysis treatment represents a significant use of artificial vessels, with 52 percent of dialysis patients receiving therapy through this route (Tokars et al., 2001). Treatment guidelines for renal failure from the National Kidney Foundation advocate the use and placement of an artificial graft for permanent vascular access when a native fistula cannot be created (NKFDOQI, 1997).

20.5.2 Indications

A number of situations can necessitate the placement of an artificial vascular graft. Vascular grafts can be placed for primary diseases of the vasculature, such as aneurysms or severe atherosclerotic narrowing, for secondary causes such as trauma, or for chronic vascular access issues such as hemodialysis. In the case of primary disease or injury, the indications for placement are dependent upon the level of the vascular tree in which the lesion or damage is located, as well as the etiology of the illness. The choice of interventional therapy also varies, depending on whether the target vascular lesion is cardiac, thoracic, carotid, or peripheral. Replacement or bypass of a native vascular conduit is a procedure that lies on one end of the interventional spectrum for treatment of vascular insufficiency. The initial approach to addressing a case of vascular insufficiency (stenosis, occlusion, etc.) is usually a percutaneous intervention such as balloon angioplasty and stenting, followed by surgical repair or replacement of the native vessel if necessary. Some vascular patients with severe coexisting conditions are unable to tolerate the profound sedation required to directly excise and replace a damaged blood vessel. For these patients, long-tunneled extra-anatomic grafts placed outside the path of the existing diseased vessel are the preferred therapy, despite poorer long-term outcomes and patency rates compared to traditional excisional grafting (Biancari and Lepantalo, 1998; Foster et al., 1986; Connolly, 1984).

20.5.3 Current Graft Designs

Vascular grafts or prostheses can be classified as originating primarily either from biologic or synthetic sources. Biologic grafts can be harvested from other species (xenograft), from other humans (allograft), or the vasculature of the patient (autograft). As the focus of the present section is on the engineering aspects of vascular grafts, the following discussion will be limited to conduits of synthetic origin. Tissue-engineered biologic grafts will be discussed in the section covering future trends.

The ideal synthetic vascular graft would possess a number of characteristics designed to mimic native conduits, ease surgical placement and limit manufacturing complexity and cost (Brewster, 2000). A number of features supporting these design goals are listed in Table 20.2. Initially, vascular graft research focused upon the development of completely passive conduits that would not elicit a
biological response when exposed to blood. More recent research has focused on the development of
grafts that generate a favorable biological response from the body, as it has been recognized that a
perfectly inert surface may be an unattainable goal (Greisler, 1991).

Current commercial polymeric graft designs can be divided into both textile and nontextile forms
(Brewster, 2000). Textile-based grafts are generally composed of woven or knitted polyethylene
terephthalate (Dacron), while the nontextile grafts are usually fashioned from expanded
polytetrafluoroethylene (ePTFE). Other polymeric materials investigated or used in the manufacture
of vascular grafts include polyamides or nylons, nonexpanded PTFE, polyvinyl alcohol (Ivalon),
viny chloride-vinyl acetate copolymers (Vinyon-N), polyacrylonitrile (Orlon), and polyurethanes
(Brewster, 2000; Greisler, 1991; Eberhart et al., 1999]. Although the majority of these materials has
been abandoned, polyurethanes have enjoyed continued interest as a source material, especially for
small-diameter vascular grafts (Eberhart et al., 1999), despite their mixed showing in the few human
studies that have been attempted (Zhang et al., 1997; Allen et al., 1996; Bull et al., 1992) and
increased concerns over their long-term degradation performance (Eberhart et al., 1999).

The preferred graft material differs for both implantation site and use, and selection is based
upon patency rates, absence of complications, convenience, or handling characteristics, and cost
(Brewster, 2000). Large-diameter grafts for use in the aorta and major arteries have generally been
made of Dacron, while medium-size grafts are primarily constructed of ePTFE. Smaller vessels
located in the infringuinal region (below the area where the legs connect with the torso) represent
a significant challenge because of the traditionally poor patency rates with artificial grafts in these
vessels (Londrey et al., 1991; “Comparative...,” 1988; Veith et al., 1986). Current evidence
suggests replacement of the damaged vessel with an autogenous vein or artery graft is the
procedure of choice rather than implantation of an artificial graft (Paries et al., 2000).

Unfortunately, pre-existing disease, anatomic or size limitations, and other factors may rule out an
autogenic source for vessel replacement, thereby forcing the use of an artificial (usually ePTFE)
vascular graft. It is in these smaller vessels that the promise of tissue-engineered prosthesis is
expected to have the greatest impact.

The different construction techniques used to manufacture textile grafts have an effect on the final
device properties. Graft porosity is considered to be a prime factor determining a number of
handling, performance, and outcome (Wesolowski et al., 1961) characteristics for textile implants.
Knitted textile grafts possess a high porosity and generally require a special yet simple procedure
called preclotting prior to implantation to prevent excessive leakage of blood through the graft wall.
Traditionally, preclotting is performed with a sample of the patient’s blood; coagulation is initiated to
fill the open pores and interstices with fibrin. As of 1997, most (>80 percent) implanted grafts came
presealed with collagen, gelatin, or other biological compounds (e.g., albumin) directly from the
manufacturer in an effort to reduce time spent on graft preparation (Brewster, 2000) and limit surface
thrombogenicity (Greisler, 1991). In contrast, woven textile grafts do not generally require
preclotting but possess less desirable handling properties such as increased stiffness (Brewster, 2000)
and a tendency to fray when cut (Greisler, 1991). Examples of woven and knitted polyester aortic
grafts are shown in Fig. 20.8. Nontextile PTFE grafts can possess differing levels of porosity,
FIGURE 20.8 Two polyester aortobifemoral grafts (Meadox Division, Boston Scientific Corporation, Natick, Massachusetts) are shown. These large grafts are used to repair abdominal aortic aneurysms and other lesions affecting the distal aortic segment. The larger graft on the left is made of woven polyester, while the smaller graft is of knit construction. The knitted graft is significantly more elastic and can be stretched to a greater extent than the corresponding woven graft.

dependng on the processing technique employed. This feature may influence the extent of the healing process (Golden et al., 1990; Kohler et al., 1992; Contreras et al., 2000).

20.5.4 Complications and Management

Graft “healing” or incorporation into the vasculature is a complex process that is the subject of numerous studies and reviews (Greisler, 1991; Davids et al., 1999). Graft healing is affected by the graft material, the graft microstructure and surface characteristics, hemodynamic and biomechanical factors, and eventually the interplay between these characteristics and the cellular and humoral components involved in the ongoing incorporation of the graft (Greisler, 1991). Incorporation of the graft into the vasculature can occur through ingrowth of tissue from the anastomotic ends, or from tissue growth through the graft wall (Davids, 1999). Humans, in contrast to many animal models, usually fail to fully endothelialize the inner surface of a vascular graft, possessing instead some near-anastomotic endothelialization and scattered islands of endothelial cells on a surface rich in fibrin and extracellular matrix (Pasquinelli et al., 1990; Sauvage et al., 1975; Sauvage et al., 1974; Berger et al., 1972). The lack of full healing has prompted extensive research into the mechanism of endothelialization and methods to improve it in the clinical setting.

