In the 1930s, Willem Kolff, MD, developed an apparatus for treating patients with acute renal failure by hemodialysis. However, the use of this life-saving technology was limited because it required repeated access to the vascular system. In many ways, advances in the care of patients with end-stage renal disease (ESRD) have mirrored the advances in vascular access technologies. Although external Teflon shunts (Figure 1) and native arteriovenous fistulae were the initial cannulation options for dialysis access, it was clear that not all patients requiring renal replacement therapy would have the anatomy suitable to create an autogenous artery-to-vein fistula due to an array of hemodynamic or anatomic factors that would result in fistula failure.

In an attempt to solve this problem, the concept of a “bridge fistula” or dialysis graft was developed. Initially, the great saphenous vein was used as a conduit, but in the 1970s, the use of expanded polytetrafluoroethylene (ePTFE) was pioneered as a suitable vascular graft and was rapidly adopted as an alternative material for connecting arteries and veins in an array of locations in the body. The conception of prosthetic grafts revolutionized vascular access and gave rise to a number of new access sites that were previously unavailable for creating an arteriovenous fistula. However, with the advance of this new vascular access technology came a new set of complications and costs for the health care system.

Today, the health and social realities of ESRD are tremendous, with economic costs in the United States exceeding $33 billion in 2006.2

CURRENT CHALLENGES
Vascular access circuits in general and nonautogenous conduits in particular have historically been plagued by multiple difficulties. Although prosthetic conduits have been pivotal in providing vascular access for the ESRD population, patency and infection rates are inferior to those of autogenous fistulae.3-5 Venous neointimal hyperplasia occurring at the graft-vein anastomosis outflow tract is cited as the most common factor in access failure (Figure 2).6 Intimal hyperplasia is well described; however, in the case of vascular access, there are numerous potential causative factors that are not completely understood and are under active investigation.7 Anatomic and physiologic barriers also affect the success of hemodialysis grafts because no vascular access conduit will function properly without adequate arterial inflow or venous drainage. One of the most common pathologies that alters graft outflow and limits patency is central venous stenosis and/or occlusion, which typically results from prior insertion of multiple tunneled dialysis catheters (TDCs).

Thrombosis can occur as a result of numerous factors such as intimal hyperplasia, graft trauma, low flow states, and hypercoagulable disorders.8 Intimal hyperplasia causes hemodynamic conditions of low and turbulent flow states, which leads to platelet aggregation at focal points within the arteriovenous graft (AVG) and promotes thrombosis.9
In contrast, bleeding from suture holes or weeping through the graft material can lead to nerve compression, pain, infection, or graft failure. Aggressive and careless anterior wall puncture, as well as inadvertent posterior wall puncture, can lead to perigraft hematoma and subsequent graft impingement, resulting in AVG thrombosis and failure.

Finally, the renal failure population seems to be especially prone to infection secondary to a chronic inflammatory and immunocompromised state that hemodialysis tends to promote. In addition, the majority of ESRD patients suffer from multiple confounding medical comorbidities. These factors combined with the penetrating insult of dialysis cannulation three times each week significantly increase the potential to seed a prosthetic dialysis graft leading to bacteremia and/or sepsis, which ultimately may require explantation of the access conduit.

**RECENT ADVANCES**

In an attempt to provide solutions to the vexing issues that lead to graft failure, access care providers have collaborated with industry to develop a variety of conduit options and therapies to improve the care that we offer patients in need of long-term vascular access. In that regard, the main focus of access graft advances during the past 10 to 15 years has been toward improving bleeding, thrombosis, weeping, and infection of access grafts as opposed to addressing the biologic aspects of outflow vein failure and venous proliferative disease. As a result, numerous AVGs with various base scaffolding, wrap or lamination methods, bonding or graft lining, or outflow designs are commercially available for use in ESRD patients (Figure 3).

In the realm of standard ePTFE material, the choices of graft material are fairly similar and generally come in a 6-mm standard wall configuration, which is manufactured by one of five major vendors. As an example of graft modifications, Bard Peripheral Vascular, Inc. (Tempe, AZ) offers the Venaflo II AVG, which aims to optimize hemo-dynamic venous outflow patterns to reduce outflow vein intimal hyperplasia and thrombosis. Additionally, the Venaflo II and Bard’s Carboflo graft are lined with carbon, which some studies have suggested results in a reduction in platelet aggregation and thrombus formation within the graft when utilizing this technology. W. L. Gore & Associates has attempted to make an impact on long-term graft patency by aiming to reduce luminal thrombus by bonding bioactive heparin to the luminal surface of their ePTFE graft. Early studies showed encouraging data to support retention of the graft’s thromboresistant bioactive properties over time (Figure 4). Further prospective, randomized trials may be in order to more fully eluci-

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**Figure 2.** Progression of venous proliferative disease and comparative angiographic images. Shuntogram showing normal AVG anastomosis and venous outflow (A). Normal vein histology, magnification X 5 (B). Shuntogram showing high-grade stenosis at AVG anastomosis (C). Venous intimal hyperplasia, magnification X 5 (D). Bilateral upper extremity venogram revealing bilateral subclavian vein occlusions with significant venous collateralization (E). Venous occlusion, magnification X 20 (F).

