Hemodialysis Vascular Access Dysfunction: A Cellular and Molecular Viewpoint

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Hemodialysis vascular access dysfunction is a major cause of morbidity and hospitalization in the hemodialysis population. The major cause of hemodialysis vascular access dysfunction is venous stenosis as a result of neointimal hyperplasia. Despite the magnitude of the clinical problem, however, there has been a paucity of novel therapeutic interventions in this field. This is in marked contrast to a recent plethora of targeted interventions for the treatment of arterial neointimal hyperplasia after coronary angioplasty. The reasons for this are two-fold. First there has been a relative lack of cellular and molecular research that focuses on venous neointimal hyperplasia in the *specific* setting of hemodialysis vascular access. Second, there have been inadequate efforts by the nephrology community to translate the recent advances in molecular and interventional cardiology into therapies for hemodialysis vascular access. This review therefore (*1*) briefly examines the different forms of hemodialysis vascular access that are available, (*2*) describes the pathology and pathogenesis of hemodialysis vascular access dysfunction in both polytetrafluoroethylene grafts and native arteriovenous fistulae, (*3*) reviews recent concepts about the pathogenesis of vascular stenosis that could potentially be applied in the setting of hemodialysis vascular access dysfunction, (*4*) summarizes novel experimental and clinical therapies that could potentially be used in the setting of hemodialysis vascular access dysfunction, and, finally, (*5*) offers some broad guidelines for future innovative translational and clinical research in this area that hopefully will reduce the huge clinical morbidity and economic costs that are associated with this condition.

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Introduction and Types of Hemodialysis Vascular Access

Performance of a successful hemodialysis procedure requires a functional vascular access. Unfortunately, there have been no major advances in the field of hemodialysis vascular access for the past three decades, which probably has contributed to hemodialysis vascular access dysfunction being one of the most important causes of morbidity in the hemodialysis population (1). With the use of Medicare data, it has been estimated that vascular access dysfunction is responsible for 20% of all hospitalizations in the hemodialysis population (2). In 2001, vascular access composed 7.5% of the $14 billion spent by Medicare on the ESRD program (approximately $1 billion per annum) (3).

There currently are three main forms of hemodialysis vascular access: (*1*) The native arteriovenous fistula (AVF), (*2*) the polytetrafluoroethylene (PTFE) graft, and (*3*) the cuffed double-lumen silicone catheter. Each of these forms of hemodialysis vascular access has its own specific problems.

1. Native AVF: Once mature and functional, AVF are the preferred form of hemodialysis vascular access because of their relative lack of infection and thrombosis (Figure 1) (4). They are usually created through the surgical anastomosis of the radial (wrist) or brachial (elbow and upper arm) artery to the cephalic vein. Their two major complications are an initial failure to mature (primary nonfunction) and a later venous stenosis followed by thrombosis. A pooled data analysis of AVF survival that was performed at the time of the Dialysis Outcomes Quality Initiative (4) suggested a primary patency of 85% for AVF at 1 yr and 75% at 2 yr (Figure 1). These data, however, exclude fistulae that did not mature adequately to support hemodialysis. Primary nonfunction or rates of failure to mature up to 50% have been reported by some centers, particularly when an aggressive fistula placement policy is enforced (5). Therefore, primary patency rates as low as 43% (6) and 56% (7) have been reported for AVF in some instances. In addition, Miller *et al.* (5) showed a higher primary nonfunction rate in forearm fistulae as compared with upper arm fistulae (59 *versus* 34%). This difference was greatest in women, patients with diabetes, and patients who were older than 65 yr, suggesting that these patient groups perhaps should have upper arm fistulae placed as the primary access procedure. Finally, it is important to point out that the United States has an extremely low AVF rate (Figure 2) as compared with other industrialized countries. Aggressive clinical efforts are under way to improve this shortcoming (8).
2. PTFE grafts: Arteriovenous PTFE dialysis grafts remain the most common form of hemodialysis vascular access in the

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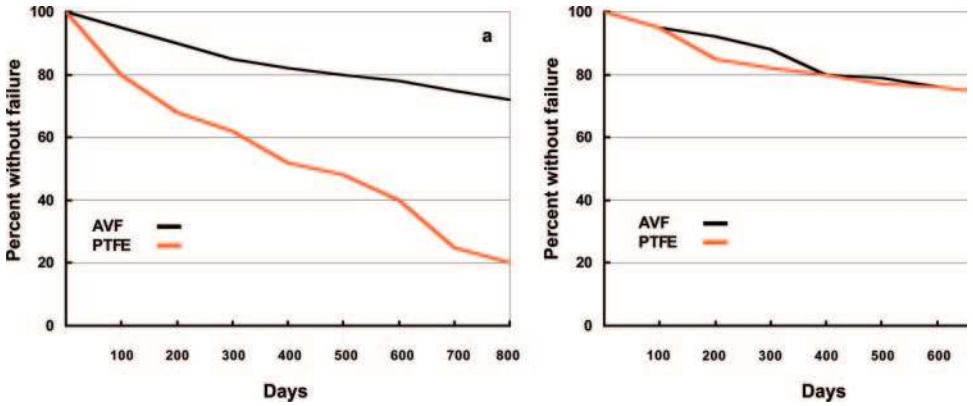

Figure 1. Comparison of patency of arteriovenous fistula (AVF) *versus* polytetrafluoroethylene (PTFE) dialysis grafts. (a) Unassisted primary patency of native AVF *versus* PTFE grafts. (b) Cumulative patency in the setting of an active monitoring and intervention program. Note that with prospective monitoring, the cumulative patency of PTFE grafts is similar to that for native AVF but at the cost of a six-fold increase in the intervention rate. Graphs are derived from the summed data analysis for the Dialysis Outcomes Quality Initiative panel. Modified from reference (4). The AVF survival curves exclude primary nonfunction (failure to mature) and show the failure rate only for AVF that matured enough to be used for hemodialysis. Currently, many centers follow an aggressive policy of early fistula salvage, and between 10 to 50% of all fistulae that are placed may need some intervention, depending on the aggressiveness of fistula placement.

United States. Although relatively easy to place and ready to use, they have extremely high rates of stenosis, thrombosis, and infection. The pooled data for the Dialysis Outcomes Quality Initiative analysis suggested a primary patency rate of 50% at 1 yr (Figure 1). Other authors have reported primary patency rates as low as 23% at 1 yr and 4% at 2 yr (9).

3. Cuffed double-lumen silicone catheters: These should be avoided at all costs because of an extremely high incidence of thrombosis and infection, except as a temporary measure or when the life expectancy of the patient is short. Unfortunately, this often is difficult to accomplish at a clinical level because this is the most convenient way to obtain immediate dialysis access.

This brief comparison of the three major forms of hemodialysis vascular access leaves us with the following messages. (*1*) We need to refine and popularize the surgical techniques and maximize the clinical use of native fistulae by optimizing logistical and practice pattern issues while developing new therapies to promote fistula maturation and reduce venous stenosis. (*2*) The stenosis and thrombosis rate associated with PTFE dialysis grafts should be reduced so that they can become truly a long-lasting form of dialysis access. (*3*) More effective anti-infective and antithrombotic therapies for cuffed double-lumen silicone catheters should be developed so that immediate blood access can be obtained if necessary, without significant morbidity.

This review focuses on the failure of the native or PTFE arteriovenous access. It critically examines the current state of knowledge with regard to the pathology and pathogenesis of their dysfunction; identifies novel concepts and therapies that could be applied to this field; and suggests strategies by which

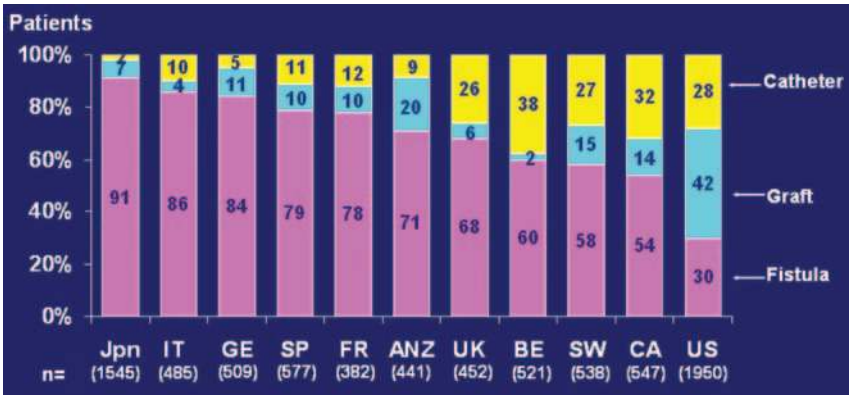

Figure 2. Dialysis Outcomes Practice Patterns Study (DOPPS) data. Note the dismal native AVF prevalence rate and the high PTFE graft prevalence rate in the United States as compared with Europe and Japan. (DOPPS data as of September 2003; courtesy of Dr. Rajiv Saran, University of Michigan, Ann Arbor, MI.)

recent advances in molecular biology, biomaterials, and drug delivery could be applied to hemodialysis vascular access dysfunction.