Graft complications can be split into those that occur with high or low frequency. High-frequency complications include graft thrombosis and anastomotic pseudointimal hyperplasia, a condition of cellular overgrowth that occurs at the site where the artificial graft meets the remaining native vessel.
Less frequent complications include prosthesis infection and structural changes such as graft dilatation, a problem more prevalent in knitted Dacron prostheses than other graft types (Robinson et al., 1999).

Because of their grave consequences, graft thrombosis and infection are of particular concern to the implanting surgeon. Thrombosis in vascular grafts is a function of surface characteristics, hemodynamic properties, and the patient’s hemostatic system, and represents a common cause of early graft failure. In hemodialysis patients, for whom vascular access is critical, the thrombosis rate of ePTFE access grafts averages 45 percent per year (Kaufman, 2000) and is often secondary to venous stenosis (Palder 1985). Although treatment differs by graft location, results from a randomized clinical trial involving thrombosed lower-extremity grafts revealed that catheter-based thrombolytic therapy with urokinase or t-PA (tissue plasminogen activator) restores patency in most patients for whom catheter access is successful. This treatment can also reduce the extent of surgical revision is such revision is subsequently required (Comerota et al., 1996).

Graft infection occurs in less than 1 percent of cases as an early (<30 days) complication, but may afflict as many as 5 percent of graft recipients over the longer term (Bandyk and Esses, 1994). The usual culprit is a staphylococcal species, but many other species have been known to infect vascular grafts (Bunt, 1983), with different complications and rates of progression (Bandyk and Esses, 1994). Although there is some leeway in regard to the level of therapy, infections can often be fatal unless aggressive surgical means are coupled with antibiotic treatment. Because residual infection is a common cause of therapeutic failure, extensive debridement and graft excision with in situ or extra-anatomic prosthetic replacement is warranted in most cases (Calligaro and Veith, 1991; Seeger, 2000). Even with aggressive therapy and placement of an extra-anatomic bypass, graft infections result in amputation rates up to 30 percent and a mortality rate approaching 40 percent (Bandyk and Esses, 1994).

20.5.5 Future Trends

An excellent text on efforts to produce improved vascular grafts through tissue engineering has been recently released (Zilla and Greisler, 1999). Current research is focused on improving the performance of existing vascular graft designs, although attempts have been made to create entire tissue-engineered vessels as well (L’Heureux et al., 1998; Niklason et al., 1999). Novel coatings have been developed to steer the biological response to an implanted vascular graft toward endothelialization and improved biocompatibility, while moving away from the proliferation of cellular components linked to vessel narrowing and failure (Greisler, 1996). Various approaches to improving graft performance, healing, and long-term patency include endothelial cell seeding (Park et al., 1990; Williams et al., 1992) and the use of antithrombotic and antibiotic coatings (Devine and McCollum, 2001). Clinical experiences with some of these approaches (endothelialization) have shown promising results (Deutsch et al., 1999) compared to traditional grafts, while others, such as antibiotic coatings, lack definitive outcomes (Earnshaw, 2000).

20.6 ARTIFICIAL KIDNEYS

20.6.1 Market Size

According to the United States Renal Data System, the number of Americans in end-stage renal disease (ESRD) is expected to rise from around 370,000 current patients to greater than 660,000 in 2010 (USRDS, 2000). Treatment modalities used to replace the failing kidney are few, including hemodialysis with an artificial kidney or hemodialyzer, peritoneal dialysis, or kidney transplantation. Hemodialysis remains the dominant therapy for ESRD in the United States, doubling in use in the last decade with about 280,000 patients supported in 2000 (USRDS, 2000). Hemodialysis is also the dominant therapy worldwide, with 71 percent of ESRD patients receiving dialysis in 1991.
(Klinkmann and Vienken, 1995). In the United States, kidney transplantation follows hemodialysis in the number of patients treated, but a limited donor pool prevents dramatic expansion of this option. Peritoneal dialysis trails hemodialysis and transplantation with only 13.5 percent of U.S. ESRD patients supported (USRDS, 2000). The combined cost for ESRD is staggering, with approximately $11 billion expended in the Medicare ESRD program alone in 1998, most of which is applied to hemodialysis treatment (USRDS, 2000). The present section focuses on the use of hemodialyzers as a cardiovascular device addressing kidney failure.

### 20.6.2 Indications

Two physical processes, diffusion and convection, are in widespread use as methods to mimic the excretion functions of the native kidney. Therapies utilizing predominantly convective transport are accurately termed hemofiltration, while diffusion-dependent methods are grouped under hemodialysis. Both hemodialysis and hemofiltration are used in the inpatient and outpatient setting to treat renal and nonrenal diseases. In general, the purpose of these therapies is to either remove toxins circulating in the blood or reduce the blood volume by removal of water.

The indications to initiate hemodialysis for end stage renal disease are variable but involve clinical and symptomatic manifestations related to uremia, a buildup of metabolic toxins in the blood. Indications requiring immediate initiation of therapy include encephalopathy or a change in mental status, disturbances in either the sensory or motor pathways, effusions in the pericardial space or pleura due to uremic irritation, uncontrollable metabolic derangements such as high serum potassium and low pH, and excessive water retention (Denker et al., 2000). Because of evidence suggesting improved outcomes in patients receiving early dialysis intervention, patient symptoms resulting in a reduced quality of life (fatigue, cognitive changes, itching, and malnutrition) can be considered as indications for the initiation of dialysis (Hakim and Lazarus, 1995).

Indications for renal replacement therapy in the acute setting and for other disease processes are different from those for ESRD. A common mode of ESRD therapy in the outpatient setting is intermittent hemodialysis (IHD) where a patient receives intense treatment over the course of a few hours several times a week. Acute renal failure in the inpatient setting is often treated with continuous renal replacement therapy (CRRT), which is applied for the entire duration of the patient’s clinical need and relies upon hemofiltration to a higher degree than IHD (Meyer, 2000). Other nonrenal indications for CRRT are based on the theoretical removal of inflammatory mediators or toxins and elimination of excess fluid (Schetz, 1999). These illnesses include sepsis and systemic inflammatory response syndrome, acute respiratory distress syndrome, congestive heart failure with volume overload, tumor lysis syndrome, crush injury, and genetic metabolic disturbances (Schetz, 1999).

