Local Drug Delivery for the Prevention of Restenosis
Fact, Fancy, and Future

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More than 600,000 percutaneous coronary revascularization procedures were performed worldwide in 1993. Despite extensive investigation into a variety of adjunctive therapies and mechanical techniques during the past 15 years, it can be anticipated that 30% to 50% of patients with successfully treated coronary lesions will develop recurrent stenoses (restenosis) over the ensuing 3 to 6 months.1 The cost of treating patients who will require repeat revascularization will exceed 2500 lives and $3.5 billion.2 The importance of this problem is magnified by the fact that the process of restenosis following vascular injury may also serve as a paradigm for atherosclerosis, a disease nearly endemic to Westernized civilizations.

Recent pathological3,4 and intravascular ultrasound5,6 studies have suggested that the pathogenesis of restenosis is multifactorial. A dominant process leading to luminal renarrowing of many lesions may be neointimal hyperplasia, and investigations in animal models have characterized this mechanism of arterial "response to injury,"7,8 thereby permitting rational approaches to its prevention. Other mechanisms that are variably important, however, include angiographically inapparent inadequate result, elastic vessel recoil, and mural thrombosis (Fig 1).

Against this complex process, many of the new devices for percutaneous revascularization have been developed and advocated, including intraluminal stents, lasers, and atherectomy catheters. Unfortunately, observational series and a few controlled trials using these techniques have generally demonstrated restenosis rates that are not dissimilar from those obtained with conventional balloon angioplasty.9-17 The recent STRESS and BENESTENT trials18,19 have shown significant reductions in restenosis rates using the Palmaz-Schatz stent, albeit in a relatively select group of patients and with a significant risk of hemorrhagic or thrombotic complications; these findings reinforce the suggestion, however, that an inadequate initial result or elastic recoil may contribute to restenosis in certain settings.

Pharmacological therapy has not fared better than new devices for the treatment of restenosis. Numerous pharmacological agents have been tested which, by virtue of their effects in reducing neointimal proliferation in one or more animal models, might be expected to favorably influence different components of the arterial response to injury in humans. However, clinical trials with these drugs have yet to demonstrate an unequivocal reduction in the incidence of restenosis.20 These disappointing results may be due in part to interspecies differences in the process of neointimal proliferation in humans and animal models21 or to the incomplete role of neointimal hyperplasia in the causation of human restenosis.3,5 Modification of the mode of administration of pharmacological agents, like by local delivery, would not be expected to yield substantial incremental benefit under such circumstances, whereas mechanical techniques such as intraluminal stenting may be efficacious. However, many of the failures of pharmacological therapy for restenosis in humans relative to animal models may be related to systemic intolerance of doses required to achieve local beneficial effects or difficulty in providing controlled administration of the drugs for adequate periods of time. For example, both cilazapril and enoxaparin have been shown in animal models to potently inhibit neointimal proliferation following arterial injury,22,23 yet each has failed to reduce the angiographic restenosis rate in human placebo-controlled trials.24,25 However, dosages of these agents (adjusted for body weight) in animal studies were 10- to 70-fold higher than those used in the human trials.

Interest has accordingly shifted away from systemically administered agents for prevention of restenosis to local administration of potentially useful compounds directly to the site of arterial injury following coronary angioplasty. There are several possible advantages to this form of therapy. First, local drug delivery would allow very high local concentrations of drug to be achieved, even of agents that are rapidly degraded when administered systemically. Second, by concentrating the drug at the target site without substantial systemic dosing, systemic adverse effects can be minimized. Finally, with certain forms of local delivery, prolonged administration or residence time of drug may be achievable.

Overview of Local Delivery

Drug delivery has been called "the potential Achilles' heel of biotechnology's peptide drug industry,"26 largely
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Many peptides greatly reduce restenosis and proliferation (IFP) at site of PTCA 4 months later (AP indicates atherosclerotic plaque; L, lumen). B, Photomicrograph of restenosis with minimal layer of IFP at site of PTCA 5 months after the procedure. Immediate postprocedure result revealed a 10% residual percent stenosis. Predominant mechanism of restenosis appears to be vessel wall recoil. Reprinted with permission.9

Fig 1. A, Photomicrograph of restenosis and intimal fibrous proliferation (IFP) at site of percutaneous transluminal coronary angioplasty (PTCA) 4 months later (AP indicates atherosclerotic plaque; L, lumen). B, Photomicrograph of restenosis with minimal layer of IFP at site of PTCA 5 months after the procedure. Immediate postprocedure result revealed a 10% residual percent stenosis. Predominant mechanism of restenosis appears to be vessel wall recoil. Reprinted with permission.9

because the typically rapid clearance or protease degradation and poor oral bioavailability of unprotected peptides greatly diminished their clinical effectiveness. Many of the techniques developed to circumvent this problem may have relevance to the treatment of restenosis: such techniques have focused on the synthesis of nonpeptide mimetics; microsphere encapsulation of active drug with synthetic or biopolymers, proteinoids, or other coatings; respiratory delivery; or transdermal inophoresis or electroporation (the latter two methods use either constant low-level electric current to push charged molecules through the skin or millisecond pulses to induce changes in the skin to allow passage of drug, respectively).27-29