Pathology and Pathogenesis of Native Fistula and PTFE Graft Failure

Pathology of Native Fistula and PTFE Graft Failure

The two main causes of native AVF failure are an initial failure to mature followed by a later venous stenosis. The exact pathology that results in primary nonfunction of these fistulae is unclear, but the characteristic lesion is a juxta-anastomotic stenosis (Figure 3a). It is unclear, however, whether the primary factor that causes this stenosis is venous constriction or venous neointimal hyperplasia. The pathology of late venous stenosis in native fistulae is believed to be similar to that of venous stenosis in the setting of PTFE dialysis grafts (see below). The stenoses occur at or around the anastomotic region in wrist fistulae (Figure 3b) and in the proximal vein in the setting of fistulae that are constructed at the elbow (Figure 3c) (10). Recent work also documents a high incidence of inflow arterial stenosis (11). Stenosed AVF have been shown to have venous neointimal hyperplasia composed of smooth muscle cells with expression of cytokines and mediators such as endothelin, PDGF, and TGF-β (the last has been shown to co-localize with markers of oxidative stress) within the media and intima (12,13).

The major cause of PTFE graft failure is a venous stenosis that results in thrombosis, either at the graft–vein anastomosis or in downstream or proximal vein (14). More recently, there seems to be a rise in stenoses at the graft–artery anastomosis and within the intragraft region as well (11) (Figure 4). Venous stenosis in PTFE dialysis access grafts is due to venous neointimal hyperplasia, which is characterized by the presence of smooth muscle cells, myofibroblasts, and microvessels within the venous neointima. In addition, there is a significant amount of adventitial angiogenesis and a large number of macrophages that line the perigraft region (a major difference from the venous stenosis that occurs in native fistulae) (15–17). Our group also has demonstrated the presence of cytokines, such as PDGF, vascular endothelial growth factor, and basic fibroblast growth factor, and of matrix proteins, such as collagen and tenascin, within the lesion of venous neointimal hyperplasia (15) (Figure 5).

Pathogenesis of AVF and PTFE Graft Failure

The pathogenesis of early native arteriovenous fistula failure (juxta-anastomotic stenosis) is complex and multifactorial (Figure 6). Causative factors include a small artery (<1.5 to 2 mm) and a small vein (<2.0 to 2.5 mm), surgical manipulation and less-than-ideal technique, previous venipunctures, the development of accessory veins that direct blood away from the primary venous drainage channel, hemodynamic stressors (see below), and a possible genetic predisposition to vasoconstriction and neointimal hyperplasia after endothelial and smooth muscle injury (18,19). It still is unclear whether vascular constriction, neointimal hyperplasia, or a combination of the two factors is responsible for the early maturation failure of native fistulae.

The pathogenesis of venous neointimal hyperplasia in PTFE dialysis grafts and late failure in native fistulae is better understood and comprises a cascade of events that are best discussed under the heading of upstream and downstream events. Upstream events primarily are the factors that are responsible for endothelial and smooth muscle injury, which then set into motion the complex interplay of cells, cytokines, and mediators (downstream events) that result in venous neointimal hyperplasia.

The upstream events in the pathogenesis of venous neointimal hyperplasia in the setting of dialysis grafts and fistulae include (*1*) hemodynamic stress at the graft–vein or artery–vein anastomosis as a result of a combination of low shear stress, turbulence, and compliance mismatch between noncompliant graft/artery and compliant vein (20,21); (*2*) surgical injury at the time of creation of the arteriovenous conduit (this perhaps could be most significant in the setting of AVF, in which the vein often is stretched and manipulated (Dr. Klaus Konner, University of Cologne, Germany, personal communication,

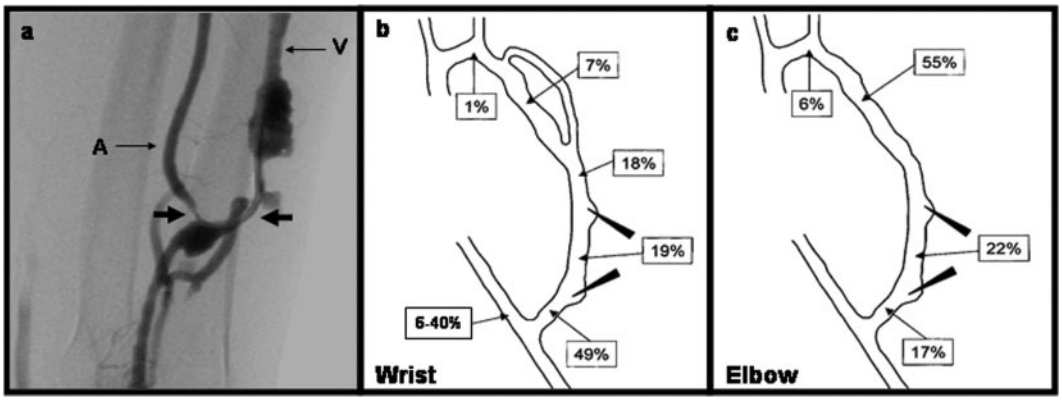

Figure 3. AVF problems. (a) The classic angiographic picture of a juxta-anastomotic stenosis (arrows) resulting in a failure to mature (courtesy of Dr. Tony Samaha, Cincinnati, OH). These lesions can be diagnosed and treated aggressively (angioplasty), with excellent results. (b and c) The sites of venous stenosis for native AVF at the wrist (b) and at the elbow (c). Adapted from reference (10) with the addition of recent data (7), on the increasing incidence (recognition) of arterial stenoses.

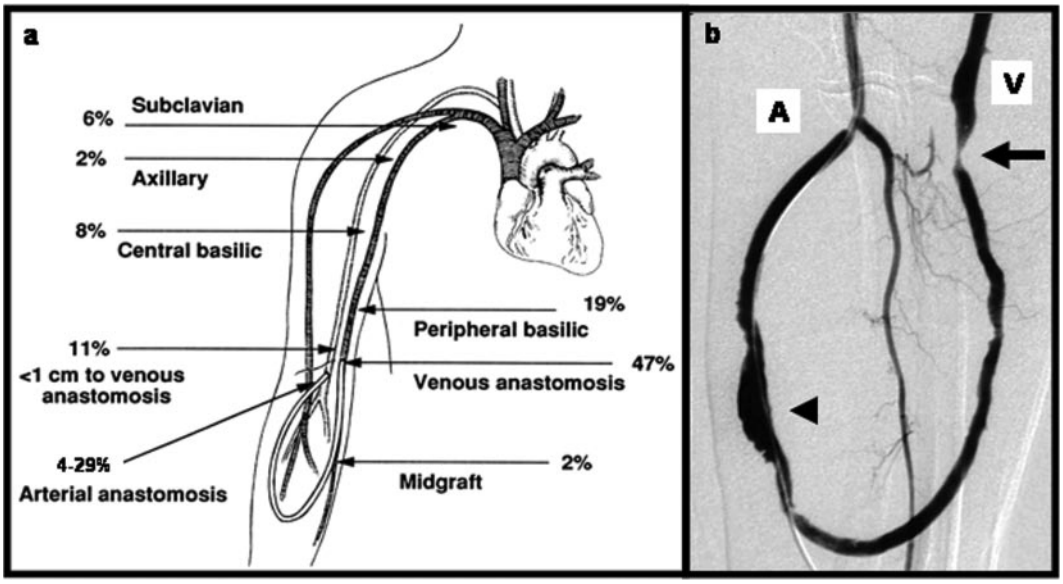

Figure 4. Sites of venous stenoses in PTFE dialysis grafts. (a) The sites of venous stenosis in PTFE dialysis grafts. Note the preponderance of lesions at the graft–vein anastomosis or within 6 to 10 cm of the anastomosis and also at the arterial anastomosis. (b) Angiogram of a PTFE dialysis graft with a developing pseudoaneurysm (arrowhead) and stenosis (arrow) at the graft–vein anastomosis (courtesy of Dr. Tom Vesely, Malinckrodt Institute of Radiology, St. Louis, MO).