### 20.6.3 Device Design

Three physical processes determine the removal rate for uremic toxins through membrane-based devices. **Convection** results in toxin removal through a semipermeable membrane that separates blood from dialysate and can be used to remove excess fluid. A pressure gradient across the membrane is responsible for the solvent flow, and toxins are removed as a function of their concentration in solution, the ultrafiltration rate or rate of fluid removal, and the sieving coefficient of the particular toxin across the membrane barrier. Membranes for convection-based therapies exclude molecules larger than their pore size but permit improved removal of the middle molecules (500 to 5000 daltons) implicated in uremia (Meyer, 2000). Depending on the amount of fluid removed, replacement electrolyte solution may be required to maintain adequate hemodynamic volume. **Diffusion**-based solute removal primarily affects smaller molecules with high diffusion coefficients and possessing a favorable concentration gradient from the blood to the dialysate. **Adsorption** is the third and least characterized method of solute removal in renal replacement therapies (Klinkmann and Vienken, 1995). Controlled by electrostatic and Van der Waals forces between solute and membrane, adsorption-based removal can be beneficial or harmful depending on the compound involved, such
as removal of proinflammatory cytokines versus a needed anticoagulant (Klinkmann and Vienken, 1995). Convection and diffusion remain the dominant physical processes by which membranes and devices are designed.

Although hemodialysis and hemofiltration are often considered separate therapies, some clinical treatments rely on a combination of the two and therefore can be classified as hemodiafiltration procedures. Treatment techniques can be further stratified as to whether they are intermittent or continuous in nature, and whether the vessels accessed are both venous, or arterial and venous. Due to a lack of definitive prospective randomized trials, the relative advantage of continuous versus intermittent treatment is unknown, although continuous administration is felt to be more “gentle” in some circles, allowing greater time for toxin equilibration and removal (Meyer, 2000).

**Unit and Membrane Design.** Hemodialysis units have undergone a variety of changes since the first practical design, a rotating drum dialyzer, was introduced in the 1940s (Kolff et al., 1944). As recently reviewed by Clark, subsequent unit designs have progressed through coil and parallel flow dialyzers to the current dominant design of the hollow fiber dialyzer, which was introduced to address performance and use limitations inherent in the earlier devices (Clark, 2000). Subsequent to the introduction of the hollow fiber dialyzer, much of the improvement and development in artificial kidney devices has focused on the membrane barrier materials and device operating conditions. An example of a standard hollow fiber dialyzer is shown in Fig. 20.9, and there have been few major changes in the design since its introduction decades ago (Ronco et al., 2000).

**FIGURE 20.9** Hemodialysis exchangers are disposable units similar to membrane oxygenators in construction. (a) Note the simple design of the device as shown in the upper portion of the figure (Artificial Organs Division, Travenol Laboratories, Inc., Deerfield, Illinois), (b) Close-up view of hollow fibers used to separate the patient’s blood from the dialysate fluid. Toxins in the blood diffuse through the fiber walls to the dialysate fluid.
As of 1995, more than 30 different polymer blends were being used in the manufacture of membranes for hemodialysis and hemofiltration (Klinkmann and Vienken, 1995). The various membrane types used for renal replacement therapy can be divided into membranes derived from cellulose (83 percent of 1991 worldwide total) and from synthetic materials (the remaining 17 percent) (Klinkmann and Vienken, 1995). Synthetic membranes have been constructed from such materials as polyacrylonitrile (PAN), polysulfone, polyamide, polymethylmethacrylate, polycarbonate, and ethylvinylalchohol copolymer (Klinkmann and Vienken, 1995). In the United States, use of cellulosic materials for membrane construction predominates at around 95 percent of the total number of membranes used (Klinkmann and Vienken, 1995).

Membrane material selection is dependent upon the mode of therapy employed. Convective therapies such as hemofiltration require a high hydraulic permeability and a large pore size, which might permit large molecules such as cytokines to pass through the fiber wall. Synthetic membranes are well suited for this role and are desired for most continuous, convective techniques (Jones, 1998).

**Design Performance Evaluation.** Removal of uremic toxins and excess fluid is the central purpose of an artificial kidney. A proposed artificial kidney design should undergo transport testing that encompasses the spectrum of molecules encountered in a uremic state at the appropriate flow conditions. Mock circulatory circuits can approximate hemofiltration and hemodialysis flow environments, generating ultrafiltration rates, sieving coefficients (larger molecules) and clearances (smaller molecules) for sample fluids as simple as salt solutions up to uremic human blood (Leypoldt and Cheung, 1996). Many of the toxins responsible for uremia are unknown and are approximated with marker molecules spanning a large size spectrum, including small solutes, middle molecules, and albumin (Leypoldt and Cheung, 1996). Small solutes used for in vitro studies include the clinically relevant compounds urea and creatinine, while middle molecules such as beta2-microglobulin can be approximated with inulin and dextrans (Leypoldt and Cheung, 1996). Albumin is used to approximate high-molecular-weight oncotic substances in the blood, and its clearance is believed to be negligible (Leypoldt and Cheung, 1996). The transport properties derived using mock circulatory loops may not reflect clinical performance because of complex solute—carrier protein interactions and membrane surface fouling by plasma proteins (Leypoldt and Cheung, 1996).

### 20.6.4 Complications and Patient Management

Complications that occur during hemodialysis and hemofiltration can be divided into problems related to vascular access and those due to exposure of the blood to the exchange circuit. Depending upon the method used, vascular access problems associated with renal replacement therapy are similar to those experienced in patients with vascular grafts or catheters and are covered in those respective sections.

The complications associated with blood exposure to the dialysis or filtration membrane are related to the activation and upregulation of various homeostatic systems. Inflammatory and hemostatic cascades can become activated by protein adsorption onto the significant surface area that these devices necessarily present to the blood. As part of the inflammatory response to dialyzer perfusion, activation of the complement system results in the generation of anaphylatoxins C3a and C5a and can potentiate activation of polymorphonuclear leukocytes and monocytes (Johnson, 1994; Grooteman and Nube, 1998). These activated leukocytes release cytotoxic compounds and inflammatory mediators that normally would be reserved for the killing of bacteria and infectious agents. The release of these inflammatory mediators is implicated in sequelae such as fever, cardiovascular instability, and increased catabolism of muscle protein (Pertosa et al., 2000). Since the nature and extent of protein adsorption impacts the inflammatory response, the surface properties of dialyzer membranes are of interest as a means to limit this response. In studying surface properties and complement activation, the presence of surface hydroxyl groups has been implicated as a potential trigger for pathway activation (Chenoweth, 1984).

Activation of the coagulation cascade and platelet deposition in the artificial kidney circuit is obviously undesirable, leading to reduced device performance or failure. To minimize this phenomenon,
patients on hemodialysis are usually anticoagulated with heparin during the dialysis session on either a systemic or regional (extracorporeal circuit only) level (Denker et al., 2000). Patients with a sensitivity or contraindication to heparin therapy can be anticoagulated regionally with citrate as well (Denker et al., 2000). Minimizing the potential of membrane surfaces to activate both the hemostatic and inflammatory pathways is of interest to device manufacturers as they seek to reduce complications associated with artificial kidney use.