**Figure 3.** Microscopic images of common AVG material: ePTFE, magnification X 400 (A) (Courtesy of Ann Schmierer, PhD; and W. L. Gore & Associates, Flagstaff, AZ); polyetherurethaneurea, magnification X 50 (B) (Reprinted with permission from Sant’Anna SS, de Souza DA, de Araujo DM, et al. Physico-chemical analysis of flexible polyurethane foams containing commercial calcium carbonate. Materials Research. 2008;11:433-438); and ProCol bioprosthesis, magnification X 100 (C) (Courtesy of Hancock Jaffe Laboratories, Inc., Irvine, CA).
date the graft’s long-term performance when compared to standard ePTFE dialysis AVGs.

Other manufacturers have modified ePTFE technologies to increase graft wall strength in an attempt to decrease cannulation misadventures, needle hole bleeding, and weeping. The Flixene graft (Atrium Medical Corporation, Hudson, NH) utilizes a trilaminate composite construction and a hydrostatic protection membrane, which dramatically increases burst and suture strength. Because of its construction, the Flixene graft claims to eliminate graft ultrafiltration syndromes that standard ePTFE grafts can develop. Vascutek (Terumo Interventional Systems, Somerset, NJ) offers the Seal ePTFE wrap AVG that uses a gelatin coating to reduce friction while tunneling, intraoperative bleeding, and graft “sweating.” Although not marketed for this indication, it has been found that these grafts also may not require 2 to 3 weeks for tissue incorporation before cannulation for hemodialysis and have been labeled by some in the vascular access community as a type of “early stick” graft. Virtually all companies that offer ePTFE for hemodialysis have developed tapered configurations at the arterial end of the graft, with the hope of reducing complications such as steal syndromes and high-output heart failure.

The Vectra graft (currently distributed by Bard Peripheral Vascular) is a bridge conduit constructed of a polyetherurethaneurea as an alternative to ePTFE. This rubbery, elastic-type material handles quite differently than the ePTFE grafts, and studies have suggested that this material seals after cannulation within 1 to 5 minutes, abrogating the requirement for tissue incorporation into the graft before cannulation for hemodialysis.10 The company suggests that this graft can be used for hemodialysis 24 hours after implantation.

Two companies offer a bioprosthesis for hemodialysis access, and both grafts are constructed of bioengineered bovine tissue. These xenografts are preserved in a tissue fixation solution and therefore require some back table preparation in the operating room before implantation. Artegraft (North Brunswick, NJ) offers a tightly woven and cross-linked natural collagen matrix conduit derived from bovine carotid artery. This was the first bioprosthetic vascular graft approved by the US Food and Drug Administration (FDA) in 1970. Hancock Jaffe Laboratories, Inc. offers the ProCol bovine mesenteric vein graft. Early studies showed primary patency rates comparable to ePTFE but boasted higher secondary patency rates with significantly fewer thrombosis and infectious complications.11 Both grafts offer conduit compliance superior to that of traditional inert prosthetic grafts, which may account for a degree of their long-term success. These grafts are somewhat more expensive than those mentioned previously but can be a useful option for patients in immunocompromised states who have small vessels or those plagued by early thrombosis or chronic infection.

And finally, as a means to provide care for end-stage access patients with central venous stenosis and/or occlusion, Hemosphere, Inc. has developed a hybrid vascular access device. The Hemodialysis Reliable Outflow (HeRO) device is now FDA approved for use in the upper extremities of patients who would otherwise be catheter dependent, and it...
was made available for commercial use in mid 2008. When this device is properly implanted, arterial blood is shunted from the donor artery into the central venous system without having to create a formal venous anastomosis. The device is a completely subcutaneously implanted device that can bypass central venous stenosis and/or occlusion by traversing the lesion endovascularly and terminating in the right atrium or any available large outflow target vein (Figure 5). This device consists of two components: a conventional ePTFE graft and an endoluminal, large-bore, single-lumen, nitinol-reinforced, silicone outflow component. The silicone outflow component is inserted into the internal jugular, subclavian, or femoral vein utilizing the Seldinger technique or via TDC exchange and then coupled with an ePTFE graft, which is tunnelled subcutaneously in the standard fashion and anastomosed to an upper extremity artery or inflow conduit of choice. Preliminary studies have shown that this device has primary and secondary patency rates equal or superior to conventional AVGs and has superior infection rates when compared to TDCs.12

ON THE HORIZON

Vascular access scientists, industry, and clinical investigators are continually developing new technologies to improve upon the modes of vascular access graft failure. These advancing technologies continue to provide the surgical community with a multitude of artificial options for access grafts. Currently, there is strong interest in developing early cannulation AVGs that will help avoid the need for a bridging TDC, which could save billions in health care dollars. Many of these prototypes seem to use varying methods of ePTFE wraps, lamination techniques, and/or alternative self-sealing materials as a medial layer laminate.

