# RESTENOSIS: THE ACHILLES HEEL OF CORONARY ANGIOPLASTY

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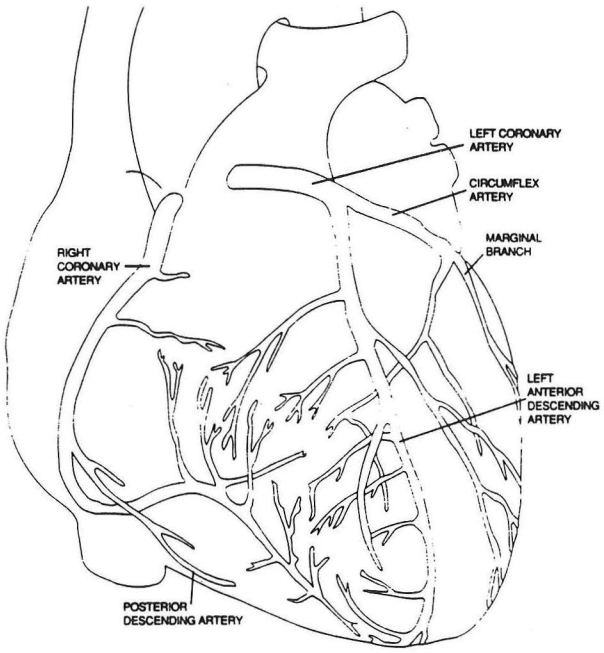


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In September 1977, Andreas Gruentzig performed the first percutaneous transluminal coronary angioplasty (PTCA) [1,2]. Despite initial skepticism about the procedure's utility, it has gained widespread acceptance as the procedure of choice in many patients with coronary artery disease. In the United States alone, over 300,000 coronary angioplasties are performed annually [3]. In patients with coronary artery disease, PTCA has been effective in relieving angina pectoris, increasing exercise tolerance, reducing episodes of silent myocardial ischemia, and reestablishing antegrade coronary blood flow in those with acute myocardial infarction from coronary thrombosis [4-6].

With advances in angioplasty and radiographic equipment technology and increased operator experience, clinical success rates have continued to increase (85-95%) and the incidence of acute complications has fallen (3-5%) despite application of the procedure on more complex lesions, total occlusions, multivessel disease, saphenous vein graft, and in acute myocardial infarction [7] (Table 1).

**TABLE 1. ANGIOGRAPHIC AND CLINICAL SUCCESS OF CORONARY ANGIOPLASTY IN 1977-1981 AND 1985-1986.**

| | 1977-1981 | 1985-1986 |
|---|---|---|
| **Angiographic Success** (lesion dilated ≥ 20%) | 67% | 88% |
| **Clinical Success** (all lesions reduced ≥ 20% and no death, infarction, or bypass surgery) | 61% | 78% |

Data from the National Heart, Lung, and Blood Institute Registry [7].

Although the incidences of initial success and complications have improved steadily since the procedure's inception, the frequency of restenosis has not changed. In light of the large number of patients undergoing PTCA, even a modest decrease in the restenosis rate would significantly impact patient care and costs. By one estimate, a reduction in the incidence of restenosis from 33% to 25% could result in yearly savings of up to $450 million in the United States alone [8]. My purpose today is to review the clinical features, pathogenesis, and strategies for prevention of restenosis following successful coronary angioplasty.

## DEFINITION AND INCIDENCE

Restenosis in the days, weeks, or months following successful coronary dilatation may occur in 12 to 43% of patients (Table 2).

**TABLE 2. RESTENOSIS RATES FOLLOWING SUCCESSFUL PTCA FROM THE LARGER REPORTED SERIES**

| Study | Patients (n) | Follow-up (%) | Interval from PTCA-Restudy (months) | Restenosis (%) |
|---|---|---|---|---|
| Holmes [9] | 665 | 84 | 6.2 | 34 |
| Kaltenbach [10] | 356 | 94 | 5.6 | 12 |
| Leimgrubber [11] | 1758 | 57 | 7.0 | 30 |
| Bertrand [12] | 1741 | N/A | 7.7 | 31 |
| Val [13] | 181 | 98 | 6.0 | 29 |
| Ernst [14] | 1163 | 63 | 4.5 | 24 |
| Gruentzig [15] | 133 | 93 | 6.0 | 30 |
| Serruys [16] | 342 | 86 | 4.0 | 30 |
| Nobuyoshi [17] | 229 | 96 | 3.0 | 43 |
| Hirshfeld [18] | 693 | 74 | 4.0 | 40 |

Abbreviations: N/A = not available

The wide variability in the reported incidence of restenosis is due to several factors, including differences in (a) patient populations; (b) completeness of angiographic follow-up; (c) assessing the severity of coronary artery stenosis (visual vs quantitative analysis); and, (d) defining restenosis.