Local drug delivery has been used for a number of noncardiac applications in humans.30 A progesterone-releasing intrauterine device (Progestasert) releases ste-

roid locally over a period of more than 1 year from its polymer reservoir coating. Polymer implants containing very low doses of tetracycline have been used to locally treat periodontal disease. Sustained local delivery of pilocarpine for the treatment of glaucoma has been achieved using a polymer reservoir (Ocusert) designed to float in the conjunctival cul-de-sac. Polymeric disks containing chemotherapeutic agents are under clinical investigation as postsurgical local therapy for brain tumors.

Drug-impregnated controlled-release polymeric matrices have been used experimentally in animal models for the treatment of various cardiovascular disorders, including ventricular arrhythmias and bioprosthetic heart valve calcification.31,32 A local drug delivery device that has been applied clinically for a cardiovascular indication is the steroid eluting pacemaker lead (Medtronic, Inc). The corticosteroid dexamethasone is released over a period of months to years from a silicone polymer reservoir in the metallic tip of this pacemaker lead directly to the site of endocardial pacing, thus attenuating the fibrosis and concomitant rise in pacing thresholds that typically accompany long-term endocar-dial pacing.33

Experimental Studies of Local Delivery for Restenosis

Several experimental studies in small-animal models have provided “proof of concept” of local delivery for the prevention of the myointimal response that contributes to restenosis. Most of these experiments have used drug delivery from polymers or other reservoirs surgically implanted exterior to the injured vessel, with “inward” diffusion of drug from the adventitia to the media and neointima. Although these techniques of local drug delivery are not practical for treatment of restenosis in humans, for whom placement of drug reservoirs external to the coronary artery is not feasible, such experimental studies have allowed the principle of local drug delivery to be tested.

In the first study to explore the effectiveness of local delivery for restenosis, Edelman and colleagues34 treated rats that had been subjected to carotid artery injury with placebo, heparin delivered intravenously, heparin administered from a polymer matrix implanted under the dorsal skin, or heparin eluted locally from a polymer matrix placed adjacent to the injured carotid artery. Although both intravenous and local heparin delivery markedly diminished neointima formation compared with placebo, local delivery was associated with no change in activated partial thromboplastin time (aPTT), whereas intravenous delivery resulted in significant systemic anticoagulation. This study demonstrated that local drug delivery could produce a beneficial effect on the arterial response to injury that may be uncoupled from unwanted systemic effects.

More recently, Simons and associates35 treated rats after carotid injury with antisense oligonucleotides to the proto-oncogene c-myb, administered from an adventitial “pluronic” polymer. Vessels treated with local delivery of antisense oligonucleotides showed significant inhibition of neointimal formation compared with control vessels. Of importance is that this inhibitory effect of antisense oligonucleotides occurred only within
those segments of carotid artery that had been locally treated by the pluronics coating; more proximal segments of artery that were balloon injured but not treated locally failed to demonstrate a reduction in neointimal formation.

In a design similar to that of the c-myb antisense experiment, Villa and associates\textsuperscript{36} studied the local release of dexamethasone from adventitial silicone polymers in the rat carotid injury model. Within the vessel segments coated with polymer, dexamethasone resulted in nearly complete abolition of neointimal proliferation, whereas the extent of inhibition was significantly less in more proximal unwrapped (but injured) vessel segments. Thus, dose-related inhibition of neointimal proliferation by local delivery of dexamethasone was incremental to that resulting from systemically absorbed drug.

**Local Delivery Devices for Restenosis**

For local drug delivery to be useful for human applications to prevent restenosis, practical methods of locally administering drug percutaneously must be achieved. Despite the intuitive simplicity of delivering drugs through a catheter perhaps not dissimilar to those currently used to perform angioplasty, a number of obstacles must be overcome before such treatment becomes clinical reality. These may be summarized as follows: how to deliver, what to deliver, when to deliver,
where to deliver, how to keep the drug in place long enough to achieve full activity, how to overcome the potential deleterious effects of inhibition of wound healing, how to identify patients most likely to benefit, and how to overcome potential regulatory hurdles to bring a novel and potentially beneficial treatment to clinical practice. Clearly, these issues are somewhat interrelated as, for example, the choice of what to deliver influences how, when, and where the drug should be delivered.