20.6.5 Future Trends

Artificial kidney designs will likely continue to experience incremental improvements in the materials and hemodynamic areas. New developments in biocompatible materials, superior transport methods for toxin removal, and improved patient management techniques will allow further maturation of hemodialysis and hemofiltration therapy. For example, considerable benefits could be realized from selective toxin removal without concomitant elimination of beneficial proteins. It has been suggested that future devices might utilize the absorption removal pathway with affinity methods as a primary technique to eliminate specific uremic toxins (Klinkmann and Vienken, 1995).

The promise of a true revolution in artificial kidney design comes from the area of tissue engineering. The living kidney performs a number of important metabolic, endocrine, and active transport functions that are not replaced with current hemofiltration and hemodialysis therapy. An artificial kidney that successfully replaces these functions could be a significant improvement when used in conjunction with existing therapies. Researchers have developed a bioartificial renal tubule assist device that successfully reproduces many of the homeostatic functions of the native kidney during in vitro studies and that responds in the proper manner to known physiologic regulators of the various homeostatic functions (Humes et al., 1999).

20.7 INDWELLING VASCULAR CATHETERS AND PORTS

20.7.1 Market Size

Catheters, in their simplest form, are merely tubes inserted into a body cavity for the purpose of fluid removal, injection, or both (Thomas, 1989). The term catheter has been expanded to include a number of tubing-based percutaneous interventional devices used for tasks such as stent delivery and deployment, clot removal, radio-frequency ablation, and intra-aortic balloon cardiac support. Because of their prevalence and representative uses, the present section will be limited to vascular infusion catheters and access ports. Stenting and cardiac support applications utilizing catheter-based techniques are discussed elsewhere in this chapter.

In 1991 it was estimated that more than 150 million intravascular catheters were being procured in the United States each year (Maki and Mermel, 1998). Of this number, more than 5 million were central venous catheters (Maki and Mermel, 1998). Catheters have a critical role in modern health care and are used in increasing numbers for central access of the major arteries and veins, as well as for an ever-expanding array of invasive procedures (Crump and Collignon, 2000).

20.7.2 Indications

Catheters are placed when there is a clinical need for repeated sampling, injection, or vascular access, usually on a temporary basis. In kidney failure, catheters allow emergent blood access for hemodialysis and hemofiltration (Canaud, 2000), and provide temporary access as more permanent sites such as arteriovenous fistulas or grafts mature (Trerotola, 2000). Placement of a catheter or access port is routine for the administration of chemotherapeutic agents and intravenous nutritional supplements. Catheters are often placed when frequent, repeated doses of medication are to be
injected, blood samples are to be taken, and hemodynamic performance is to be monitored in critically ill patients (Pearson, 1996).

The anatomic location for temporary central venous catheter (CVC) insertion and placement can be dictated by certain patient or disease restrictions, but the most common sites are the internal jugular vein (neck), the femoral vein (groin), and the subclavian position (upper chest). The internal jugular approach is the first choice for placement of a hemodialysis CVC, while femoral placement is favored when rapid insertion is essential (Canaud et al., 2000). Subclavian vein access has fallen from favor because of a higher incidence of thrombosis and stenosis associated with this site, which can ultimately prevent use of the veins in the downstream vascular tree for high-flow applications such as dialysis (Cimochowski et al., 1990; Schillinger et al., 1991).

### 20.7.3 Device Design

Design considerations for vascular access devices include ease of handling, insertion, and use; minimal thrombotic and other biocompatibility-related complications; structural and operational reliability over time; and optimization for application-specific performance issues (Canaud et al., 2000). Three different catheter tips are shown in Fig. 20.10 to illustrate these variations in design and structure. Because of the distinct characteristics of the different treatments and agents deployed through catheters, it is not practical to provide specific values for flow rates, pressure drops, viscosities, and other important transport properties.

Catheter device selection is based on a number of factors, including the planned application and placement site, duration of implantation, composition of fluids infused, and frequency of access (Namyslowski and Patel, 1999). Vascular catheters can be divided into two general groups: short-term, temporary catheters that are placed percutaneously, and long-term, indwelling vascular catheters that usually require a surgical insertion. Temporary catheters include short peripheral venous and arterial catheters, nontunneled central venous and arterial catheters, and peripherally inserted central catheters (Pearson, 1996). Tunneled central venous catheters and totally implantable intravascular...
devices (i.e., ports) are used for therapies requiring long-term vascular access (Pearson, 1996). The term tunneled refers to the placement of the catheter exit site at a location away from the area where the vasculature is penetrated, with the portion of the catheter between these two locations lying in a subcutaneous position. Peripheral venous catheters are the most common devices used for intravascular access, while the nontunneled central venous catheter is the most common central catheter (Pearson, 1996). Subcutaneous ported catheters are the preferred long-term route given an infrequent need for vascular access (Namyslowski and Patel, 1999). Figure 20.11 contains an example of a double-ported fully implantable catheter used for longer-term access.

As mentioned previously, hemodialysis is a common indication for catheter placement. Polysiloxane tunneled central venous catheters and, more recently, totally implantable intravascular port devices are utilized in hemodialysis for long-term vascular access (Schwab and Beathard, 1999). Temporary central venous catheters for hemodialysis access are further subdivided into different groups based on catheter flexibility and the length of time the device will be in use (Canaud et al., 2000). The longer the catheter will be in place, the more supple the material used for construction. Short-term use catheters possess a high stiffness and are fabricated from polytetrafluoroethylene, polyethylene, polyvinyl chloride, and rarely polyurethane (Schwab and Beathard, 1999; Canaud et al., 2000). Medium-term (8 to 30 days) catheters are primarily constructed of polyurethane, while catheters implanted for longer periods of time are usually based on polysiloxane, although polyurethane can be used (Canaud et al., 2000).

Catheters have been permeated, coated, or surface-modified with a variety of compounds in an effort to minimize thrombosis, infection, and friction (Marin et al., 2000; Triolo and Andrade, 1983). The ultimate goal is an improvement in catheter handling characteristics and long-term performance. Some of the more common strategies for imparting microbial resistance include saturating the catheter material with silver sulfadiazine and chlorhexidine (Maki et al., 1997), coating the surface with antibiotics (Raad et al., 1997), or bonding heparin to the surface of the catheter (Appelgren et
al., 1996). Results with antibacterial and antiseptic coatings have been mixed, but a recent meta-analysis involving several randomized controlled trials has shown a significant reduction in hospital-acquired infections when catheters modified for bacterial resistance are used (Marin et al., 2000). The meta-analysis revealed a significant decrease in the number of catheter-related infections for all experimental catheters versus standard devices, plus a substantial reduction in infections for catheters employing antimicrobial systems other than silver sulfadiazine and chlorhexidine when compared to those systems (Marin et al., 2000). A randomized trial comparing bacterial colonization and catheter-related bloodstream infection rates associated with two antimicrobial catheters came to a similar conclusion, with minocycline- and rifampin-coated catheters being linked with significantly fewer events than chlorhexadine- and silver sulfadiazine–coated catheters (Darouiche et al., 1999). In an effort to improve handling characteristics, radio-frequency glow discharge has been used to alter the surface properties of common catheter materials to increase hydrophilicity (Triolo and Andrade, 1983) and reduce friction. This latter property is important in the double catheter systems used for some interventional procedures (Triolo and Andrade, 1983).

