Vein graft stenosis has been the focus of much vascular research since it was first systematically described by Imparato in 1972, although Carrel had noted the phenomenon in experimental studies undertaken in the early years of this century. Recently interest in vein graft stenosis has been rather overshadowed by the concentration of research on restenosis after arterial angioplasty. Substantial similarities exist between post-angioplasty restenosis and vein graft stenosis: the incidence of both conditions is around 25-40% of all cases with no very clearly definable risk factors. Histologically the major feature is intimal hyperplasia and the predominant cytological component is the proliferating vascular smooth muscle cell and its secreted matrix. The following comments are mostly drawn from angioplasty restenosis data but, to some degree, they will probably be applicable to vein graft stenosis.

Research into restenosis has followed a predictable pattern. After initial screening assessing the effect on smooth muscle cells in culture an agent is tested in an animal model of vascular injury. This is normally balloon injury to the endothelium of the rat carotid artery. Promising results are followed by similar experiments in a larger animal. If activity against the smooth muscle cell proliferative response to injury is confirmed, the agent is then investigated in a human trial. This is usually in restenosis after coronary angioplasty. Quantitative angiography is used to measure the outcome of the angioplasty with a re-study 6-12 months later. In all such trials (and to date there are nearly 70 published studies and probably an equal number of unpublished ones) agents such as heparins, aspirin, warfarin, ACE inhibitors, statins, steroids, fish oils, and numerous others, have universally failed to make an impact on the incidence of coronary restenosis.

Success admits few interpretations, failure admits many. Explanations for this puzzling disparity between animal models and human disease are legion: maybe the agent works, but not in the doses or regimens that can be given to humans (a singularly unhelpful explanation); maybe quantitative angiography is too much concerned with millimetres and not enough with clinical utility; maybe normal vessels in young animals subjected to injury behave differently from diseased vessels in elderly humans, and many more.

Surely there have been studies that have shown positive results in preventing restenosis? There have been such studies, but due to major design faults, these reports have never gained much credit. A recurring problem has been the use of an inferred endpoint, with restenosis diagnosed without angiographic confirmation; an exercise which has been repeatedly shown to be unreliable. In this context, it is interesting to note the widespread notion that the platelet integrin receptor antagonist abciximab, (ReoPro) is active against restenosis, when the study contains no angiographic measurement at all.

Could smooth muscle cell proliferation be the wrong target? Other components contributing to restenosis are elastic recoil after arterial stretching and constrictive remodelling. Remodelling is an interesting concept, first demonstrated by Glagov as compensatory enlargement of the lumen in the presence of eccentric atherosclerotic plaque. Studies using intravascular ultrasound in coronary arteries have shown
that a decrease in the cross-sectional area of the whole artery might be a more important contributor to restenosis than an increase in the cross-sectional area of the arterial wall.¹ The mechanisms responsible for this phenomenon have not been adequately addressed; experimental studies have implicated roles for adventitial constrictive scarring, for vessel wall cell apoptosis and for extracellular matrix remodelling, all termed together as "vascular remodelling". There has not been any confirmation of a major role for vascular remodelling in restenosis in human histological samples.

Vascular remodelling after angioplasty certainly occurs, and is likely to contribute to restenosis, particularly in small arteries subject to deep wall injury but seems less likely to contribute to vein conduit restenoses. An approach to reduce the impact of elastic recoil and constrictive remodelling is the use of intravascular stents.

Two large trials of coronary stenting have shown a definite decrease in restenosis. However, this decrease is rather moderate, from around 35% to around 25%.² Three The nature of stent efficacy is interesting. The devices appear to excite more smooth muscle proliferation and intimal hyperplasia. However, this produces less luminal restenosis because of the greater initial gain in diameter from stent deployment. The longer term implications of greater smooth muscle cell proliferation are not known, but the use of coronary Palmaz stents appear to be associated with benign outcomes even 4–6 years post-insertion.³

What about other new vascular devices? Restenosis complicates all high technology methods of revascularisation and results are not so favourable as stents. Laser angioplasty has no advantage over conventional angioplasty and may in fact precipitate a greater rate of restenosis.⁴ Atherectomy in the coronary arteries or in the femoropopliteal segment has not been shown to reduce restenosis compared to angioplasty and again may result in a greater rate of restenosis.⁵

What therefore are the prospects for the inhibition of restenosis after angioplasty and bypass grafting? Firstly, I must complain about the relative paucity of studies in bypass grafting. Lower limb bypass is common, the stenosis rate of around 25–30% is significant, follow-up is often complete and objective assessment of stenosis is available with duplex scanning in most vascular centres, obviating the need for invasive angiographic re-study. In purely theoretical terms the bypass graft has considerable advantages for study, as there is no pre-existing stenosis and vessel wall injury is minor in comparison to angioplasty. This renders the bypass graft a "cleaner" model for study, certainly in respect of agents proposed to have activity against smooth muscle cell proliferation. Additionally there is an important technical advantage; measurement error of quantitative angiography or ultrasound is dependent on equipment rather than on whether coronary or peripheral segments are being imaged. This error therefore represents a smaller coefficient of variation in larger peripheral arteries than in smaller coronary vessels.

The prospects for prevention of bypass graft restenosis are uncertain. Moody et al.'s findings that there was no part of a vein conduit that was particularly susceptible to graft stenosis, and that stenosis could not be related to sites of valves or clamp injury reinforces the view that improvements in surgical technique are unlikely to affect restenosis.⁶ Some agents shown to be ineffective in coronary restenosis might prove effective in graft restenosis, due to the potentially different roles of remodelling and intimal hyperplasia in the two situations. Progress in this area depends on the energy of vascular researchers and the entrepreneurial spirit of the pharmaceutical industry (which has sadly been somewhat dented by the lack of progress thus far).

The prospects for prevention of angioplasty restenosis, by contrast, reflects substantial activity in this field for 10 years. New devices appear to have disappointing effects, as have drugs with other cardiovascular actions. Stents have demonstrated a proven, though modest improvement in restenosis. Further trials are building upon this finding by seeking improvements in instrumentation, stent design and impregnation of stent material with heparin and possibly other agents which might be active against smooth muscle cell proliferation. Very preliminary results from a heparin bonded stent trial in coronary disease have shown restenosis rates in single figures, but these figures need to be interpreted cautiously.⁷

In the longer term, the prospects for restenosis prevention will depend on greater understanding of the molecular mechanisms of restenosis. The gene therapy approach to restenosis represents a realistic research tool to dissect out the molecular pathways involved in smooth muscle cell hyperplasia. In my view, the insertion of human nucleotides into the vascular wall to prevent a complication that rarely leads to life or limb loss without warning symptoms is not justified. I would modify this position to state that such therapy might be justified in the future should adult genetic manipulation be shown to be safe, effective and without major side effects. However, the model situations to demonstrate this are likely to be in cancer rather than in vascular disease.
Local pharmacology holds more promise in the restenosis field. High concentrations of active agents can be delivered in prolonged release preparations, or bonded to stents at the site of vascular intervention. This is logistically simpler in the context of surgical bypass than in angioplasty. Advances on this front may lead to revisiting trials of agents previously ineffective in systemic doses. A logical extension of this concept, localised beta irradiation as cytostatic therapy, is under investigation.

Restenosis research is a prime example of the failure of empiricism. The investigation of drugs useful in other areas of cardiovascular medicine, on the assumption that encouraging findings in simple animal models would translate into human efficacy has been a spectacular and expensive failure, for a variety of reasons. I suggest that the vascular clinician should lead the regrouping of research effort in this area by the promotion of human peripheral bypass and angioplasty as the best models for further study.

References