A number of different devices have been developed to this end, most of which may be broadly classified as delivery balloon catheters, polymeric or coated stents, or devices or techniques for “facilitated diffusion.” Such devices may be evaluated on the basis of many criteria. Particularly for pharmacological agents that are costly or have potential systemic toxicity, efficiency of drug transfer becomes of paramount importance, in that a primary goal of local delivery is to minimize systemic relative to target tissue uptake. Efficacy of administered drugs is also likely to be influenced considerably by homogeneity of transfer and the duration of delivery or residence time at the target site. A drug delivery device should produce minimal or no vascular trauma aside from that induced by the percutaneous revascularization procedure itself, as experimental and clinical studies suggest that the extent of late neointimal proliferative response is proportional to the degree of initial arterial injury. Finally, an ideal drug delivery device would be relatively simple to use, may have additional utility for lesion dilation or as a temporary stent, and would maintain distal coronary perfusion if prolonged delivery times were required.

Assessment of Local Drug Delivery Devices

Efficiency and uniformity of macromolecular transfer by local delivery devices may be assessed using various marker substances. Early experiments documented arterial wall permeability with systemically administered agents such as labeled albumin or fibrinogen. More recently, horseradish peroxidase (HRP), a 44-kd enzyme, has been used by a number of investigators to delineate the distribution of solute transfer throughout the arterial wall following either systemic or local catheter delivery. The peroxidase reaction of HRP with the enzyme substrate 3,3’-diaminobenzidine (DAB) produces a characteristic brown precipitate within the arterial tissue, which may be detected by standard light microscopy. A major advantage of the HRP technique is that absolute quantification of molecular uptake and radial concentrations is possible by measurement of light transmission through tissue sections compared with tissue standards incubated with known concentrations of HRP. An important limitation of the HRP marker, however, is its requirement of an aqueous environment for development of the DAB reaction product, thus rendering this technique unsuitable for measurement of solute transfer into lipid components of plaque or the arterial adventitia.

Other soluble substances that have been used in the evaluation of local drug delivery include fluoresceinated heparin or marker dyes. During perforated balloon delivery, green dye appears to be transported by bulk convection to sites of tissue disruption and intramural vascular spaces (vasa vasorum or plaque neovascularization), with little penetration into the arterial tissue itself. Fluorescence following local administration of fluoresceinated heparin, in contrast, has been demonstrated to be distributed throughout the media into the adventitia, although this agent was found to be toxic to arterial medial cells, regardless of infusion pressure, in at least one study. In addition, no technique to quantitatively assess tissue uptake with these substances has been reported. In an effort to overcome the limitations of washout via the vasa vasorum of soluble tracers such as HRP, heparin, or dye, nondiffusible polymer microparticles have also been injected directly into the vascular wall. Although this technique has thus far been used only for qualitative assessment of local delivery, potential advantages of microparticle injection as a means of drug delivery include the demonstrated prolonged retention (14 days) throughout the media and adventitia, concentrated along planes of vascular dissection and injury. Each of these means of assessing macromolecular transfer suffers, however, in that they fail to provide relevant data regarding the retention and local metabolism of prospective antirestenosis agents.

Delivery Balloon Catheters

Several designs of local delivery balloon catheters are under investigation. The double-balloon catheter (USCI Division of C.R. Bard, Inc) was the first percutaneous drug delivery device. This catheter is passed to the treatment site over an intra-arterial guidewire, in a manner analogous to that with an angioplasty balloon. By inflating two small balloons proximal and distal to the vessel segment to be treated, drug can be instilled through a small hole into the chamber thus formed between the balloons (Fig 2A). Although this device produces minimal trauma at the chamber site, prolonged dwell times are required to achieve significant drug levels by passive diffusion, thus rendering this device impractical for coronary arteries due to distal myocardial ischemia. In addition, although the double-balloon catheter is suitable for peripheral vessels, the occurrence of sidebranches every 2 to 4 mm in coronary arteries results in loss of infusate when the device is used in the coronary tree. To overcome some of the limitations of the double balloon, the Wolinsky perfused-balloon catheter (USCI Division of C.R. Bard, Inc) was developed (Fig 2B). With twenty-eight 25-μm holes drilled by a laser into a noncompliant balloon, inflation of the balloon causes streaming of infusate through the holes into the apposed vessel wall. This catheter has been shown to result in solute transfer throughout the arterial media and into the adventitia, with the depth of delivery related to infusion pressure. The chief disadvantage of this device is the potential for vascular trauma from the fluid jets, an effect that also appears to be related to infusate pressure. Only 5% of canine arteries treated with this catheter ex vivo in one study had no apparent traumatic effects. Such acute trauma, ranging from disruption of elastic laminae to dissection or frank arterial perforation, likely also has significance in terms of long-term sequelae, with greater acute injury translating to a greater long-term arterial neointimal response in animal models. An additional limitation of this device arises from the tendency of the perforations to become intermittently obstructed, resulting in nonhomogeneous solute delivery.
A microporous balloon (Cordis Corp) was designed to limit the trauma induced by the perforated balloon (Fig 2C). Instead of discrete 25-μm holes, this balloon material consists of a membrane with thousands of pores with a diameter of <1 μm. Administered solute "sweats" from the microporous membrane without jet effects, substantially enhancing the homogeneity of infusion and reducing the potential for arterial injury.47 Other delivery catheters have been designed to allow balloon dilation with the same device that is used for drug delivery or to maintain distal myocardial perfusion during drug administration. The channel catheter (Boston Scientific Corp) consists of a central angioplasty balloon surrounded on its exterior surface by 24 channels, each with a single 100-μm hole through which drug is delivered (Fig 2D), thus separating the chambers used for lesion dilation and drug infusion.49 As low infusion pressures appear to minimize vascular trauma, this design allows balloon inflation pressure to be dissociated from drug infusion pressure and permits the catheter to be used for both high-pressure lesion dilation and low-pressure drug infusion. This arrangement particularly simplifies the procedure of postangioplasty local drug delivery, in that exchange of a dilation for a delivery catheter is unnecessary. A similar design is used in the Transport coronary angioplasty catheter (Cardiovascular Dynamics), which consists of an inner balloon for lesion dilation and an outer porous balloon for drug infusion.50 The Dispatch delivery catheter (SciMed Life Systems Inc), recently approved by the Food and Drug Administration for intracoronary drug infusion, uses a helical balloon design that allows infused drug to be held against the arterial wall in the spaces formed between the helices while distal coronary blood flow is maintained through a central lumen (Fig 2E). This device thus functions effectively as a "temporary stent" during drug delivery, allowing periods of infusion in excess of 30 to 60 minutes without clinical evidence of resultant myocardial ischemia.