20.7.4 Management and Complications

Infection and thrombosis are common across a variety of catheter designs and applications, while other complications arise as a result of the particular nature of the therapy being administered, such as recirculation in hemodialysis. Catheter malfunction and related morbidity and mortality represent an area where significant strides are currently being made.

Infection is a common complication associated with intravenous catheters and represents the primary cause of hospital-acquired bloodstream infection (Valles et al., 1997), resulting in significant morbidity and mortality. Proper care and maintenance is essential for the continued functioning of a catheter, and a number of strategies have been implemented in an effort to minimize infection risk. The use of special coatings and antimicrobial-saturated devices was discussed above in the section on device design. Careful exit site management with a dedicated catheter care team, antibiotic flushes, and possibly catheter tunneling can lower the risk of infection (Raad, 1998), as can the use of a totally implantable intravascular device, which has the lowest infection rate among standard vascular access devices (Maki and Mermel, 1998). Tunneled catheters are fitted with a Dacron cuff that stimulates accelerated healing and ingrowth of tissue distal to the insertion site, thereby providing a host barrier to pathogen migration. In addition, antiseptic cuffs have been placed on catheters to inhibit bacterial migration (Maki et al., 1988; Hasaniya, 1996) but overall results are mixed, suggesting that infecting organisms often migrate through the luminal route or that the cuff loses its antibiotic function over time (Sitges-Serra, 1999). Once a catheter-related infection is detected, the approach to care is dependent upon the patient condition, the number of remaining access sites, and other factors such as the suspect organism, but the catheter is usually removed and antibiotic therapy initiated (Mermel et al., 2001).

Thrombotic complications are common with catheter use. The development of a fibrin sheath is a near universal occurrence on intravascular devices such as central venous (Hoshal et al., 1971) and hemodialysis catheters, and can have a profound effect upon blood flow in the device (Trerotola, 2000). This sheath can be removed either by stripping (Rockall et al., 1997; Crain et al., 1996) or fibrinolytic medical therapy (Twardowski et al., 1998), or the catheter can be replaced to restore adequate flow performance. Recent randomized controlled clinical trials have revealed improved long-term outcomes with catheter exchange versus fibrin sheath stripping (Merport, 2000), while no outcome differences were realized in patients randomized to either fibrin sheath stripping or thrombolytic therapy (Gray, 2000).

20.7.5 Future Trends

Improvements in catheter design are likely to be evolutionary, representing progress in materials, surface treatments, and functional monitoring as catheters are expected to perform for increasingly
extended periods. Surfaces with active antithrombotic and antimicrobial activity will continue to be developed and evaluated, as will surfaces designed to minimize protein and cellular adhesion.

20.8 CIRCULATORY SUPPORT DEVICES

20.8.1 Market Size

Heart disease remains the leading cause of death in the United States (AHA, 2000). The devices discussed in the current section provide cardiac support for a spectrum of indications and durations, spanning damage due to an acute myocardial infarction to the long-term decline that accompanies chronic congestive heart failure. The section excludes therapies such as extracorporeal membrane oxygenation and the use of cardiopulmonary bypass pumps as a support method since these are described in the following section on artificial lungs.

The most commonly used means of mechanical circulatory support is the intra-aortic balloon pump (IABP). In 1990, it was estimated that IABP therapy was provided to 70,000 patients annually (Kantrowitz, 1990). As described below, the IABP can provide only limited cardiovascular support, as its effects are limited to pressure unloading of the ventricle, in contrast to artificial hearts and ventricular assist devices, which provide volume unloading (Mehlhorn et al., 1999). To be effective, the IABP requires that the patient maintain some native pumping capacity, as the movement of blood due to the balloon is minimal.

Unlike the IABP, ventricular assist devices (VADs) and total artificial hearts (TAHs) aid or replace the function of the native organ for an extended period of time. A cardiac transplant is the last resort for many patients who fail other medical and surgical therapy. Unfortunately, donor organs remain limited, creating the market for both temporary and extended cardiac support. It has been estimated that up to 100,000 patients in the United States alone would benefit from the implantation of a long-term cardiac support device, with between 5000 and 10,000 requiring biventricular support (Willman et al., 1999). However, the need for mechanical support has not been met by existing designs because of mechanical and biocompatibility limitations. The ongoing need continues to spur development of novel approaches to chronic cardiac support.

20.8.2 Indications

As discussed in recent articles (Mehlhorn et al., 1999; Torchiana et al., 1997), the indications for IABP placement have changed over the years, as has the insertion method. Current indications can be divided into hemodynamic indications, due to cardiogenic shock, congestive heart failure, and hypotension, which are characterized by low cardiac output and systemic perfusion, or ischemic indications such as those caused by coronary artery disease, which result in poor cardiac perfusion and dysfunction (Torchiana et al., 1997). Current trends indicate an increased use of IABP support for ischemia in patients undergoing percutaneous cardiac therapies such as balloon angioplasty, with a dramatic shift from almost 100 percent surgical implantation to near universal percutaneous implantation (Mehlhorn et al., 1999; Torchiana et al., 1997). The number of IABPs placed for ischemic indications now exceeds those placed for hemodynamic concerns, with the trend for hemodynamic causes staying relatively flat (Torchiana et al., 1997).

The indications for implantation of TAHs and VADs are similar to those for the IABP, but are usually reserved for patients who have failed balloon pump support and/or maximal medical therapy. Current FDA-approved VADs are placed for postcardiotomy support or as a bridge to either transplantation or recovery (Willman et al., 1999). Investigators are also evaluating chronic mechanical circulatory support as an alternative to transplantation for patients who do not meet the criteria to become a donor heart recipient (Rose et al., 1999).
20.8.3 Current Device Design

**Intra-aortic Balloon Pump (IABP).** The first clinical use of the intra-aortic balloon pump was reported in 1968 (Kantrowitz et al., 1968). Although updated with electronics and computer control, the basic equipment of the modern IABP system remains similar to units introduced decades ago. An IABP system consists of an external pump control console that monitors physiologic patient variables (electrocardiogram and blood pressure) and delivers a bolus of gas to a catheter-mounted balloon located within the patient’s aorta (Bolooki, 1998a). Figure 20.12 demonstrates the approximate location of the balloon inside the patient along with the exit site in the femoral artery. Gas delivery is controlled via a solenoid valve and is timed to correspond with the onset of diastole, during which the left ventricle is filling with blood and the aortic valve is closed (Bolooki, 1998a). Inflation of the balloon at this time, as demonstrated in Fig. 20.13a, results in blood being pushed back toward the heart and forward to the systemic vasculature, allowing improved perfusion of the target tissues. Figure 20.13b demonstrates active collapse (via vacuum) of the balloon during systole or ventricular contraction, which results in a reduction of the pressure the ventricle must work against and eases blood ejection. The reduced workload lowers myocardial oxygen consumption, reducing angina and other more serious consequences of a heart oxygen deficit (Bolooki, 1998b).