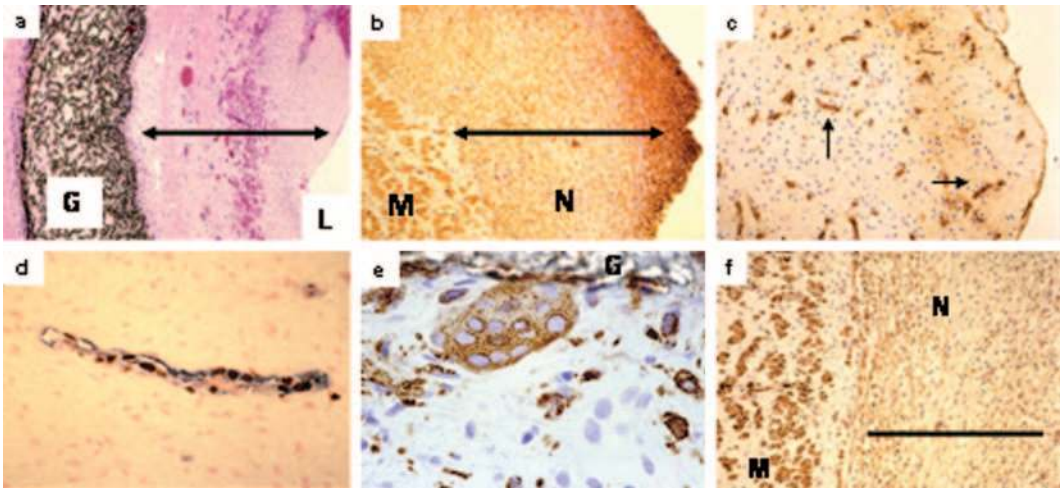

Figure 5. Venous neointimal hyperplasia in PTFE dialysis grafts (human samples). (a) PTFE graft. Note the significant venous neointimal hyperplasia (extent of arrow) between the graft (G) and the lumen (L). (b) Downstream (proximal) vein (N, neointima; M, media), α smooth muscle actin (SMA) demonstrates that the majority of cells in downstream vein are smooth muscle cells. (c) Downstream vein (neointima). Note the prominent angiogenesis within the neointima (arrows) as assessed by this endothelial cell marker. (d) Downstream vein (neointima). High-power view of a microvessel within the neointima of downstream vein. Note the distinct co-localization of blue (endothelial) and brown (proliferating) cells indicating active endothelial cell proliferation (angiogenesis). (e) Upstream graft (neointima). High-power view of a macrophage giant cell adjacent to the neointimal surface of PTFE graft (G). Also note the large number of macrophages in this area (thin arrows). (f) Downstream vein (media and neointima). There is strong expression of this cytokine in the venous media (M) and by smooth muscle cells/myofibroblasts within the neointima (N; bar). Adapted from reference (15). Magnifications: ×200 in a (hematoxylin and eosin); ×400 in b (SMA), c (von Willebrand factor [vWF]), and f (PDGF); ×800 in d (vWF and Ki67); ×2000 in e (PG-M-1).

March 18, 2004); (*3*) the presence of the PTFE graft itself, which has been shown to attract in macrophages, producing a plethora of cytokines (15); (*4*) graft injury from dialysis needles (this probably is most relevant in the setting of intragraft stenoses); and (*5*) the presence of uremia, which has been shown to exacerbate endothelial dysfunction (22) and predispose to venous neointimal hyperplasia even before the creation of an arteriovenous dialysis access. After development of an initial stenosis, it is likely that the most important factor that predisposes to repeat stenoses is endothelial and smooth muscle cell

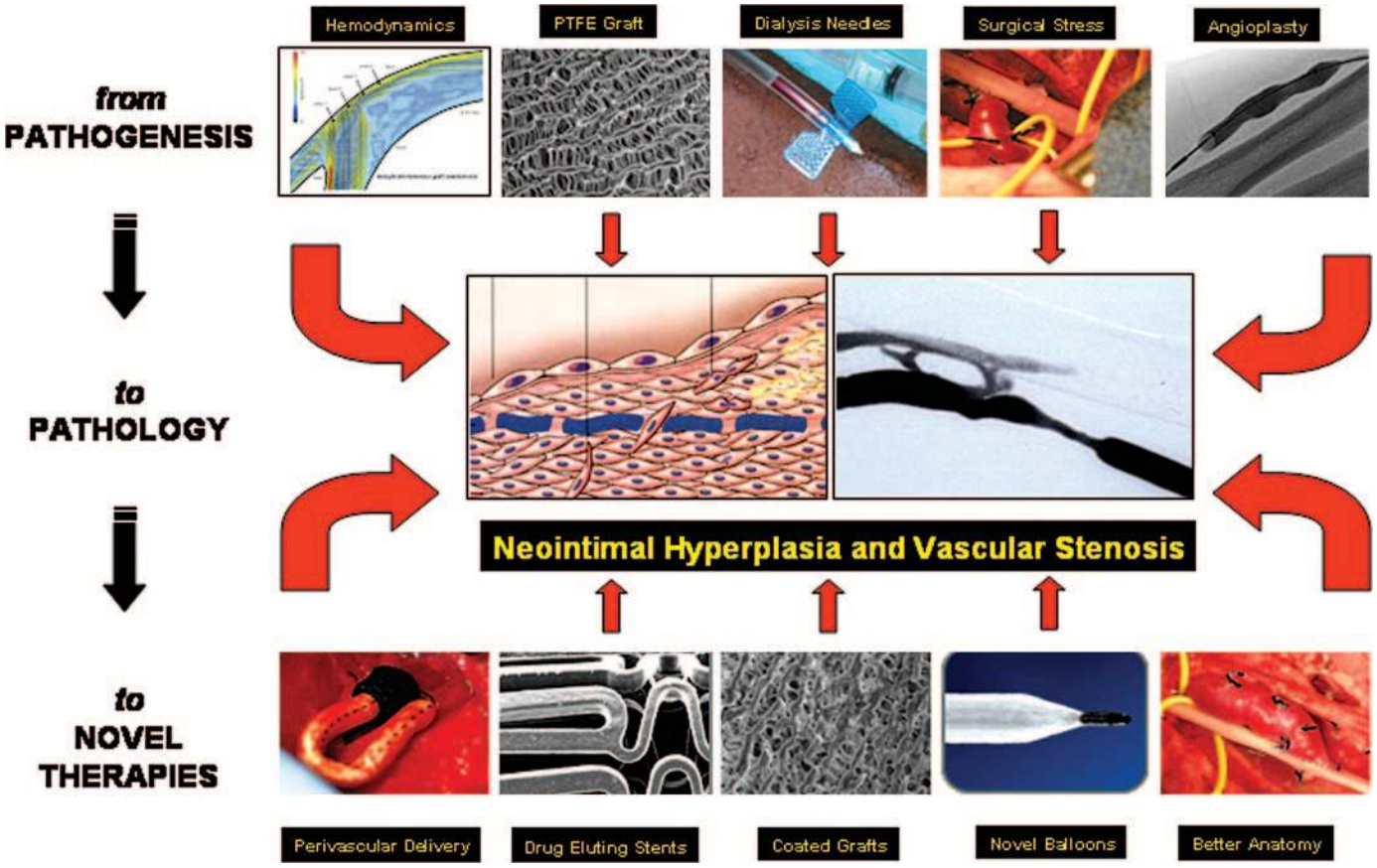

Figure 6. From pathogenesis to pathology to novel therapies. This figure identifies the different pathogenetic mechanisms that result in dialysis access stenosis and directs attention to potential novel therapies. The pathogenetic factors include hemodynamic and surgical stressors, inflammatory stimuli from dialysis needles and PTFE graft material, and the unavoidable vascular injury that occurs at the time of angioplasty (see text for a more detailed discussion). Novel therapeutic modalities include perivascular drug delivery, drug-eluting stents, coated grafts, novel balloons (picture of Conquest balloon courtesy of Bard Peripheral Vascular), and better final surgical anatomy (see text for a more detailed discussion).

injury at the time of angioplasty for the treatment of the initial stenosis. Chang *et al.* (23) demonstrated a significant increase in the proliferation index within the venous neointima and media in patients with aggressive restenotic lesions as compared with patients with primary stenotic lesions. Their study emphasizes the need for concomitant administration of antiproliferative therapy at the time of balloon angioplasty of dialysis access grafts and fistulae (as is currently the standard of care after coronary angioplasty).