As an alternative technique to allow lesion dilation with the same catheter used for drug delivery, angioplasty balloons have also been coated with a thin layer of hydrophilic polyacrylic acid polymer (Hydrogel, Boston Scientific Corp), which can act as a drug-absorbing sponge. Once loaded with drug, the catheter is introduced into the coronary artery, and the drug is "pressed" into the arterial wall during balloon inflation.51 This device produces no additional arterial trauma, as drug delivery occurs simultaneously with lesion dilation. The major limitation of the Hydrogel balloon is rapid washout of drug from the balloon polymer coating on entry into the blood stream, necessitating an effective but somewhat cumbersome telescoping sheath arrangement placed over the balloon before inflation. Another novel delivery catheter design consists of an infusion sheath (Infusion Sleeve, Localmed, Inc), which can be placed over a standard angioplasty catheter and advanced to the lesion after balloon dilatation.52

There have been no direct comparative studies assessing transfer efficiencies of the different delivery balloon designs. Qualitatively, bulk convective transfer provided by devices such as the perforated, microporous, and channel balloons appears to be somewhat superior to that obtained by passive diffusion with the double-balloon catheter, although prolonged dwell times achievable with autoperfusion devices such as the Dispatch catheter may prove to be particularly desirable. In the porcine coronary artery model, local vessel wall transport of the tracer HRP by the microporous balloon was 8- to 40-fold more efficient than administration by more conventional techniques, such as intracoronary or intravenous infusion.53 Nevertheless, absolute efficiency (medial tracer concentration divided by infusate concentration, corrected for extracellular fluid partition coefficient of the media) may be as low as 1% to 2% in nondiseased coronary arteries; the presence of atherosclerotic plaque likely will modify drug uptake with this and other delivery devices, as will the increased density of vasa vasorum present in advanced atherosclerotic disease.54

Homogeneity of drug transfer by delivery balloon catheters is likely dependent on a variety of factors, including the number and propensity of perforations to become obstructed and the presence or absence of discrete fluid jets. In animal models, tracer concentrations are typically greatest initially at the luminal aspect of the media;55 interestingly, however, HRP delivered even to the superficial (luminal) media by a Hydrogel-coated balloon appears to washout "in waves" into the adventitia within 6 hours (R. McKay, MD, Hartford Hospital, personal communication), perhaps via vessels draining the vasa vasorum. In addition, changes induced in the vascular wall by atherosclerotic disease and the extent of preexistent or induced vascular wall disruption also appear to influence the homogeneity of transport, with infusate likely preferentially transported along dissection planes (Fig 3).45

The potential for prolonged drug residence at a target site following local delivery from a balloon catheter appears to be a function of the characteristics of the administered agent, rather than of the delivery device. For certain agents, depending on solubility, molecular size, or the presence of binding or uptake sites within the tissue, retention within the arterial wall may be quite prolonged. When methotrexate was infused with the Wolinsky catheter into balloon-injured porcine carotid arteries, activity of radiolabeled drug in the carotid wall remained nearly 100-fold greater than that in the blood for at least 8 days.55 In contrast, in a similar experiment where tritiated heparin was delivered to porcine coronary arteries using the Dispatch, washout of 85% of the labeled heparin from the arterial wall occurred within 90 minutes.56

**Polymeric or Coated Stents**

A potential technique for providing sustained local administration of drug would be to implant an intraluminal stent composed of or coated with polymer or other materials into which drug has been impregnated. Stents have an additional theoretical advantage over other drug delivery devices in that the mechanical structural support provided by a stent would limit elastic recoil and optimize the initial result of percutaneous revascularization, thus potentially acting on several of the pathways leading to restenosis. Although permanent metallic intracoronary stents appear to have been well tolerated in long-term clinical studies,57,58 biodegradable drug-release polymer systems have the advantage of gradual biological elimination without a residual
Implant structure. These preparations would be particularly useful in settings, such as prevention of restenosis, where only a finite period of drug delivery is likely to be required.