Even now, there is no consensus among investigators as to the best definition of restenosis. The most commonly used ones are displayed in Table 3. As Figure 1 shows, the incidence of restenosis varies markedly depending upon which definition is used. In most reports, the National Heart, Lung, and Blood Institute's definition of restenosis is used

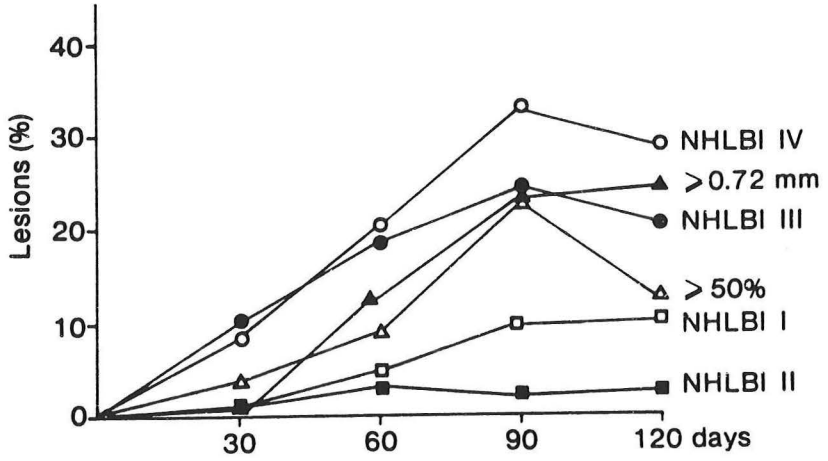
(NHLBI-1 or NHLBI-3): an increase in luminal stenosis of ≥30 percent in comparison with the appearance of the arterial segment immediately after angioplasty or a loss of ≥50 percent of the initial improvement in the cross-sectional diameter of the lumen [9].

**TABLE 3. COMMONLY EMPLOYED DEFINITIONS OF RESTENOSIS**

1. An increase of ≥30% from the immediate postangioplasty stenosis to the follow-up stenosis (NHLBI-1)
2. An initial stenosis <50% after angioplasty, increasing to ≥70% at follow-up angiography (NHLBI-2)
3. An increase in stenosis at follow-up angiography to within 10% of the predilatation stenosis (NHLBI-3)
4. A loss of ≥50% of the gain achieved by angioplasty (NHLBI-4)
5. A postangioplasty stenosis of <50% increasing to >50% at follow-up angiography
6. A decrease in the lesion minimal luminal diameter of >0.72 mm from the immediate postangioplasty stenosis to the follow-up stenosis

Abbreviations: NHLBI = National Heart, Lung and Blood Institute

**FIGURE 1. PERCENTAGE OF LESIONS THAT FULFILLED THE VARIOUS RESTENOSIS DEFINITIONS IN PATIENTS UNDERGOING REPEAT ANGIOGRAPHY** (from ref 19)