The downstream events are essentially a response to endothelial and smooth muscle cell injury secondary to the upstream events. According to the "traditional theory" of neointimal hyperplasia, endothelial and smooth muscle injury results in the migration of smooth muscle cells and myofibroblasts from the media into the intima, where they proliferate and form the lesion of venous neointimal hyperplasia. This process of injury followed by migration and proliferation is orchestrated by a large number of mediators, which include the cell-cycle regulators (p27 and p16, retinoblastoma protein, p38 mitogen-activated protein kinase); cytokines (PDGF, basic fibroblast growth factor, and TNF-α); chemokines (monocyte chemoattractant protein-1 and RANTES); vasoactive molecules (nitric oxide [NO] and endothelin); adhesion molecules (intercellular adhesion molecule-1 and P-selectin); and molecules such as osteopontin, apolipoprotein E, matrix metalloproteinase-2, and human hepatocyte growth factor (24). It should be emphasized, however, that most of this information is derived from arterial angioplasty models rather than from vascular (venous) anastomosis models.

At a clinical level, dialysis access grafts and fistulae develop stenosis and thrombosis far more aggressively as compared with arterial grafts or even interposition saphenous vein conduits in coronary artery bypass surgery. This may be due to the following factors. (*1*) At an anatomic level, veins tend to have a less well-defined internal elastic lamina, which could predispose to the migration of smooth muscle cells and myofibroblasts from the media to the intima. (*2*) At a physiologic and molecular levels, veins tend to produce less NO and prostacyclin, which could predispose to endothelial injury (25). Recent studies have also demonstrated significant differences in gene expression between normal arteries and veins (26). Whether differences in the expression of these genes translates into a more aggressive response to injury is unknown. (*3*) Puncture of dialysis grafts and fistulae could cause platelet thrombi and cytokine release (27). (*4*)

The presence of uremia could predispose to endothelial dysfunction and stenosis.

It also is important to identify differences in the response of arteries and veins to vascular injury. This could allow us to develop novel therapies that effectively target venous stenosis and also identify currently available therapies that are most likely to be effective in the context of venous stenosis. For example, recent work by our groups has demonstrated that venous smooth muscle cells are more sensitive to the effects of antiproliferative agents (28) but less sensitive to the effects of radiation as compared with arterial smooth muscle cells (29).

Finally, we need to mention that in the past few years, a number of excellent animal models of arteriovenous graft and native fistula stenosis that closely mimic the clinical lesion have been developed. This has greatly helped our understanding of the pathology and pathogenesis of arteriovenous stenosis and clearly will be a valuable resource as we move forward to test out novel therapies in this field (30–33).

Novel Concepts in the Pathology and Pathogenesis of Vascular Injury and Stenosis: Relevance to Hemodialysis Vascular Access Dysfunction

Importance of Vascular Remodeling

The functional determinant of hemodialysis vascular access dysfunction is luminal cross-sectional area at the site of stenosis (Figure 7). This is dependent not only on the magnitude of neointimal hyperplasia but also on the pattern of vascular remodeling (vasoconstriction or vasodilation) (34). Indeed, studies in coronary angioplasty models have suggested that adverse vascular remodeling or vasoconstriction is responsible for >50% of the final luminal stenosis (34). The factors that are responsible for adverse (rather than beneficial) vascular remodeling are unknown, but adventitial angiogenesis and scar formation (adventitial fibroblasts) are thought to play a role (35,36). Therefore, the ideal therapy for vascular stenosis is likely to be an intervention that can block both adverse vascular constriction (adverse remodeling) and neointimal hyperplasia. This hypothesis is supported by the recent success of drug-eluting stents for the treatment of coronary stenosis (see below) (37,38).

Alternative Origins for Neointimal Cells (Adventitia and Bone Marrow)

Adventitia-Derived Neointimal Cells: A Role for Fibroblasts and Myofibroblasts. The traditional view on the pathogenesis of neointimal hyperplasia has emphasized the migration of differentiated contractile smooth muscle cells from the media to the intima, where they proliferate and contribute to the formation of neointimal hyperplasia. A number of groups, however, have shown that after experimental coronary angioplasty or saphenous vein grafting, there is a migration of fibroblasts from the adventitia, through the media, and into the intima, where these cells acquire the phenotype of myofibroblasts (expressing smooth muscle α actin) and contribute to the final neointimal volume (Figure 8) (39–41). Our own work supports the presence of a similar paradigm in the setting of PTFE dialysis grafts and fistulae in that almost 50% of neointimal cells at the graft–vein anastomosis of PTFE dialysis grafts are fibroblasts and myofibroblasts rather than contractile smooth muscle cells (42). Although it is possible that these cells originally were contractile differentiated smooth muscle cells that dedifferentiated, the presence of fibroblasts within the actual graft material suggests that there is an active migration of these cells from the adventitial side. The possible role of the adventitia, both in vascular remodeling and as a source of neointimal cells, emphasizes that the adventitia is *not* an innocent bystander in the pathogenesis of neointimal hyperplasia. Rather, these concepts make a strong case for the development of therapeutic interventions that (*1*) focus on the adventitia and (*2*) target

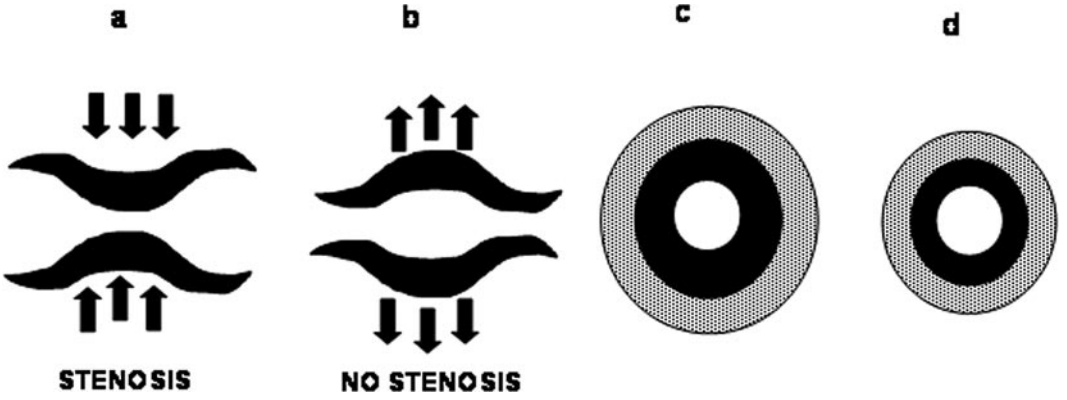

Figure 7. Adventitial remodeling. The degree of luminal stenosis depends on both the magnitude of neointimal hyperplasia and the degree of vascular remodeling. With the same amount of neointimal hyperplasia, vascular constriction and unfavorable remodeling results in luminal stenosis, whereas favorable remodeling in b prevents the occurrence of luminal stenosis. A similar situation is described in c and d. In both panels, the white area is the lumen. The area in black is the neointima, which is bordered on the outside by the internal elastic lamina and on the inside by the lumen. The hatched area comprises the adventitia and the media. Note that the luminal (white) area in both c and d are identical, despite that d has much less neointima (black area). The reason for this is adverse vascular remodeling in d, which has resulted in a decrease in the area enclosed by the external elastic lamina. This latter parameter is a good indicator of the amount of vascular or adventitial remodeling. Adapted from reference (24).