The intra-aortic balloon consists of a single, long (approximately 20 cm) inflatable polyurethane sac mounted circumferentially upon a polyurethane catheter (Bolooki, 1998c). Multi-chambered balloons have been investigated (Bai et al., 1994) but failed to enter clinical use despite potential theoretical advantages. Because of its lower viscosity and better transport speeds, helium is used as the shuttle gas to inflate modern balloons, although carbon dioxide and even air were used in older models (Bolooki, 1998a).

**Ventricular Assist Device (VAD) and Total Artificial Heart (TAH).** Ventricular assist devices can be divided into pulsatile and nonpulsatile designs. Available pulsatile VADs can be further classified as intracorporeal or extracorporeal, depending on whether the pump is placed internally or externally. There are three intracorporeal pulsatile LVADs available for commercial use in the United States: the Novacor electric pump (World Heart Corp., Ottawa, Ontario) and the pneumatic and vented electric Heartmate pumps (Thoratec Corp., Pleasanton, California) (McCarthy and Hoercher, 2000). These devices all utilize pusher-plate technology, with the Novacor using opposing, electrically activated
plates to compress a smooth polyurethane sac, and the Heartmate using one moving plate to compress a polyurethane sheet into a housing coated with sintered titanium. The force comes from compressed air in the case of the pneumatic Heartmate device and from an electrically driven cam mechanism in the vented-electric model. Each device requires a percutaneous lead for power, venting, and device monitoring (McCarthy and Hoercher, 2000). Figure 20.14 demonstrates the anatomic placement of the Heartmate VE and other current implantable VAD designs.

Available extracorporeal VAD designs include the ABIOMED BVS-5000 (ABIOMED, Inc., Danvers, Massachusetts) and Thoratec (Thoratec Corp., Pleasanton, California) VADs (Dowling and Etoch, 2000). The potential advantages of extracorporeal systems include the ability to be implanted in smaller patients (<1.5 m² body surface area), multiple sites for cannulation of the heart, reduced surgical time, and most importantly, biventricular support if needed by allowing the simultaneous use of two devices (Dowling and Etoch, 2000). Drawbacks include large percutaneous cannulation sites with a potential for infection, plus limited patient mobility because of the larger console size that is required for the pneumatic drivers of both devices (Dowling and Etoch, 2000). Figure 20.15 presents a sampling of current FDA-approved intra- and extracorporeal VAD designs and demonstrates the relative size differences between the intracorporeal (Heartmate VE and Novacor) and extracorporeal (Thoratec) designs. Both the Thoratec and BVS-5000 consist of polyurethane blood sacs housed in rigid plastic shells that are compressed with air provided by a driver console. For all practical purposes, the BVS-5000 does not allow patient mobility because of the large driver console and the need for gravity filling for the artificial ventricles. The Thoratec dual driver console is a wheeled, dishwasher-sized unit that is not intended for extensive mobile use. Of note, the recently FDA-approved Thoratec II portable pneumatic driver console promises to allow much more patient freedom.

A number of new device designs will be reaching maturity in the near future, including pulsatile and nonpulsatile VADs and pulsatile TAHs. Of the nonpulsatile or continuous-flow designs, there are two general categories: axial-flow pumps and centrifugal pumps. The axial-flow devices that have recently entered or will soon enter clinical trials in the United States include the Jarvik 2000 (Jarvik Heart Inc., New York, New York), the MicroMed DeBakey (MicroMed Technology, Inc., Houston, Texas), and the Heartmate II (Thoratec Corp., Pleasanton, California) VADs. An example of the latter

![FIGURE 20.13](image_url) The balloon inflation-deflation cycle is demonstrated, (a) Balloon inflation occurs during diastole, or filling of the ventricle. At this point in the cardiac cycle, the aortic valve is closed. Inflation of the balloon forces blood back toward the heart and into the systemic circulation. The increased pressure developed by the balloon allows better perfusion of the heart muscle during the filling phase, (b) Balloon deflation coincides with systole, or ejection of blood from the heart. Deflating the balloon at this time decreases the pressure in the aorta, reducing the effort required by the heart to eject blood. (Datascope Corporation, Cardiac Assist Division, Fairfield, New Jersey.)
Centrifugal pumps at this stage of development include the Heartmate III (Thoratec Corp.) and the TandemHeart percutaneous VAD (CardiacAssist, Inc., Pittsburgh, Pennsylvania) shown in Fig. 20.17. Other centrifugal pumps are under development at various universities and companies throughout the world (Clark and Zafirelis, 2000). The potential advantages of the nonpulsatile VADs include smaller size (with correspondingly smaller patient size requirements), fewer moving parts (increased reliability and lifespan), and reduced power requirements. The lack of valves could reduce the likelihood of thrombotic complications involving these sites, which have been shown to be problem areas in previous studies (Wagner et al., 1993).
However, the bearings used to support the rotors in most continuous flow devices could act as a nidus for thrombus formation (Stevenson et al., 2001). Hemolysis due to the high shearing forces is of some concern, and the effect of chronic nonpulsatile flow upon the human body is unknown.

IABP support is an invasive procedure possessing an overall complication rate ranging from 12 to 30 percent in most reports (Cohen et al., 2000). The most common complications seen during balloon pump support are vascular in nature, with limb ischemia being the dominant problem (Busch et al., 1997). Other vascular complications include bleeding and hematoma formation (Busch et al., 1997), aortic dissection (Busch et al., 1997), embolism (Kumbasar et al., 1999), and rare events such as paraplegia due to spinal infarction (Hurle et al., 1997). Nonvascular complications include infection and mechanical or device-related failures such as balloon rupture (Scholz et al., 1998; Stavarski, 1996). Factors increasing the risk of complications vary among different studies, but generally include peripheral vascular disease, diabetes, and female sex (Cohen et al., 2000; Arafa et al., 1999; Busch et al., 1997). Results have been mixed as to whether smaller catheter sizes and shorter periods of support can limit the complication rates, despite the theoretical advantages (Cohen et al., 2000; Scholz et al., 1998; Arafa et al., 1999).

Complications associated with TAH and VAD use can be divided into those experienced shortly after implantation and events occurring later in the implant period. Postoperatively, the major
concerns include hemorrhage, and in the case of isolated left ventricular VAD support, right heart failure or dysfunction resulting in low pump outputs (Heath and Dickstein, 2000). Bleeding management can include infusion of blood products, but in some cases surgical intervention may be required. Right heart performance can often be improved through reduction of the pulmonary vascular resistance with various drug infusions and inhalants (Heath and Dickstein, 2000). Long-term VAD complications include infection, thromboembolism, and rarely, device failure (Kasirajan et al., 2000). Infection can involve (1) the percutaneous connections of the pump or (2) the pump interior or exterior surfaces, or can be systemic in nature (Holman et al., 1999). Management includes antibiotics, debridement, and in severe cases involving the pump pocket, removal or replacement of the pump (Holman et al., 1999; Kasirajan et al., 2000). Thromboembolism is limited through the use of anticoagulant medications such as heparin perioperatively and warfarin in the long term, although not all pumps require such therapy (Kasirajan et al., 2000). Antiplatelet regimens such as aspirin are also used to prevent emboli (Kasirajan et al., 2000). Pump failure is a rare occurrence (Kasirajan et al., 2000), but the dire consequences require careful monitoring of pump performance.