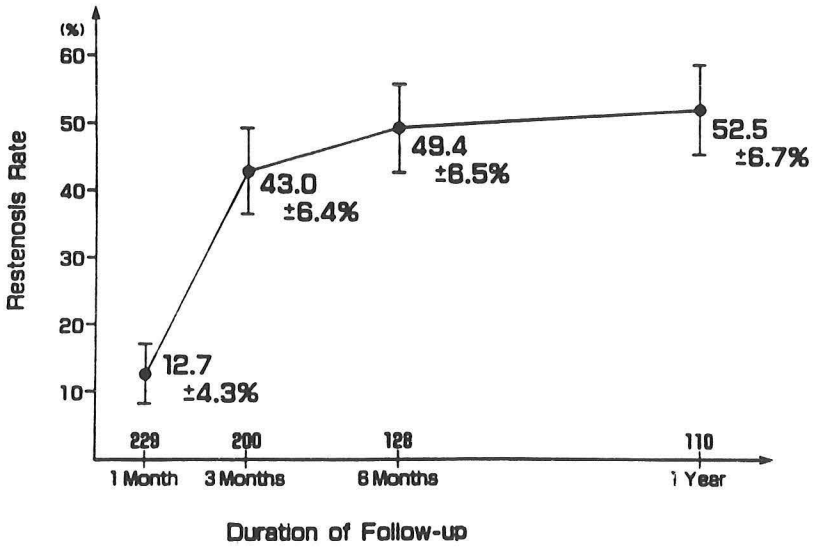


## CLINICAL PRESENTATION AND TIMING

Most patients with restenosis after successful PTCA present with recurrent chest pain; however, approximately 25% are asymptomatic [9]. Rarely is myocardial infarction the initial presentation of restenosis. When restenosis occurs, the severity of coronary artery narrowing is usually similar to that before PTCA. However, when angioplasty is performed in a minimally narrowed coronary artery, the restenosis may be more severe than what was present initially [20]. Consequently, "cosmetic angioplasty" - performed to improve the appearance of a minimally diseased vessel - is not advisable.

Recent serial angiographic studies [17, 19] have demonstrated that restenosis occurs early following angioplasty. These studies utilized computer-assisted quantitative coronary analysis of serial angiograms to demonstrate a rapidly increasing incidence of restenosis 1 to 3 months following angioplasty and a peak incidence by 3 to 6 months (Figure 2). After this time period it is rare for restenosis to develop. Of 1502 patients from Emory who had patent coronary arteries 4 to 12 months after PTCA, only 4% subsequently required repeat dilatation of the same site [21].

**FIGURE 2. ACTUARIAL RESTENOSIS RATE IN 229 PATIENTS WITH SERIAL ANGIOGRAPHIC FOLLOW-UP AFTER SUCCESSFUL PTCA (from ref 17)**



Patients with recurrent angina pectoris within 1 month of PTCA usually have incomplete revascularization or no coronary narrowing at cardiac angiography. Those who develop recurrent symptoms 1 to 6 months after PTCA usually have restenosis, and those with angina recurring more than 6 months after PTCA usually have developed significant coronary artery narrowings at other sites [22]].

## MECHANISMS OF STENOSIS DILATATION WITH PTCA

To understand the biologic mechanisms involved in the pathogenesis of restenosis, an understanding of the pathologic changes induced by coronary angioplasty is central. Pathologic examination of material from laboratory animals and cadaveric human hearts immediately following experimental angioplasty demonstrates endothelial denudation with deposition of platelets and fibrin; varying degrees of cracking, splitting, or rupture of the atherosclerotic plaque and intima, occasionally extending fully through the media; localized medial dissections; dehiscence of the intima and plaque from the underlying media; and stretching of the media and adventitia with persistent aneurysmal dilatation of the treated vessel segment [23-27] (Table 4). Since atheromatous plaque in man is usually hard and firm, there is no significant expression of fluid or liquid components when the plaque is compressed. Successful angioplasty induces a "controlled injury" of the intima, media, and adventitia of the diseased arterial segment followed by favorable vessel remodeling and repair.

**TABLE 4. MECHANISM OF LUMINAL ENLARGEMENT FOLLOWING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY**

| |
|---|
| FOCAL PLAQUE AND/OR INTIMAL SPLIT, CRACK OR TEAR |
| ABOVE, WITH LOCALIZED MEDIAL DISSECTION |
| DEHISCENCE OF THE INTIMA AND PLAQUE FROM THE UNDERLYING MEDIA |
| STRETCHING OF PLAQUE-FREE SEGMENT OF ARTERY WITH PERSISTENT ANEURYSM FORMATION |
| PLAQUE COMPRESSION OR EXTRUSION OF ATHEROMA CONTENTS |
| FAVORABLE VESSEL REMODELING AND REPAIR |

Similar observations have been made on necropsy specimens from humans dying shortly after coronary angioplasty [28-31], and at angioscopic observation in living subjects after successful stenosis dilatation [32]. The exfoliated endothelium, intimal-medial splits, medial-adventitial aneurysms, and localized dissections cause the immediate increase in luminal size, intimal flaps, and intraluminal haziness frequently noted angiographically after PTCA [28,33].