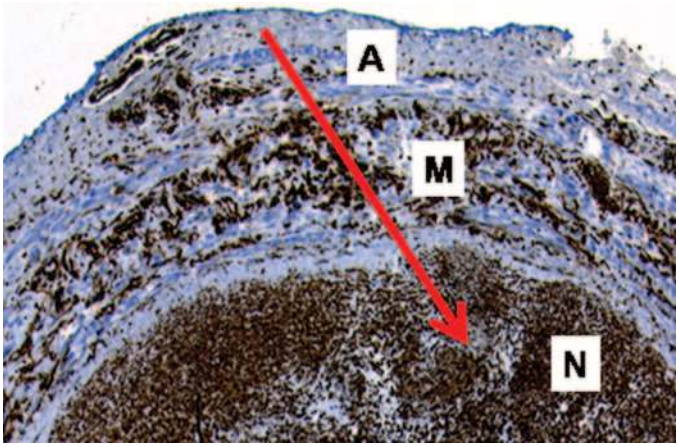

Figure 8. Adventitial cells migrate to the intima. High-power view of the stenotic venous limb, which has been used to depict a cartoon representation of the migration of adventitial fibroblasts from the adventitia, through the media, and into the intima, where they can acquire the phenotype of myofibroblasts or smooth muscle cells. Magnification, ×800 (vimentin).

multiple cell types (fibroblasts, myofibroblasts, and smooth muscle cells) instead of only the differentiated contractile smooth muscle cell.

Bone Marrow–Derived Neointimal Cells (Figure 9). Recent data also suggests a role for bone marrow derived smooth muscle progenitor cells in the pathogenesis of neointimal hyperplasia. Thus Sata *et al.* (43) have shown that up to 60% of both endothelial and smooth muscle cells within the lesion of neointimal hyperplasia after femoral angioplasty are bone marrow-derived cells. Bone marrow-derived cells that have acquired a smooth muscle phenotype have also been identified in a mouse model of venous neointimal hyperplasia (44). From a therapeutic standpoint, the local perivascular administration of sirolimus has been shown to have a beneficial effect on neointimal hyperplasia by reducing the number of circulating smooth muscle progenitor cells within the lesion of neointimal hyperplasia. Unfortunately, sirolimus also reduced the number of endothelial progenitor cells (see below) which resulted in a decrease in endothelialization (45).

Endothelial Progenitor Cells and Vascular Repair. Endothelial progenitor cells (EPC) are circulating bone marrow–derived cells that express both hematopoietic (CD34) and endothelial cell markers (vascular endothelial growth factor receptor 2) (46,47). In addition to promoting angiogenesis, an important role of EPC seems to be the rapid endothelialization of regions of vascular injury (Figure 10) (48,49). For example, the infusion of EPC in the setting of angioplasty or surgical graft placement results in enhanced endothelialization, which translates into a reduction in neointimal hyperplasia (50,51). This is in keeping with previous data that demonstrate an inhibitory effect of endothelialization and endothelial-derived factors such as NO on smooth muscle cell proliferation and migration (52–54). Most important, a number of agents can enhance the mobilization of EPC from the bone marrow (statins, erythropoietin, GCSF, and matrix metalloproteinase-9) (48). Indeed, Kong *et al.* (55) demonstrated that GCSF therapy results in an increase in endothelialization *and* a reduction in neointimal hyperplasia in a mouse angioplasty model.

The collective data presented in this section suggest a completely new paradigm for both the pathogenesis and the therapy of neointimal hyperplasia. Specifically, it seems that therapies that (*1*) prevent the adventitial response to injury and (*2*) optimize the balance between smooth muscle progenitor cells (less is good) and endothelial progenitor cells (more is good) may have the best chance of inhibiting vascular stenosis as a result of neointimal hyperplasia. In contrast, traditional therapies that aim to prevent the migration and proliferation of smooth muscle cells from the media to the intima may not be as effective at blocking neointimal hyperplasia as a result of the presence of these alternative pathogenic pathways.

Possible Therapies for Hemodialysis Vascular Access Dysfunction: From Currently Available Intervention to Future Innovation

The information on the pathology and the pathogenesis of vascular stenosis, presented in the previous two sections, helps to identify potential therapies that could be used to prevent hemodialysis vascular access dysfunction. The focus is on the use of therapies that can promote native AVF maturation and prevent vascular stenosis, because these are the major problems that are associated with hemodialysis vascular access dysfunc-

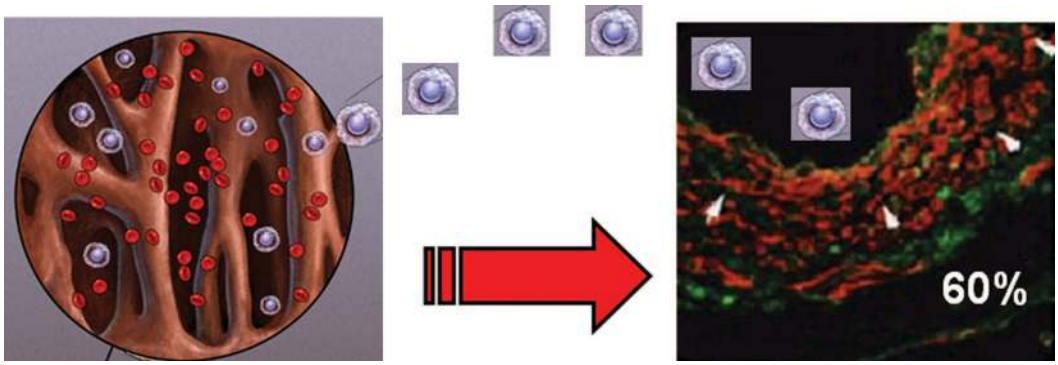

Figure 9. Smooth muscle progenitor cells contribute to neointimal hyperplasia. Smooth muscle progenitor cells have been shown to contribute significantly to total neointimal volume. Adapted from reference (43). Left figure courtesy of Dr. M. Kutryk.

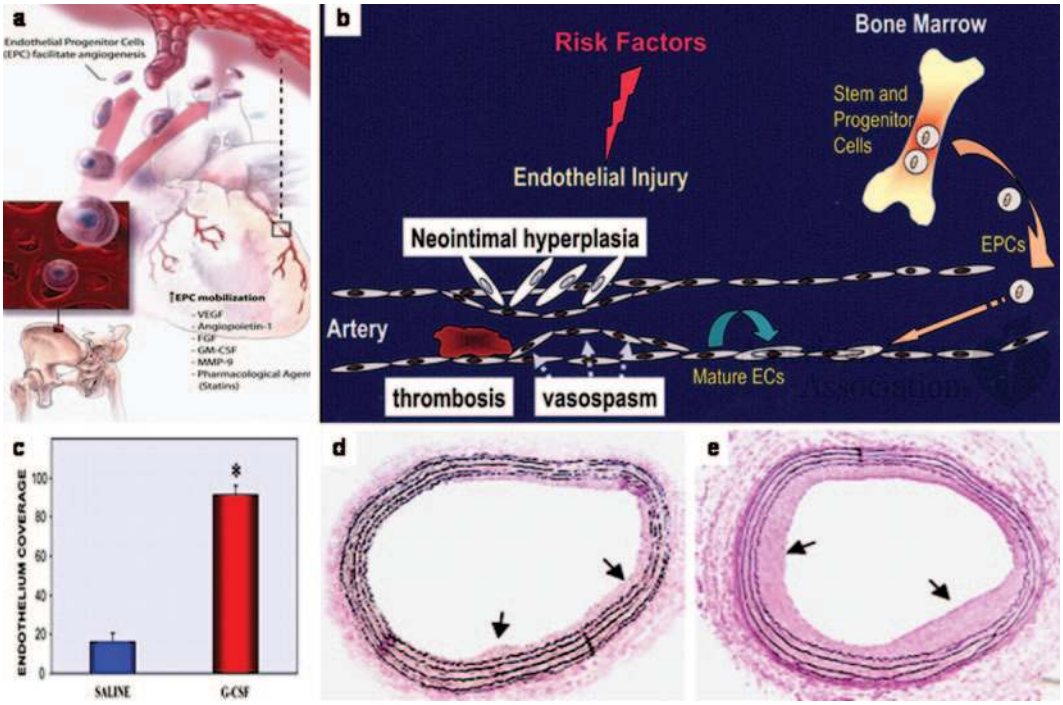

Figure 10. Endothelial progenitor cells (EPC). EPC are produced in the bone marrow and can be mobilized by a number of different factors, including GCSF (a). EPC function as the repair mechanism for the endothelium. (b) EPC bind to injured endothelium possibly to prevent vasospasm, thrombosis, and neointimal hyperplasia. (c) Increased endothelial coverage of the region of vascular injury in mice that were treated with GCSF after balloon angioplasty. This increase in endothelial coverage translated into a reduction in neointimal hyperplasia in mice that were treated with GCSF (d) as compared with untreated mice (e). Adapted from references (48) (a), (49) (b), and (55) (c through e).