Release of drug from a polymer may occur through multiple mechanisms. Diffusion-based systems take the form of either “reservoirs,” in which a drug core is surrounded by a polymer film governing the release rate, or “monolithic matrices,” wherein drug is uniformly dispersed or dissolved within the polymeric material. Chemical mechanisms for drug elution involve either biodegradation of polymeric matrices, with concomitant release of dispersed drug, or solvent cleavage of drug bound to a polymer backbone. The kinetics of drug release can be extensively tailored to specific applications by design or modification of pore size, hydrophobicity, implant dimensions and shape, and the erosion rates and properties of biodegradable systems.

Potential disadvantages of polymer stents as delivery devices include the limited amount of active agent that can be loaded onto their relatively small surface area. Furthermore, because current stent designs cover only 5% to 12% of the arterial surface area, drug may need to diffuse widely to “fully treat” the disrupted surface, and substantial inhomogeneity of drug transfer may result. These limitations may be partly overcome by using highly potent pharmacological agents that would be active at even low concentrations in the target tissue, as well as by configuring the polymer into a sheath or webbing around a metallic backbone to increase the surface area available for drug elution from the stent. Stability of the drug contained within the polymer over the anticipated time course of elution must also be ensured. Finally, compatibility of the polymeric material at the blood/tissue interface within the vasculature and the potential to produce inflammation or accelerated thrombosis must be carefully investigated.

Experimental studies with a polyethylene terephthalate (Dacron) stent performed by Murphy and colleagues at the Mayo Clinic suggested that tissue incompatibility may prove to be a major obstacle in the development of polymer stents for intravascular drug delivery. This nonbiodegradable polymer, when deployed in a self-expanding stent design into porcine coronary arteries, was associated with an intense proliferative inflammatory response that resulted in complete arterial occlusion by 28 days’ follow-up. More recently, a study testing the intravascular compatibility of several biodegradable and nonbiodegradable polymers in the porcine coronary artery has been described.

All of the test polymers used in this study had previously been determined to be “biocompatible” in animal models; several, including the biodegradable poly(d,l-lactide/glycolide) copolymer (PGLA) and the nondegradable polyether urethane urea, medical grade silicone, and Dacron, have had extensive medical use in humans for nonintravascular applications. By 28 days after implantation in the porcine coronary artery, however, all of the test polymers were found to evoke variable degrees of hyperplastic response, with...
severe cellular inflammation and destruction of vessel architecture.

In contrast to these data, other reports have suggested that at least some polymers may be biocompatible within the coronary vasculature. A group at Duke University has developed an entirely biodegradable stent composed of a high molecular weight poly-l-lactic acid (PLLA) (Fig 4A); results of canine implants suggest that this polymer is well tolerated for as long as 18 months, with stable reendothelialization and no inflammatory response.62 Experiments in other animals that may be more relevant models of restenosis have not been reported. Another design using a metallic backbone coated with PLLA polymer has shown promise as a drug eluting stent in preliminary experiments (Fig 4B).63 After implantation within injured porcine coronary arteries, release of the test agent dexamethasone from the monolithic polymer matrix was documented to occur for at least 28 days. Although the dexamethasone proved ineffective in reducing neointimal proliferation in this model, the PLLA polymer did not evoke an inflammatory reaction and appeared to be an effective
and well-tolerated method of sustained intravascular drug delivery.

A novel approach to the development of polymer-coated stents has been to use the biopolymer fibrin. Exogenous porcine fibrinogen is catalyzed with thrombin to form a fibrin sheath, which is coated onto a tantalum coil stent to form a “fibrin stent” (Fig 4C); residual thrombin is inactivated with heparin or hirudin to prevent further fibrin formation within the coronary artery. This stent is intended to provide a relatively inert synthetic mural thrombus at the site of implantation within the coronary artery, thus theoretically limiting uncontrolled thrombosis and subsequent smooth muscle cell proliferation. In addition, the fibrin may serve as a matrix for drug elution. Preliminary studies with this device have demonstrated that the fibrin stent appears to be well tolerated within the coronary artery, with nearly complete replacement of the fibrin by smooth muscle cells within 28 days (R. Schwartz, MD, Mayo Clinic, personal communication).