Endothelialization and favorable remodeling of the "controlled" plaque disruption and intimal injury after angioplasty results in improved vessel patency. Angioscopic examination of the region of balloon dilatation one year after successful PTCA has demonstrated smooth endoluminal surfaces, despite the presence of multiple endothelial flaps and pseudolumina observed immediately after the procedure [32]. Angiographic evidence of intimal disruption most frequently disappears by 1 month following successful angioplasty [17]. Given the degree of vessel injury frequently induced by PTCA, it is indeed remarkable that only the minority of dilated segments develop clinically important restenosis.

## PATHOPHYSIOLOGIC CHANGES IN RESTENOSIS

Recent clinical and experimental observations suggest that restenosis results from a complex interaction of biologic processes, initiated by vessel injury, and dependent upon the release of thrombogenic, vasoactive, and mitogenic factors [34-36]. Restenosis is not a single process, but the end result of numerous and diverse reparative processes, each with its own time course of appearance and means of prevention (Table 5).

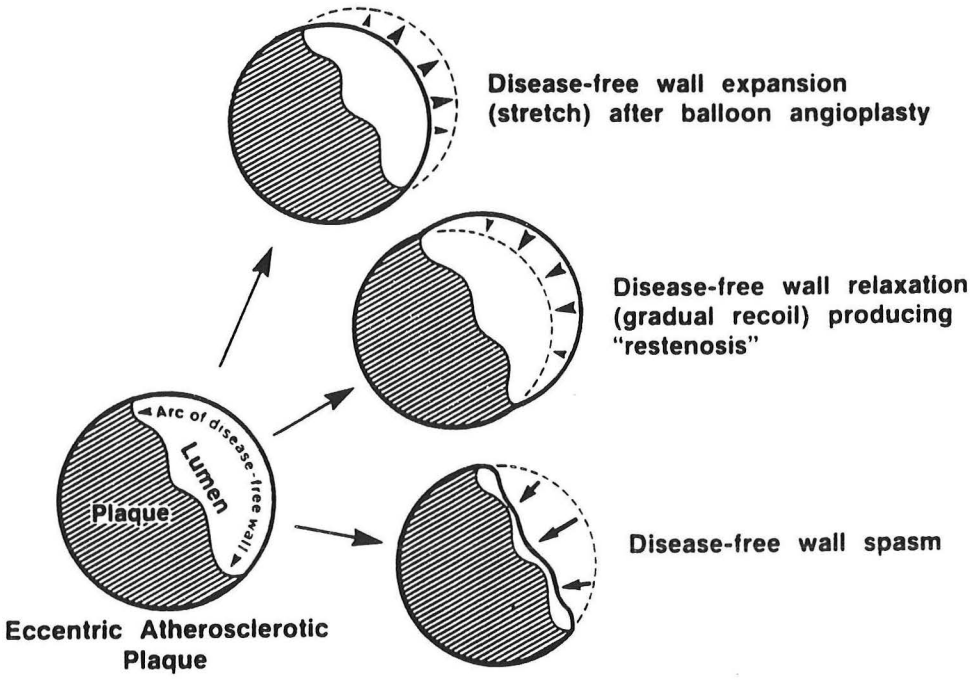
**TABLE 5. PATHOLOGIC MECHANISMS OF RESTENOSIS AFTER PTCA**

| |
|---|
| **EARLY (MINUTES TO DAYS):** |
| PROGRESSIVE (NON-OCCLUSIVE) PLAQUE TEARS, INTIMAL FLAPS, AND PLATELET/THROMBUS DEPOSITION |
| RECOIL, RESTITUTION OF TONE, AND VASOCONSTRICTION |
| **LATE (WEEKS TO MONTHS):** |
| ORGANIZATION OF INTIMAL OR MEDIAL THROMBUS |
| SMOOTH MUSCLE AND FIBROCELLULAR PROLIFERATION |
| ACCELERATED DEVELOPMENT OF ATHEROSCLEROTIC PLAQUE |

Early restenosis (within days of PTCA) most likely results from vasoconstriction and relaxation of the stretched vessel wall (so called, "elastic recoil"). Later restenosis (within weeks to months of PTCA) results from the ensuing reparative process in which myointimal and fibrocellular proliferation are exaggerated and sufficiently severe to impede arterial flow again.