Others have focused on developing a conduit with a more biocompatible inner flow lumen in contrast to a relatively inert material, such as ePTFE, in an attempt to reduce the incidence of thrombosis secondary to protein and chemical mediator activation. There are reports of endothelialized prosthetic conduits, as well as technologies to culture the extracellular matrix to form bridging grafts. NanoVasc, Inc. (Alameda, CA) has created a polyurethane graft that incorporates a biomimetic scaffold, which allows for endothelial cell ingrowth. Early animal studies have suggested superior primary patency rates and significantly decreased bleeding times at decannulation compared to ePTFE.13 Humacyte, Inc. (Research Triangle Park, NC) has developed the technology to engineer human extracellular matrix, offering properties similar to native vasculature, and thus has created a novel conduit for hemodialysis access. Both the NanoVasc and Humacyte technologies are in ongoing animal studies.

In stark contrast to the opportunities for graft material modifications outlined in the previous section, during the past 5 to 10 years, increasing research efforts have focused on the venous proliferative disease of the access graft outflow tract and its affect on hemodialysis access. We will discuss three main avenues of investigation: flow dynamics, cell therapy, and gene therapy.

Shear stress has long been implicated as a cause of intimal proliferation and graft failure. Flow models have proven this theory and have led to attempts at engineering a conduit and venous outflow connection that may alter the impact of hemodynamic shear on the outflow vein. Veryan Medical (Horsham, West Sussex, UK) has developed the Swirlgraft, which essentially “riffles” blood flow into the venous outflow and may reduce low wall shear stress in the recipient vein. Early studies have shown promise, but this graft is not yet available for commercial use.14 Atrium has developed a graft with a prefabricated venous junction at 35º within a nitinol stent graft. This outflow mechanism is thought to reduce the venous outflow turbulence that may limit neointimal hyperplasia. Also, the University of Limerick has developed a novel bifurcated AVG (Prolong) that reconvenes at the venous interposition anastomosis. This creates a significant reduction of shear forces as the two flow lumens mix and virtually cancel the shear stresses (Figure 6).

Pervasis Therapeutics, Inc. (Cambridge, MA) has harnessed the technology to embed allogeneic aortic endothelial cells in a gelatin matrix. This gelatin matrix, known as Vascugel, has been shown to inhibit intimal hyperplasia and reduce inflammation and stenosis in AVG models. Preliminary studies are quite encouraging but will require ongoing, larger, randomized clinical trials to ultimately succeed.15

Lastly, gene therapy is moving toward the forefront in vascular surgical disease. Ark Therapeutics Group plc (London, UK) has developed the expertise to create a

Figure 6. Computational fluid dynamics of the Prolong graft (University of Limerick, Limerick, Ireland). The Prolong AVG (A), the graft-vein junction of the Prolong AVG (B), and velocity contours and vectors within the graft-vein junction of the Prolong AVG (C).
replication-deficient adenoviral vector, which encodes for vascular endothelial growth factor D (VEGF-D). The fundamental mechanism for the vasculoprotective effect of VEGF-D, which is distinct from its more widely appreciated “angiogenic” role, is that it acts on surface receptors on endothelial cells, resulting in increased production of nitric oxide and prostacyclin. This gene therapy is applied locally around the venous anastomosis and is isolated from circulation and tissue absorption by a biodegradable gelatin collar (Figure 7). Again, early clinical studies have shown promising results but will require larger randomized studies to gain more insight. A phase-3 FDA efficacy clinical trial is currently underway in the United States.

CONCLUSION
The limiting factors that affect all foreign bodies continue to plague dialysis access grafts. Because these patients are oftentimes immunocompromised and represent a cohort with multiple comorbidities, they are often less tolerant to infectious or technical insults. Technology in this area has not really excelled during the past 40 years, and as such, the most common prosthetic graft in use today remains ePTFE. Ease of handling, cost, and good technical results make it the most commonly placed AVG in dialysis patients. It is often available in most facilities and comes in a varied size profile. More recent advances in science and medicine are tapping cellular and genetic therapies to address a core issue of vascular disease. As science and technology continue to advance, our patients will one day enjoy an ideal vascular access that is impermeable, thromboresistant, compliant, biocompatible, durable, easy to sew, easy to sterilize, resistant to infection, readily available, and cost effective.

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