20.8.5 Future Trends

Improvements in electronics and software development will undoubtedly be incorporated into future IABP designs. Closed-loop designs requiring minimal operator intervention have been investigated (Kantrowitz et al., 1992), and results suggest that independent device control could be achieved. Catheters coated with antithrombotic agents have been shown to reduce thrombosis and thrombotic deposition even in immobile (noninflating) balloons when compared to similar uncoated designs.
DESIGN OF MEDICAL DEVICES AND DIAGNOSTIC INSTRUMENTATION

Hydrophilic coatings have also been placed on balloon catheters, with recent results showing a 72 percent reduction in ischemic vascular complications when modified devices are used (Winters et al., 1999). Antibiotic coatings for indwelling catheters could be used to coat intra-aortic balloons if such treatment is proven to be efficacious.

In contrast to the IABP, VADs are undergoing a revolution in design and indications for use. The current rush of devices entering clinical trials shows improvements in a variety of areas, including power transmission (transcutaneous versus percutaneous), method of propulsion (electric centrifugal

![FIGURE 20.17 The TandemHeart percutaneous VAD (CardiacAssist, Inc., Pittsburgh) is shown. Intended as a short-term support device, the TandemHeart has the advantage of not requiring a major surgical procedure for implantation, and can be placed by interventional cardiologists in a catheterization laboratory. It is a centrifugal pump with novel integrated anticoagulation system that discharges into the pump chamber. It has been used successfully in Europe and is undergoing clinical trials in the United States. (CardiacAssist, Inc., Pittsburgh).](image-url)
and axial flow versus pneumatic pulsatile), and size reduction. The largest obstacle to the widespread use of these devices on a scale commensurate with heart disease are the complications that face these patients over the long term. The most critical future developments will focus on patient management issues with a significant impact on morbidity and mortality, such as infection control and thromboembolism, as well as device issues affecting quality of life and durability.

### 20.9 ARTIFICIAL LUNGS

#### 20.9.1 Market Size

According to the National Hospital Discharge Survey (Owings and Lawrence, 1999), approximately 300,000 membrane oxygenators were used in the United States in 1997 for acute surgical cardiopulmonary bypass. The number of oxygenators required for acute cardiopulmonary bypass use dwarfs the number used for extended support of the failing lung, a modality termed extracorporeal membrane oxygenation (ECMO). Changing ECMO demographics suggest new developments in alternative medical therapies might be causing a reduction in the number of neonatal patients supported via ECMO therapy, a standard of care for respiratory support for over a decade (Roy et al., 2000).

#### 20.9.2 Indications

The indications for cardiopulmonary bypass are surgical in nature, and are based on whether the procedure requires the heart to be stopped. Currently, most cardiac surgical procedures fall into this category (McGiffin and Kirklin, 1995). Cardiopulmonary bypass provides the surgeon with a stable, blood-free field to perform intracardiac repairs and procedures such as coronary artery bypass grafting. Recent trends in minimally invasive surgery have led to surgical systems that allow some procedures such as coronary artery bypass grafting to be performed in the absence of oxygenator support (Svennevig, 2000).

In contrast to cardiopulmonary bypass, medical criteria are the primary indicators for ECMO support. Conventional treatment of acute respiratory failure calls for high-pressure mechanical ventilation with an elevated percentage of oxygen in the ventilation gas. Unfortunately, the high oxygen concentration can result in oxidative damage to lung tissue (oxygen toxicity) and, in the case of the newborn, proliferation of blood vessels in the retina leading to visual damage (retinoproliferative disorder) (Anderson and Bartlett, 2000). The high pressures used to achieve maximum ventilation area also cause lung damage through a process known as barotrauma. In essence, the lungs are being subjected to further damage by the therapy employed, preventing the healing necessary to restore proper lung function. The purpose of ECMO is to take over the burden of gas exchange and allow the native lung tissue time to heal.

ECMO is considered a standard therapy for the treatment of respiratory failure in neonatal patients (Anderson and Bartlett, 2000). In adult and pediatric patients, it is a treatment of last resort for individuals who would otherwise die despite maximal therapy (Anderson and Bartlett, 2000; Bartlett et al., 2000). Even in neonatal cases, ECMO is a therapy reserved for those patients with severe respiratory compromise and a high risk of death who are failing traditional ventilator-based interventions. Common causes of respiratory failure in the neonatal population that are treatable with ECMO support include pneumonia or sepsis, meconium aspiration syndrome, respiratory distress syndrome, persistent fetal circulation, and congenital diaphragmatic hernia (Anderson and Bartlett, 2000). Contraindications to ECMO support include root causes that are unresolvable, such as a major birth defect or genetic abnormality, and comorbid conditions such as intracranial hemorrhage or fetal underdevelopment that suggest a poor outcome (Anderson and Bartlett, 2000). Indications for ECMO use in the pediatric and adult populations are not dissimilar from those of the neonate, but the causes for respiratory or
cardiopulmonary failure are different, and many individuals suffer from comorbid conditions. Indications include pneumonia, aspiration pneumonitis, acute respiratory distress syndrome, and recoverable heart failure as caused by infection or postsurgical complications (Anderson and Bartlett, 2000).

20.9.3 Device Design

Although the first oxygenators were described in the late 1800s, it would not be until 1951 that total cardiopulmonary bypass would be performed on a human patient (Stammers, 1997). Oxygenators, or artificial lungs, have undergone a dramatic evolution in the 5 decades since the first total CPB operation. The initial clinical units are described as film oxygenators because a rotating cylinder was used to generate a large, thin film of blood on the cylinder surface where it contacted the exchange gas (Wegner, 1997). Although effective, these early film oxygenators suffered from a number of failings that eventually led to their replacement. The direct gas-blood interface allowed for adequate gas exchange but extensive cellular damage and protein denaturation resulted from the blood-gas interface (Wegner, 1997). The large blood priming volume and time-consuming, complicated maintenance and use procedures characteristic of film oxygenators were addressed through the advent of bubble oxygenators (Stammers, 1997). Direct gas-blood contact remained in bubble oxygenators, but the large surface area of the dispersed oxygen bubbles resulted in greater mass transfer and a reduction in priming volume (Wegner, 1997). In addition, these devices were simple and disposable, consisting of a bubbling chamber, defoaming unit and a return arterial reservoir (Wegner, 1997; Stammers, 1997). However, the blood damage seen with film oxygenators was not corrected with the new bubbling technology, and concerns regarding blood trauma during longer perfusions contributed to the movement toward membrane oxygenators (Wegner, 1997; Stammers, 1997). The use of a semipermeable membrane to separate the blood and gas phases characterizes all membrane oxygenator designs. Membrane oxygenators can be further divided into flat-sheet/spiral-wound and hollow-fiber models. The flat-sheet designs restrict blood flow to a conduit formed between two membranes, with gas flowing on the membrane exterior; these systems were the first membrane oxygenators to enter use (Wegner, 1997). Spiral-wound oxygenators use membrane sheets as well, but are arranged in a roll rather than the sandwich formation of the original flat-sheet assemblies. Polymers such as polyethylene, cellulose (Clowes and Hopkins, 1956), and polytetrafluoroethylene (Clowes and Neville, 1957) were used for membranes in these early designs as investigators searched for a material with high permeability to oxygen and carbon dioxide but that elicited mild responses when in contact with blood. The introduction of polysiloxane as an artificial lung membrane material in the 1960s provided a significant leap in gas transfer efficiency, particularly for carbon dioxide (Galletti and Mora, 1995). These membranes remain in use today for long-term neonatal ECMO support.