**Recoil, restitution of tone, and vasoconstriction:** Approximately 60-70% of coronary atherosclerotic lesions are eccentric with a portion of the coronary arterial wall not involved with plaque [38,39]. Based upon pathologic examination of angioplasty restenosis sites from patients dying after PTCA, Waller et al [35,39] discerned two major types of restenosis lesions: (a) those with intimal proliferation (with or without evidence of healed angioplasty); and, (b) those with fibrous atherosclerotic plaques only (without morphologic evidence of a previous dilatation injury). Since accelerated atherosclerosis is unlikely to account for fibrous plaques as early as 3 months following PTCA, restenosis lesions composed solely of atherosclerotic plaque are thought to result from elastic "recoil" or "restitution of tone" of the overstretched disease-free segments of eccentric lesions [36]. Thus, in some individuals, gradual relaxation of the aneurysmal plaque-free segment over several hours, days, or weeks following balloon angioplasty may decrease the initially favorable luminal diameter to its predilation state (Figure 3).

**FIGURE 3. DIAGRAM SHOWING CAUSES OF EARLY RESTENOSIS**
(From ref 35)



Computer assisted quantitative angiographic assessment of coronary vessels before, during, and immediately after angioplasty confirms that nearly 50% of the theoretically achieved cross-sectional area (i.e., cross-sectional area of the inflated balloon) is lost shortly after balloon deflation as a result of elastic recoil [40]. This may explain the observation of Nobuyoshi and colleagues that 11.4% of 237 "successfully dilated" coronary lesions had developed restenosis by one day following PTCA 17].

In addition to the passive recoil which may occur following PTCA, disruption of endothelial integrity following balloon angioplasty results in diminished local production of vasodilators (i.e., endothelial-derived relaxing factor and prostacyclin) and release of potent vasoconstrictors (i.e., thromboxane $A_2$ and serotonin) from platelets [41]. Together, these may account for the coronary vasoconstriction frequently observed at the site of balloon dilatation and in segments of the artery distal to the dilatation [42,43]. Furthermore, spontaneous and ergonovine-induced coronary spasm has been reported to occur *de novo* in man at the site of previous successful balloon dilatation, and is associated with a high incidence of restenosis [44,45]. Intense vasospasm is thought to be capable of producing chronic intimal injury with continued platelet deposition and release of platelet derived growth factors, ultimately leading to increased rates of restenosis.