Facilitated Diffusion

Very little has been reported regarding the use of facilitated diffusion techniques for cardiovascular applications. Local diffusion of drug into the arterial wall may be enhanced by iontophoresis, a process whereby charged solute is transported across an electrical gradient established by an electrode catheter placed within the coronary artery. Preliminary experiments with one such device suggest that delivery efficiency may be considerably improved by iontophoresis compared with that obtained by passive diffusion. The potential for arterial wall trauma with iontophoresis is unknown, but deleterious effects noted with dermal applications include burns, fibrosis, and delayed absorption (deposit effect).

Local Delivery Vehicles for Restenosis

Local delivery vehicles may be considered as distinct from local delivery devices, in that delivery vehicles serve as carriers of drug to the target tissue or cell. These vehicles are intended to enhance target specificity, cellular uptake, or residence time of a locally delivered agent. Local delivery vehicles may be combined with delivery devices to optimize drug administration. Delivery vehicles may be broadly classified as controlled-release matrices, gene vectors, and techniques for “affinity-based” delivery.

Controlled-Release Matrices

Controlled-release matrices that may be delivered percutaneously generally consist of microparticles, composed of biodegradable polymers such as PGLA, non-degradable polymers, or biopolymers such as albumin or starch. Once transferred to the arterial wall, typically with balloon delivery catheters, the typical microparticle size (range 5 to 15 μm) limits its diffusion out of the arterial wall. Drug impregnated within the microparticle is gradually eluted by diffusion through pores and/or breakdown of a biodegradable matrix. Preliminary studies in animal models have suggested that polymeric microparticles do result in prolongation of drug residence times within the arterial wall; in one study, for example, fluorescent marker loaded into microspheres was documented to persist within the arterial wall following microporous balloon infusion for at least 4 weeks, whereas fluorescent marker delivered in a similar manner without microspheres disappeared within 72 hours. Suspensions of colloidal gold microparticles (30-nm diameter), to which pharmaceutical agents could be adsorbed, have also been investigated as local drug delivery vehicles, with deposition following microporous balloon catheter infusion noted primarily along vascular dissection planes.

Gene Vectors

There is growing interest in the use of gene therapy for the treatment of cardiovascular diseases, including restenosis. Gene therapy adds an additional complication to the local delivery problem, in that genetic material must be transported into the cell before a biological effect can occur. One approach to gene therapy is to seed the vasculature with cells that have been transfected with a desired gene; these transfected cells can express the gene product of interest and secrete this product into the surrounding environment within the cell wall. Harvested vascular endothelial or smooth muscle cells, transduced in vitro, have been shown to colonize the endothelium or smooth muscle cell layers following reintroduction into the vasculature by delivery balloons or stents. Somewhat less cumbersome and more practical, however, are techniques whereby the desired genetic material is transported directly to the target tissue, without harvest and reintroduction of cellular vectors. In vivo gene transfer may be accomplished by infusion of naked DNA (or antisense oligonucleotides), packaging of genetic material with cationic liposomes, transport by hybrid liposomes containing viral coat proteins (eg, those from the hemagglutinating virus of Japan [HVJ]), or within retroviruses or adenoviruses. Key issues that are currently under evaluation for these various techniques of in vivo gene transfer include the efficiency of gene transfer, the temporal stability of gene expression, whether gene expression can be confined to certain tissue types, and what factors will regulate the gene expression. Safety concerns, particularly when viral vectors are used, will center primarily around the risks of persistent infection, mutagenesis and malignant transformation, direct cytotoxicity of viral infection, germ cell line infection, and the development of antigenicity and inflammation.

Evaluation of the relative merits of the different techniques for in vivo gene transfer is difficult, as few direct comparative studies have been performed and different methods have been used to classify success and estimate efficiency. The proportion of susceptible cells transfected and expressing gene product by injection of bare genetic material, liposomal vectors, or retroviruses appears to be relatively low, generally <1%. In contrast, adenoviruses may be capable of infecting 20% to 30% of susceptible cells. Other advantages of adenoviral vectors include their high transfer efficiencies, their ability to transfect nonreplating cells (in contrast to retroviruses, which transfect only replicating cells), localization of transfected genetic material as plasmids without integration into the host genome (thus limiting the potential for malignant transformation), and the relatively favorable safety profile derived from experience with attenuated adenoviral vaccines. Poten-
extracellular/cyttoplasmic events

proto-oncogene/nuclear events

Fig 5. Schematic of possible pathways leading to restenosis. Note that fundamental pathways have been demonstrated but that not all are known to exist in arterial smooth muscle cells. ILGF indicates insulin-like growth factor; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; TGFβ, transforming growth factor-β; GPX, growth factor ‘X’ (unknown growth factors); and MAP kinase, mitogen activated kinase.

tial limitations to the use of adenoviruses for prevention of restenosis include poor specificity (with transfection into many different cell types), the short-lived (≤30 days) gene expression, and the complexity of the techniques required to construct the vectors.