Development of the microporous hollow fiber led to the next evolution in lung design, the hollow-fiber membrane oxygenator (Stammers, 1997). Increased carbon dioxide permeability compared to solid membranes, coupled with improved structural stability, has secured the standing of these devices as the market leader (Wegner, 1997; Stammers, 1997). The current, standard artificial lung is constructed of hollow microporous polypropylene fibers housed in a plastic shell. An extraluminal cross-flow design is used for most models and is characterized by blood flow on the exterior of the fibers with gas constrained to the fiber interior. Intraluminal flow designs utilize the reverse blood-gas arrangement, with blood constrained to the fiber interior. The laminar conditions experienced by blood flowing inside the fibers result in the development of a relatively thick boundary layer that limits gas transfer. Extraluminal-flow devices are less susceptible to this phenomenon, and investigators have used barriers and geometric arrangements to passively disrupt the boundary layer, resulting in large gains in mass transfer efficiency (Drinker, 1978; Galletti, 1993). Extraluminal-flow hollow fiber membrane oxygenators have come to dominate the market because of their improved mass transfer rates and decreased flow resistance, the latter of which minimizes blood damage (Wegner, 1997). Figure 20.18 presents a collection of commercial extraluminal-flow membrane oxygenators demonstrating a diversity of design arrangements.
Despite the major advances in surgical and supportive therapy engendered by the introduction of the artificial lung, substantial limitations remain. The complications faced by patients on oxygenator support are not infrequent and are often life-threatening. The limited duration of the average open heart procedure provides less time for major complications to occur, although a few deserve mention.

A relatively common complication suffered by patients who undergo cardiopulmonary bypass (CPB) is called postpump syndrome and is characterized by complement activation, cytokine production, activation of various white blood cell types, and depressed lung function. The depressed lung function infrequently progresses to acute respiratory distress syndrome or ARDS (0.5 to 1.7 percent of CPB patients developed ARDS), but tends to be fatal if such progression occurs (50 to 91.6 percent mortality) (Asimakopoulos et al., 1999). The inflammatory response observed is not attributed
solely to blood exposure to the extracorporeal circuit but is likely also due to a combination of operative trauma, reperfusion injury, and exposure to endotoxin during the procedure (Asimakopoulos et al., 1999). Hemorrhagic and thrombotic problems during CPB are of grave concern, and traditionally, CPB support has required the use of high doses of anticoagulant to prevent clotting in the extracorporeal circuit at the expense of a possible increase in bleeding. This bleeding risk is further magnified by the consumption of coagulation factors and platelets by extracorporeal surfaces and activation of fibrinolytic pathways. Investigations into minimizing this phenomenon have led to the development of anticoagulant (heparin) fiber coatings for the oxygenators (Wendel and Ziemer, 1999). The presence of a heparin coating has led some to reduce the amount of systemic heparin provided during CPB in an effort to limit bleeding (Aldea et al., 1996; Aldea et al., 1998; Kumano et al., 1999). Although there is evidence that bleeding is reduced, the approach is controversial in many circles, as clinical markers of blood clotting remain elevated, resulting in lingering thromboembolism concerns (Kuitunen et al., 1997). Further research is required to elucidate what and how much protective effect is provided by heparin-coated fibers.

The more chronic support provided by extracorporeal membrane oxygenation (ECMO) is plagued by complications and poor outcomes. Survival rates for ECMO support range from 88 percent for neonates in respiratory failure to 33 percent for adults in cardiac failure (Bartlett et al., 2000). As in CPB, hemorrhagic and thrombotic complications occur and have led to intense investigation into the long-term neurologic outcomes of these patients (Graziani et al., 1997; Nield et al., 2000), although the exact relationship between ECMO and outcomes remains unclear (Vaucher et al., 1996; Rais-Bahrami et al., 2000). In addition, longer-term support with hollow-fiber membrane oxygenators results in the manifestation of a particular phenomenon where plasma from the blood side seeps into the pores of the fibers in a process termed weeping. The effect of this phenomenon is to increase the diffusion distance for oxygen and carbon dioxide, thereby reducing mass transfer performance. Originally thought to be due to temperature changes and condensation of water in the fiber interior (Mottaghy et al., 1989), evidence suggests deposition of circulating phospholipid at the fluid-gas interface results in a change in hydrophobicity on the pore surface that mediates penetration of the plasma (Montoya et al., 1992).

20.9.5 Future Trends

Future developments in cardiopulmonary bypass will focus on improving the biocompatibility of the device through minimization of hematologic alterations. One current approach involves coating the oxygenator fibers with a layer of polysiloxane in an effort to limit the postperfusion syndrome (Shimamoto et al., 2000). ECMO, with its higher longevity requirements, will similarly benefit from new coatings and materials. General measures to improve the biocompatibility of the fibers include coatings and additives to limit plasma infiltration into the device (Shimoto et al., 1996), limit platelet deposition on the surface (Gu et al., 1998) and platelet activation (Defraigne et al., 2000), and minimize leukocyte and complement activation (Watanabe et al., 1999; Saito et al., 2000). Although not a new concept, novel methods to improve mass transfer through the thinning or disruption of the boundary layer are currently being developed. Some approaches include the use of fibers mounted on a rapidly spinning disk (Borovetz et al., 2000; Reeder et al., 2001) or cone (Makarewicz et al., 1994), the pulsing and distention of silicone sheets (Fiore et al., 2000), and the pulsation of a balloon mounted inside circumferentially organized fibers designed for placement in the vena cava (Federspiel et al., 1997). Some of these devices offer the opportunity to combine the features of a blood pump and artificial lung and therefore represent a significant leap over current bypass systems.

ACKNOWLEDGMENTS

The support of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh is acknowledged. Fellowship support was provided to Kenneth Gage during the writing of this chapter.
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