tion. Dialysis grafts and fistulae are ideally suited to locally delivered therapies in view of their superficial anatomic location and the prospect of repeat delivery of local agents at the time of hemodialysis through the dialysis needles. *Particular emphasis therefore is placed on these approaches.* The potential therapies discussed span the entire spectrum of drug and nonpharmacologic interventions, from agents and techniques that are currently available on the market to promising therapies that are still in the early experimental stage.

Altering Upstream Events

Although the potential benefit from manipulation of upstream hemodynamic stressors could be very significant, this has been a relatively neglected area of research and innovation. Numerous experimental studies have demonstrated clearly that turbulent, low-flow, and low-shear-stress systems predispose to neointimal hyperplasia (21,56) and that reversal of such abnormalities can reduce the degree of neointimal hyperplasia (57). Interventions that aim to prevent the development of low shear stress therefore may result in less neointimal hyperplasia. At a clinical level, however, the only such intervention in the setting of hemodialysis vascular access has been studies that have used the Venaflo hooded graft with initial studies suggesting improved survival (58). The only other "upstream" intervention that has been shown to be successful in enhancing fistula maturation is the ligation of accessory veins (59–62).

Currently Available Systemic Agents

There has been a lot of interest in the use of currently available agents that have the potential to block smooth muscle cell proliferation and migration and/or thrombosis in the setting of hemodialysis vascular access dysfunction. Unfortunately, much of these data are anecdotal and involve a very small number of patients (63). Dipyridamole (64) and fish oil (65) have been shown to prevent stenosis and thrombosis in PTFE dialysis grafts (primary prevention) in randomized clinical trials, whereas angiotensin-converting enzyme inhibitors have been shown to be of benefit in retrospective registry analyses (66). On the basis of some of these data, the National Institutes of Health–sponsored Dialysis Access Consortium is conducting two large, multicenter, randomized, prospective, primary prevention studies (Aggrenox in dialysis grafts and clopidogrel in native fistulae). Two newer agents that have been shown to have potent inhibitory effects on vascular stenosis in experimental models are sirolimus (67) and the peroxisome proliferator–activated receptor γ agonist rosiglitazone (68). In addition to blocking smooth muscle cell migration and proliferation, both sirolimus and rosiglitazone seem to modulate the relative number of smooth muscle and endothelial cell progenitors in experimental models (45,69), emphasizing the importance of these alternative mechanisms in the pathogenesis of neointimal hyperplasia. Preliminary clinical studies demonstrate a reduction in in-stent restenosis after coronary angioplasty, with the

oral administration of sirolimus (70) and rosiglitazone (71). The role of these agents in the clinical setting of hemodialysis vascular access dysfunction is unknown.

Radiation Therapy

The rationale for the use of radiation therapy for the prevention and treatment of vascular stenosis as a result of neointimal hyperplasia stems from (*1*) the potent *in vitro* antiproliferative effect of radiation therapy on smooth muscle cells, endothelial cells, and macrophages (72–74) and (*2*) possible beneficial effects on vascular remodeling (vessel wall dilation) (75). Experimental angioplasty models have demonstrated significant reductions in luminal stenosis with endovascular and external beam radiation therapy (76,77), and these findings have been confirmed in large clinical studies of catheter-based radiation therapy for coronary restenosis (78,79). Both external beam and endovascular radiation therapy have been shown to reduce vascular stenosis in experimental arteriovenous graft (80,81) and native fistula (82) models. In addition, a pilot study of endovascular radiation therapy after angioplasty (BRAVO-I) in dialysis patients with patent but dysfunctional grafts documented an improvement in 6-mo target lesion primary patency (thrombosis or angioplasty of the irradiated lesion) in the radiation group (83,84). Unfortunately, this improvement in target lesion primary patency did not translate into better cumulative patency (overall graft survival regardless of the number of thrombotic episodes/angioplasties) at either 6 or 12 mo after intervention. Some data from a larger study of endovascular radiation therapy in thrombosed PTFE dialysis grafts should be available shortly (BRAVO-II).

Gene Therapy

Gene therapy could become an effective means of local therapy for neointimal hyperplasia in dialysis grafts and fistulae (85), especially if improvements continue to be made in the safety and the efficacy of delivery techniques (86). Currently, inhibition of neointimal hyperplasia in experimental angioplasty models has been achieved by the gene transfer of endothelial and inducible NO synthase, cyclin-dependent kinase inhibitors, retinoblastoma protein, hepatocyte growth factor, and transcription factors such as Edifoligide (E2F) (24). A phase II trial of the E2F decoy is currently in progress in arteriovenous grafts, but it is unlikely that this will progress into a larger study in view of the lack of efficacy of E2F decoys in the setting of saphenous vein bypass grafting in the coronary circulation (PREVENT IV) (87) and in peripheral vein bypass grafting (PREVENT III) (88).

Local Drug Delivery

Stent Adaptations. The main advantage of stent placement after vascular injury (angioplasty) is a reduction in adverse vascular remodeling (see Importance of Vascular Remodeling section, above). Unfortunately, bare-metal stents are prone to develop an aggressive in-stent restenosis. Recent experimental (89,90) and clinical studies (37,38) with placement of drug-eluting stents that release paclitaxel and sirolimus (both are small-molecule inhibitors of cell-cycle progression) after coronary angioplasty have shown a marked reduction in in-stent restenosis as compared with bare-metal stents (Figure 11). Most impressive, this effect seems to be long lasting (up to 4 yr) (91). A recent direct comparison (SIRTAX study) between the sirolimus-eluting (Cypher; Cordis, Miami Lakes, FL) and paclitaxel-

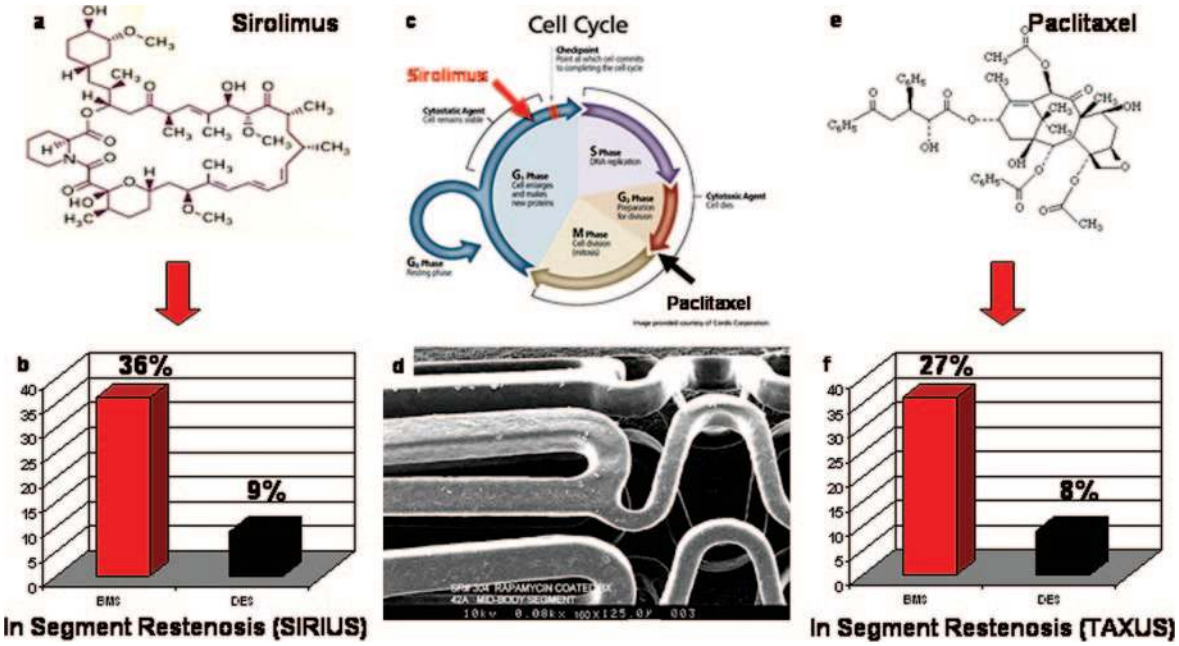

Figure 11. Drug-eluting stents. Sirolimus and paclitaxel are small-molecule inhibitors of cell-cycle proliferation (a, c, and e). When loaded into a polymer and coated onto coronary stents (d), they result in a significant inhibition of in-segment restenosis (b and f). Adapted from (37,38).