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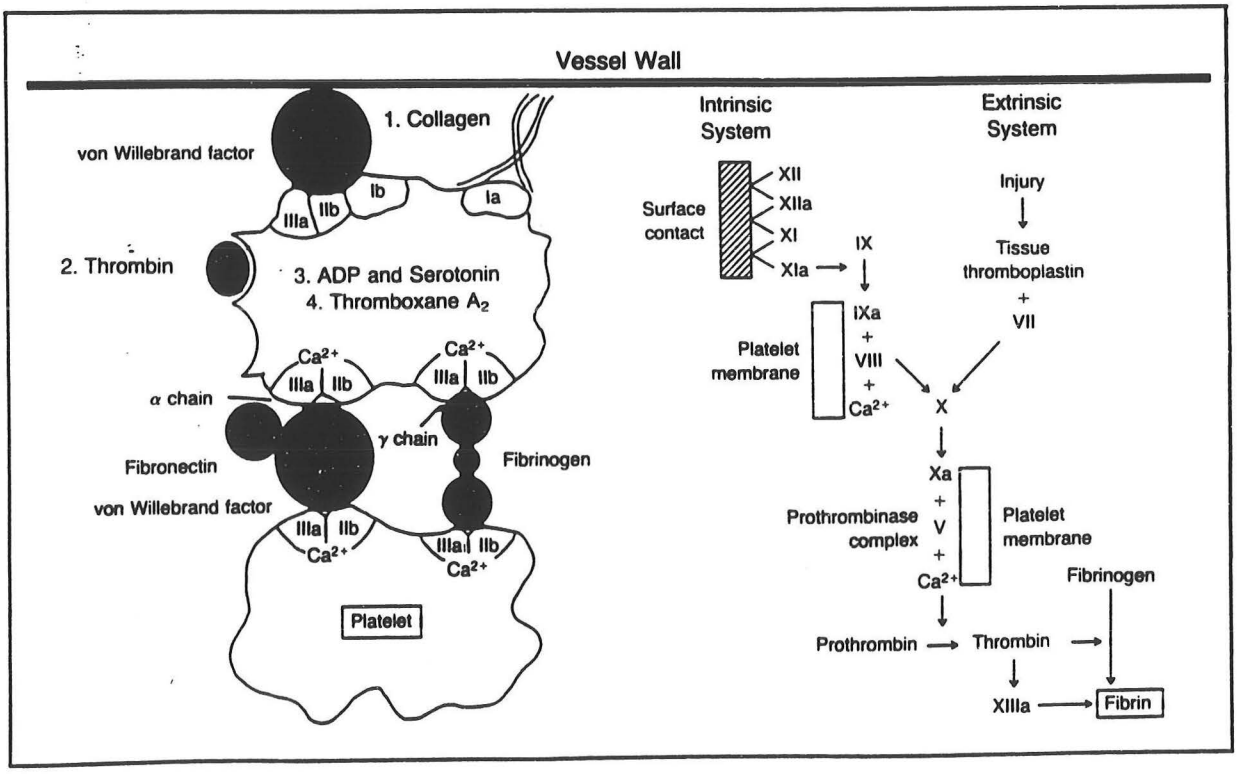
**FIGURE 4. SCHEMATIC DEPICTION OF INTERACTIONS BETWEEN PLATELETS, VESSEL WALL, AND ADHESIVE MACROMOLECULES** (From ref 48)



**Platelet aggregation and thrombus deposition.** Necropsy studies of patients who have died shortly after stenosis dilatation [30,31], and angioscopic observations in living subjects immediately after angioplasty [32], document marked platelet deposition and thrombus formation immediately following PTCA. Endothelial denudation and deep arterial injury after balloon dilatation exposes fibrillar collagen, elastin and smooth muscle cells to circulating blood elements, initiating platelet activation and the coagulation cascade [34,46] (Figure 4, above).

Platelet *adhesion* and activation is initiated by the interaction of platelet glycoprotein Ia and Ib receptors with newly exposed subendothelial type I collagen and Von Willebrand's factor respectively. Platelet activation triggers the exposure of the platelet membrane glycoprotein IIb/IIIa, which together with the adhesive macromolecules fibronectin, Von Willebrand's factor, and fibrinogen promote platelet *aggregation*. Release of granular contents (which include a variety of procoagulants, vasoconstrictors, and mitogens), initiate hemostasis, vessel repair, and potentially, the process of restenosis [46-49] (Table 6).

**TABLE 6. CELLULAR MECHANISMS OF RESTENOSIS FOLLOWING PTCA**

| **PLATELET DEGRANULATION RELEASES:** | **ENDOTHELIAL DISRUPTION DECREASES:** |
|---|---|
| **Coagulants:** | **Vasodilators:** |
| Fibrinogen | Endothelial-Derived Relaxing Factor |
| Fibronectin | Prostacyclin |
| Von Willebrand's Factor | |
| Factor V | **Tissue Fibrinolytics & Anticoagulants:** |
| Thrombin | Tissue Plasminogen Activator |
| Platelet Activating Factor | Heparin Sulfate |
| Adenosine Diphosphate | Thrombomodulin |
| **Vasoconstrictors:** | **ENDOTHELIAL DISRUPTION EXPOSES:** |
| Thromboxane $A_2$ | Type I Collagen |
| Serotonin | Thromboplastin |
| **Mitogens:** | Von Willebrands' Factor |
| Platelet Derived Growth Factor | |
| Epidermal Growth Factor | |
| Transforming Growth Factor | |

Modified with permission from [49].