Affinity-Based Delivery

Affinity-based delivery vehicles exploit the selectivity of cytokines and growth factors for certain cell types as a means of delivering toxins to particular target cells. Several fusion toxins have been tested, each consisting of a cell recognition growth factor moiety, such as basic fibroblast growth factor (b-FGF), transforming growth factor-β (TGFβ) or endothelial growth factor, coupled to a toxin such as saporin, diphtheria toxin, or pseudomonas toxin. Only activated cells expressing receptors for these growth factors are capable of binding to and internalizing these toxins, and thus only those cells are susceptible to toxic ablation. The FGF-saporin fusion toxin has been demonstrated in the rat carotid injury model to markedly limit neointimal formation compared with placebo, with substantial killing of medial smooth muscle cells.

Drugs and Effector Agents

An extremely large number of potential agents have been suggested or tested in one or more cell culture or animal models to prevent myointimal hyperplasia or “restenosis.”1,84 In part because this process is believed to be the same or analogous to the very fundamental process of wound healing, multiple and redundant signaling pathways are suspected to be operative. Animal studies suggest a sequential cascade of activation involving platelets, medial smooth muscle cell migration, proliferation, macrophage infiltration, and late matrix formation.65,66 Therefore, intuitively, it is likely that the optimal approach to stop the process would be either to interrupt an early stage of the process before amplification can take place or to inhibit a final common pathway, should one actually exist. Precise targeting of such pathways awaits a more complete understanding of the interactions among stimuli, growth factors, receptors, second messengers, proto-oncogenes, and other factors involved in transcription, translation, and post-translational events, but sufficient knowledge is available to begin to organize these events conceptually (Fig 5).

Early Pathway Antagonists

Platelets may promote restenosis via their adhesion and secretion of relevant constituents such as growth factors, as well as their contribution to bulk thrombus formation via their capacity to aggregate. Platelet deposition is an attractive target due to its early occurrence after arterial injury.94 The potential importance of platelets in restenosis is underscored by the fact that severe thrombocytopenia in some models appreciably decreased later smooth muscle cell proliferation,95 as well as by the fact that blockade of platelet aggregation by a GP IIb/IIIa antibody in a recent large clinical trial was associated with a reduction in the incidence of late repeat revascularization.96 It does appear that platelet degranulation is an early event, and that to be blocked, adhesion itself must be prevented97; blockade of aggregation might be useful if organization of large amounts of thrombus plays a major role in the restenotic process.

To block platelet adhesion, one must inhibit the platelet glycoprotein GP Ia–collagen and GP Ib–IX interactions98 or perhaps antagonize thrombin directly.99 Platelet aggregation is primarily dependent upon the GP IIb/IIIa receptor.99 Inhibition of amplification loop factors such as cyclooxygenase (aspirin and thromboxane inhibitors) appears likely to be “too little and too late.” Experimental animal studies have suggested that prolonged systemic administration of agents directed at the early platelet-thrombus phase, such as hirudin,100 anecrod,101 or tick anticoagulant peptide,102 may be efficacious in diminishing myointimal proliferation, whereas local administration of hirudin via a porous balloon without a method of retaining it in the vessel wall apparently only delays and does not inhibit restenosis (V. Fuster, MD, Mt Sinai Medical Center, personal communication). Thus, the role of local drug delivery for management of the early platelet-thrombus phase of restenosis remains to be defined.

Late/Possible Common Pathway Antagonists

Smooth muscle cell proliferation presents a common event that could be targeted to block restenosis. Accord-
ingly, agents that react with proliferating but not quiescent cells may be useful in inhibiting restenosis. It has been suggested that the c-myb, c-myc, and other proto-oncogenes or the cdc-2/proliferating cell nuclear antibody (PCNA) complex directly involved in regulation of the G1→S→G2→M cycle may represent smooth muscle cell proliferation-related targets for antisense technology. It remains uncertain, however, whether these antisense approaches represent a specific effect or are simply the result of any of several nonspecific events.

Other Potential Targets

Other factors potentially located along a common pathway include the variety of growth factor–related tyrosine kinase receptors (Fig 5) and the generation of extracellular matrix, which makes up the vast bulk of the mature restenotic tissue. Transforming growth factor–β appears to play a major role in matrix formation, but it may be too multifunctional to be a good target for inhibition. Basic FGF is known to stimulate smooth muscle cell proliferation and has been targeted successfully in several restenosis models. Other potential inhibitors noted to be effective in at least one model include corticosteroids, interferon-α and interferon-γ, HMGCoA reductase inhibitors, and a variety of antioxidants.