eluting (TAXUS; Boston Scientific, Natick, MA) stents suggested that the sirolimus-eluting stent is superior with regard to target lesion revascularization and late lumen loss (92).

In the setting of dialysis access dysfunction, there does not seem to be any benefit from the routine placement of bare-metal stents after angioplasty (93,94). There is no information on the placement of drug-eluting stents in patients with dialysis grafts and fistulae, although a recent study in a pig model of arteriovenous graft stenosis demonstrated an improvement in luminal stenosis at 28 d when sirolimus-eluting stents, as compared with bare-metal stents, were placed at the time of surgery (95). One potential disadvantage of drug-eluting stents in the hemodialysis population could be an increased risk for bleeding if both aspirin and clopidogrel are required after stent placement (96).

Local Perivascular Drug Delivery. The theoretical advantages of perivascular drug delivery for neointimal hyperplasia are as follows. (*1*) Application of the drug of choice directly to the adventitia ("outside-in approach") may be far more effective in blocking adventitial activation and fibroblast migration as compared with local endovascular application through a drug-eluting stent ("inside-out approach"). This could be of great clinical relevance in view of the importance of the adventitia in the pathogenesis of neointimal hyperplasia (discussed in Pathology and Pathogenesis of Native Fistula and PTFE Graft Failure section, above). (*2*) Delivery of the therapeutic agent to the adventitia results in a gradient of drug concentrations, with the highest levels in the adventitial layer and the lowest levels at the endothelial layer. In the specific context of antiproliferative agents (the most common type of drug therapy for neointimal hyperplasia), lower drug concentrations at the endothelial layer actually could be beneficial by allowing endothelialization of the region of vascular injury. (*3*) The direct local application of a small amount of drug can result in high concentrations at the site of vascular injury (neointimal hyperplasia) with minimal systemic toxicity (as a result of the small dose used). Most important, the validity of such an approach has been documented in a number of experimental angioplasty models using agents such as NO, paclitaxel, and the tyrphostins (24).

In most cases, perivascular delivery systems involve the use of polymer-based systems that are not drug specific. A variety of simple small-molecule drugs, antibodies, or nucleotides can be incorporated into the polymers and delivered locally (see examples above). Some polymers, such as a triblock co-polymer of polylactide-polyethyleneglycol-polylactide, exhibit a temperature-dependent reversible transition between solution and gel phases. The co-polymer dissolves in water to form a free-flowing liquid at low temperatures but turns into a water-insoluble gel within seconds at body temperature. Therefore, these polymers can be mixed with drugs in the aqueous phase and *injected* perivascularly, whereby they form a gel depot at the desired location for sustained drug release. In addition, both *in vitro* (97) and *in vivo* (98) pharmacokinetic studies in the porcine model have demonstrated that drugs such as dipyridamole that are delivered by these polymers perivascularly diffuse through arteries, veins, and PTFE grafts and therefore are available throughout the thickness of the vessel for the inhibition of smooth muscle cells or myofibroblasts.

Paclitaxel has been incorporated into these thermosensitive polymers, injected into the perivascular area of hemodialysis grafts several weeks after graft placement, and shown to inhibit neointimal hyperplasia in a canine model (32). An alternative approach that involves the placement of paclitaxel-loaded wraps around the graft–vein anastomosis also has been shown to be effective in reducing neointimal hyperplasia and luminal stenosis (99). In both instances, the polymer in which the drug is trapped provides a mean of sustained delivery, at the anastomoses between the native vessels and the graft, allowing the gradual release of the drug over weeks or months. Theoretically, repeated percutaneous injection of antiproliferative drugs at various time intervals using these polymers may provide sufficiently high local concentrations for months to years for the prevention of graft stenosis.

In addition, the release profile of drugs from thermosensitive polymeric gels can be manipulated further by combining the thermosensitive gels with a variety of drug platforms such as poly(lactide-co-glycolide) microspheres (100). Using dipyridamole as the test molecule, it can be demonstrated clearly that the combination of thermosensitive gel with dipyridamole encapsulated in microspheres further delays and decreases the rate of release of this drug. The delay and decrease in release rate can be manipulated by altering the molecular weights of the polymers that are used in the preparation of the microspheres. Therefore, slow or fast release rates at different time points after injection of the perivascular polymers can be achieved, and this then can be titrated so that the drug release profile can have a maximal impact on the known temporal course of arteriovenous graft stenosis.

We believe that perivascular drug delivery using a variety of polymer combinations for the sustained delivery of antiproliferative drugs and perhaps antiplatelet agents is an intriguing and promising approach to the clinical problem of hemodialysis vascular access dysfunction, which needs further development. It is likely that dialysis access grafts and fistulae could be the ideal clinical model for perivascular polymer-based drug delivery systems in view of their superficial position, their remoteness from vital organs, and the potential logistic benefits of easy repeated access to the patient during the hemodialysis session.

Utilizing PTFE Graft as a Conduit for Drug Delivery. Despite their increased rates of stenosis and thrombosis, PTFE dialysis access grafts may have an important advantage over native AVF in that the graft material itself could be used as a platform for local drug delivery to prevent infection, thrombosis, and stenosis. In view of the ability of NO to stabilize endothelial cells and also block smooth muscle cell activation, Frost *et al.* (101) devised a number of different polymers loaded with NO-releasing substances that can be coated onto PTFE graft material. Pilot studies using these NO-releasing grafts have demonstrated a reduction in thrombosis and an improvement in patency, in a sheep model of arteriovenous graft stenosis (102). A similar approach with other antiproliferative and antithrombotic agents needs to be pursued aggressively.

Endothelial Seeding and Manipulation of Progenitor Bone Marrow–Derived Cells

The holy grail of experimental vascular surgery is the dream of being able to seed vascular grafts with a layer of endothelial cells that have the capacity to release endogenous inhibitors of stenosis and thrombosis such as NO and prostacyclin. Unfortunately, this has proved to be extremely challenging, although some encouraging results have been obtained through the use of shear stress activation of endothelial cells (103) and electrostatic seeding (104). It is interesting that endothelial progenitor cells seem to have a far greater propensity (as compared with differentiated endothelial cells) to attach to prosthetic stent and graft material, and the best results to date have been obtained by plating *ex vivo* cultures of EPC onto grafts and stents (Figure 12, a and b) (105,106). Unfortunately, this is a time-consuming and technically demanding process that may not be suited to clinical use. An elegant alternative approach has been the development of vascular grafts or stents that are coated with an antibody to CD34, which is an antigen that is present on EPC.