In addition to platelet adhesion and aggregation, the *clotting cascade* may be activated by exposure of blood to subendothelial surfaces (intrinsic pathway), or to tissue thromboplastin released at sites of deep endothelial injury (extrinsic pathway). This leads to the generation of thrombin, which in addition to being a very potent platelet activator, catalyzes the conversion of fibrinogen to fibrin and the formation of a growing thrombus composed of platelets, fibrin and erythrocytes.

Platelet and thrombus deposition following PTCA contribute to restenosis via several mechanisms: (1) late organization of thrombus on the intimal surface or within a medially dissected hematoma; (2) myointimal proliferation stimulated by platelet derived growth factors; and (3) local release of vasoconstrictor substances which can themselves ultimately lead to intimal injury and further platelet-thrombus deposition [46,49,50]. Finally, experimental evidence suggests that platelet deposition and thrombus formation are greatest over areas of deep arterial injury and high shear rates [46], as might occur in an individual with a large, complicated intimal dissection after balloon dilatation. Indeed, higher rates of acute closure, and restenosis are found in such patients [13].

**Intimal fibrous proliferation.** Platelets which adhere and aggregate at sites of endothelial disruption release the contents of their intracellular granules, such as heparin-neutralizing factors and several mitogens, including platelet derived growth factor (PDGF), epidermal growth factor, and beta-transforming growth factor [51]. These factors release smooth muscle cells from growth inhibition and induce smooth muscle cell proliferation and migration from the media to the intima, as well as chemotaxis of macrophages and neutrophils. The severity of this "response to injury" determines the degree of intimal fibrous proliferation observed, which, when excessive, may encroach on the arterial lumen and compromise flow [50].

In addition, PDGF-like molecules, fibroblast growth factor and insulin-like growth factor (somatomedin C) are released from endothelial cells, macrophages, and perhaps most importantly, smooth muscle cells. These act synergistically with platelet-derived growth factors to induce intimal hyperplasia and are capable of self-perpetuating their own mitogenic stimulation and smooth muscle proliferation. Thus, once smooth muscle cells transform from a quiescent state (contractile phenotype) to a proliferative state (synthetic phenotype) and migrate to the intima, their continued activity may be self-perpetuated beyond the phase of platelet deposition [34,52,53].

There is also evidence that direct injury to the smooth muscle cell itself can initiate the biologic processes leading to restenosis [50]. Endothelial cells synthesize heparin-like glycosaminoglycans which are growth-inhibitory and maintain the underlying medial layer in a quiescent

state. In addition, smooth muscle cells also produce a growth-inhibitory heparan sulfate which helps maintain them in a nonproliferating and contractile phenotype. When the endothelial layer is abraded or the smooth muscle cells disturbed by balloon dilatation, the rapid proliferation of medial smooth muscle cells, may be due, in part, to loss of the growth-inhibitory factors. In addition, platelets that adhere to areas of endothelial damage release antiheparin factors (i.e., platelet factor 4 and heparitinases) that reverse the effects of growth-inhibitory heparan sulfates synthesized by smooth muscle cells [34].

In the experimental animal models of restenosis, myointimal proliferation begins early after PTCA [54-56]. With bromodeoxyuridine labeling, one can demonstrate that 20-35% of the medial smooth muscle cells being to proliferate within 24 to 48 hours of balloon injury. Approximately 4 days after angioplasty, smooth muscle cells begin to migrate to the intima where proliferation continues. This process of medial smooth muscle cell proliferation, chemotaxis, and intimal proliferation is maximal by 1 week after angioplasty. However, intimal thickening continues for up to 8 weeks as a result of the synthesis of extracellular connective tissue matrix and cellular hypertrophy.

In human necropsy specimens, initial evidence of smooth muscle cell infiltration into the intima has been identified by 5 days, and more extensive smooth muscle proliferation identified by 17 days after angioplasty [57].

**Lessons learned from tissues recovered by atherectomy devices.** The atherectomy devices provide a unique means of obtaining endarterial "biopsy" material useful for the histologic analysis of both primary, untreated lesions, and restenosis tissue. In a recent study of patients undergoing atherectomy of peripheral vascular disease, 88% of primary, untreated lesions were atherosclerotic plaque, 9% were intimal fibrous proliferation with medial calcinosis and 3% consisted of thrombus. In contrast, of excised restenosis tissue, 75% was intimal fibrous proliferation, and only 25% was classic atherosclerotic plaque [58]. Comparison of restenosis material from sites of previous balloon angioplasty, with material obtained from sites of previous atherectomy failed to reveal histologically detectable differences, suggesting that the response to vessel injury is nonspecific and independent of the inciting stimulus.