Timing and Retention

Given that the cascade of events leading to restenosis takes place over a time span of weeks to months, it is possible that pharmacological inhibition must be active for a similar time period. Agents targeted at early events (eg, platelet deposition or thrombus formation) may need to be present before or at the time of injury but possibly only for a short time thereafter, whereas inhibitors of late events (eg, matrix formation) will likely need to be active later and for long periods of time. The proliferative process may “escape” if an inhibitor is present for insufficient time, as has been described for locally delivered hierudin and some antisense oligonucleotides. As the logistics of clinical practice will likely dictate that local administration of drugs be performed at the time of percutaneous revascularization, the choice of delivery device and vehicle will need to be tailored to the residence time adequate to a specific targeted event.

Possible Risks

At present, the risk of inhibition of local wound repair is largely conjectural. Rab and colleagues have reported delayed aneurysm formation in patients treated with metallic stents and systemic steroids and colchicine. One might postulate that the trend toward increased incidence of late sudden death after directional atherectomy noted in the CAVET study may have been due to medial weakening (from partial resection) and rupture, but this is highly speculative. Nevertheless, the possibilities of aneurysm formation, stasis thrombosis, and even rupture must be considered.

Patient and Lesion Selection

Recent advances with intravascular ultrasound and molecular biology provide hope that antirestenosis therapy may be patient and lesion “tailored,” ie, based on the most likely etiologies of restenosis in a particular situation. For example, preliminary data suggest that balloon dilatation of a concentric plaque without a resultant dissection evident to intravascular ultrasound appears to be associated with a high incidence of restenosis, probably via recoil. This finding would imply that measures to prevent recoil, such as stent placement, or to change vessel wall compliance might be useful. Conversely, in situ hybridization of lesion specimens removed by directional atherectomy staining for the β isoform of nonmuscle myosin heavy chain have been found to be associated with a high likelihood of restenosis, probably due to exuberant neointima formation. Therefore, if a “frozen section” or rapid assay technique for this or another predictor of proliferation could be found to be reliable, especially aggressive antiproliferative treatment could be initiated in appropriate patients.

Development and Approval

Traditionally, pharmacologics (drugs) and devices (eg, angioplasty balloons) have been evaluated by different standards and regulatory bodies at the Food and Drug Administration. Indeed, little precedent except for steroid eluting pacemaker leads has been set for combined drug-device technologies. The guidelines for Investigational Device Exemption and Pre-Market Approval for devices, last standardized in 1989, are under revision, perhaps to be finalized by late 1994. Although the Food and Drug Administration acknowledges that drug-device combinations intended to reduce restenosis will soon need to be evaluated, this class of agents is not even part of the 1994 review. It is of some concern that guidelines for approval remain vague and therefore approval may be delayed for any of this class of agents that may become highly promising in 1994 through 1995.

Future Directions

The pathogenesis of restenosis is complex, involving incomplete mechanical displacement of atherosclerotic plaque and processes fundamental to wound healing. Prevention of restenosis, then, is likely to be equally complex and will be required to account for the multiple pathways of restenosis. Local delivery of selected agents to impair or modify myointimal proliferation has the intuitive appeal of achieving necessarily high tissue concentrations without the expected toxicity from systemic application. Substantial progress has already been made toward achieving the ideal of efficient, atraumatic intraluminal drug delivery using local delivery balloons, and clinical investigations to critically assess and compare these devices have recently been initiated.

Among the challenges for the future in this field will be the development of methods of achieving prolonged drug residence times and enhanced specificity and efficiency of cellular targeting and uptake. The principles of polymer science are only beginning to be applied in a methodical manner to the problems of intravascular drug delivery, and the potential for using controlled-release polymeric systems for the prevention of restenosis will depend on the identification of polymers that provide sustained, predictable drug release kinetics without promoting thrombosis or inflammation. Optimization of polymer stent configurations or the loading
characteristics and/or sizes of polymer particles, as well as the use of “biopolymers” or other novel compounds as drug delivery vehicles, can be expected to further enhance tissue compatibility and the efficiency and homogeneity of drug delivery. Extensive investigation into the various potential vectors for intracellular or gene delivery, particularly the viral vectors, will be required to answer important questions regarding practicality and risks for toxicity, persistent infection, or carcinogenesis; such techniques could be applied clinically for prevention of restenosis only if there is sufficient evidence that the therapy will not be “worse than the disease.”

Finally, despite the difficulties in extrapolating results from animal models to the clinical treatment of restenosis, local delivery of various pharmacological agents will need to be studied experimentally to identify potentially promising drugs (or combinations) and their most suitable methods of local administration. Refinement of techniques for assessment of individual target lesions will aid in selection of the optimal pharmacological agents and perhaps adjunctive mechanical revascularization techniques to fully control the restenotic response in each patient. It can be anticipated that a better fundamental understanding of the processes involved in restenosis and a systematic approach to this problem by local drug delivery will yield superior clinical results, compared with the previous “shotgun” approaches to the prevention of restenosis.

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