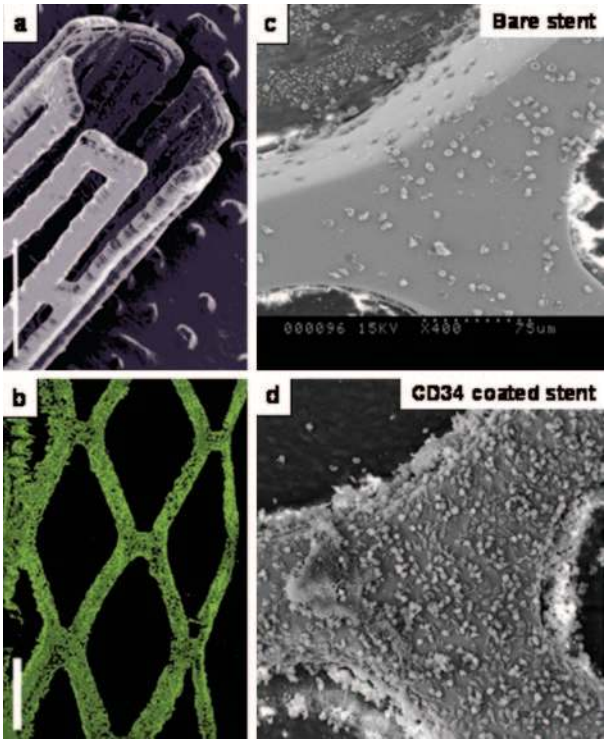

Figure 12. EPC can seed prosthetic stents and grafts. *Ex vivo* EPC cultures can successfully coat prosthetic stents with an endothelial cell layer. (a) Low-power scanning electron microscopy picture of a prosthetic stent coated with EPC (bar = 1 mm). (b) Confocal scanning laser microscopy picture of EPC stained with PicoGreen fluorescence, on an expanded stent (bar = 1 mm). Coating prosthetic stents with an antibody to the EPC marker CD34 can result in rapid endothelialization of prosthetic stents. Note the large number of cells seen on low-power scanning electron microscopy at 1 h on the CD34-coated stents (d) as compared with the noncoated stents (c). Magnifications: ×35 in a, ×30 in b. Adapted from references (105) (a and b) and (53) and Dr. M. Kutryk (personal communication) (c and d).

As expected, when these stents are placed within the vascular tree, they are able to attract in EPC and undergo rapid endothelialization, which may translate into a reduction in neointimal hyperplasia (53,107). The first clinical studies with these CD34 antibody–coated stents demonstrate both safety and feasibility (108). However, a recent study demonstrates increased neointimal hyperplasia in CD34-coated arteriovenous grafts, despite an increase in endothelialization (109).

Another approach that is completely experimental at present is optimizing the balance between neointima-enhancing smooth muscle progenitor cells and neointima-attenuating EPC. This potentially could be done by modulating integrin expression on smooth muscle progenitor cells (110) to reduce their adhesion to sites of vascular injury while enhancing the mobilization of EPC from the bone marrow to sites of vascular injury (48).

Promoting Native AVF Maturation

As the rate of AVF placement increases, a corresponding increase in the incidence of primary nonfunction (failure to mature) is expected. In marked contrast to the many therapies that have promise in reducing neointimal hyperplasia, very few novel therapies focus on enhancing fistula maturation. Part of the reason for this is that primary nonfunction is a poorly understood, multifactorial process that is unlikely to respond to single-drug therapy. An exciting alternative approach (cell-based therapy) has been pioneered by Nugent *et al.* (33,111); it involves embedding specific cell types (*e.g.*, endothelial cells) into a perivascular Gelfoam cuff. These cells then could produce an array of mediators that hopefully would mimic the two main functions of endothelial cells (promote vascular dilation *and* inhibit neointimal hyperplasia). At a practical level, however, numerous clinical studies have been able to demonstrate a significant improvement in the maturation of AVF through an aggressive preoperative ultrasound evaluation of arterial and venous diameters (112–114). Malovrh *et al.* (113), for example, demonstrated an immediate patency rate of 92% in patients with a preoperative internal diameter of >1.5 mm in the feeding artery as compared with a maturation rate of 45% in patients with an internal diameter of <1.5 mm. At 12 wk, the patency rates in the two groups were 83 and 36%, respectively.

Other Therapies

Photodynamic Therapy. The rationale behind photodynamic therapy is to administer a photosensitizer, either systemically or locally, and then expose the region of vascular injury to light radiation (external or endovascular), resulting in the production of singlet oxygen that can cause cell death in the region that is exposed to light radiation. Photodynamic therapy has been used in experimental models of peripheral and coronary angioplasty (115,116) and in an arteriovenous graft model (Miravant Medical Technologies, Santa Barbara, CA) (117) and has demonstrated safety, feasibility, and preliminary efficacy. Some anecdotal clinical data also are available, but a large phase III study in a clinical model of vascular injury is lacking.

Cryoplasty. Cryoplasty is the combination of a standard angioplasty with the simultaneous delivery of cold thermal

energy (−10°C for 60 s; CryoVascular Systems, Los Gatos, CA). Initial clinical studies in femoropopliteal angioplasty (15 patients) (118) and rapidly recurrent restenosis in arteriovenous dialysis grafts (five patients) (119) suggest safety, feasibility, and preliminary efficacy.

Stent Grafts. In contrast to the lack of data on the use of drug-eluting stents in dialysis access dysfunction and the lack of efficacy of bare-metal stents after angioplasty, a recent prospective, randomized study compared the placement of stent grafts (Bard Peripheral Vascular, Tempe, AZ) after angioplasty with angioplasty alone in PTFE graft stenosis. Placement of stent grafts resulted in a significant improvement in primary patency at 6 mo (53 *versus* 29%) (120). This is an important result that could have immediate clinical applicability.

Looking to the Future

We are in the midst of fundamental changes in the way we address the clinical problem of hemodialysis vascular access dysfunction. The purpose of this last section is both to summarize where we stand and to make suggestions for future scientific advance in this field.

There is a clear appreciation of the magnitude of the clinical problem and the understanding that prevention rather than mechanical treatment should be the goal in reducing the morbidity that is associated with hemodialysis arteriovenous access dysfunction. In particular, we now recognize that all vascular manipulations (surgery or balloon angioplasty) cause endothelial and smooth muscle cell injury, which results in a restenotic process. Therefore, these interventions need to be linked to therapies that can target both the traditional and the alternative pathways that are involved in the pathogenesis of neointimal hyperplasia and vascular stenosis (see below).

We have a reasonable understanding of the pathology and the pathogenesis of venous neointimal hyperplasia and vascular stenosis in the setting of dialysis access dysfunction. However, the past few years have seen great advances in the elucidation of alternative mechanisms that are responsible for neointimal hyperplasia, and we need to assess the impact of these new paradigms on the clinical problem of hemodialysis vascular access dysfunction.

The combination of advances in cellular and molecular pathobiology, biomaterials, and drug delivery techniques has resulted in many innovative therapies for neointimal hyperplasia. We need to identify (from this plethora of interventions) the therapies that are best suited for *clinical* use in the setting of hemodialysis vascular access dysfunction; we need to test these therapies in the excellent animal models of arteriovenous stenosis that are available to us, and we need to move the most promising of these therapies from the laboratory to the clinic.

In parallel, clinical trials need to be conducted to examine both the currently available oral agents that are known to inhibit smooth muscle cell proliferation or migration and that have already shown clinical efficacy in the arterial neointimal setting and to test therapies that target novel pathways of neointimal hyperplasia and vascular remodeling. In testing new therapies, however, we need to recognize the redundancy and the pleiotropism of biologic systems and appreciate that combination therapy may yield the greatest clinical benefits (this holds true for both experimental and clinical studies).

To optimize the use of resources, we need to standardize clinical trial end points in this field for both primary and secondary prevention studies (some guidelines are already available [121,122]) and identify population subsets (patients who are prone to early and aggressive stenosis) so that appropriate stratification can be performed.

Finally we need to emphasize that dialysis grafts and fistulae could be the *ideal clinical model* for testing new *locally delivered* therapies for neointimal hyperplasia, in view of their superficial location, the aggressive nature of the lesion, and the frequent follow-up of these patients in the dialysis clinics. The results from such trials then could be applied to other clinical conditions that are characterized by neointimal hyperplasia, such as postangioplasty restenosis, peripheral vascular disease, and coronary artery bypass graft stenosis.

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This comprehensive review of the current understanding of the vascular biology that underlies the failure of different forms of vascular access relates to three papers in the March issue of *CJASN*, including encouraging international data from the DOPPS study related to the epidemiology of access placement and function (pages 246–255), documentation of the beneficial effects of endovascular treatment in the fistula that is failing to mature (pages 275–280), and a presentation on when and how to intervene in treating the failing access (pages 332–339).