## RISK FACTORS FOR RESTENOSIS

Several retrospective studies have examined the factors that influence the incidence of restenosis following successful PTCA. Various clinical, anatomic, and procedural variables are associated with an increased likelihood of restenosis.

**Clinical Variables.** The clinical factors that are associated with restenosis are listed in Table 7. Patients with new onset angina (appearing within 2 months before PTCA) or an anginal pattern that is unstable (worsening chest pain, pain that is more easily provoked and more difficult to relieve, or pain occurring with little provocation or at rest) have an increased frequency of restenosis [9,11,18,59,60]. In addition, there is a higher incidence of restenosis in patients whose angina is vasospastic in origin [61,62]. In these patients, enhanced vasoreactivity and platelet activation are probably responsible for the clinical syndromes and enhanced restenosis.

Diabetes mellitus has been associated with an increased incidence of restenosis [9,63,64], and one small study showed that it occurred in a large proportion (81%) of patients with renal failure on long-term hemodialysis who had undergone PTCA [65].

Although the data from the National Heart, Lung, and Blood Institute PTCA Registry demonstrated a higher incidence of restenosis in males (36%) as compared to females (22%)($P<0.01$) [9,66] other studies [59,62,63,67-69] have failed to confirm an association with gender. Similarly, several studies have suggested that cigarette smoking increases the risk of restenosis [70-72] while other large retrospective analysis have not supported this association [9,11,59,62]. There are no convincing data showing that the patient's age or the presence of hypertension influences the incidence of restenosis.

**Table 7. CLINICAL VARIABLES ASSOCIATED WITH AN INCREASED INCIDENCE OF RESTENOSIS FOLLOWING SUCCESSFUL PTCA**

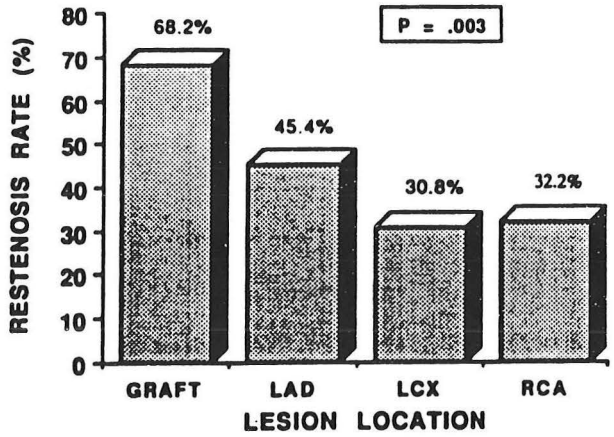
1. Unstable Angina
2. Vasospastic Angina
3. Diabetes Mellitus
4. Renal failure requiring long-term hemodialysis treatment
5. ? Male gender
6. ? Cigarette smoking

**TABLE 8. ANATOMIC VARIABLES ASSOCIATED WITH AN INCREASED INCIDENCE OF RESTENOSIS FOLLOWING SUCCESSFUL PTCA**

1. Location of Stenosis
    a. Left anterior descending coronary artery
    b. Proximal location
2. Saphenous vein bypass grafts
3. Severity of pre-PTCA stenosis
4. Chronically occluded stenoses
5. ? Eccentric, calcified or long lesions

**Anatomic Variables.** Several anatomic features are associated with an increased incidence of restenosis (Table 8). The incidence of restenosis is influenced by the location of the stenosis. Dilatations of the left anterior descending coronary artery are associated with a higher incidence of restenosis than those of the right or circumflex coronary arteries [11,73,74], and restenosis is more likely to occur in proximal stenotic segments that are successfully dilated than those located in the distal coronary tree [64,74] (Figure 5).

**FIGURE 5. RELATION OF LESION LOCATION TO CORONARY RESTENOSIS RATE (from ref 73)**

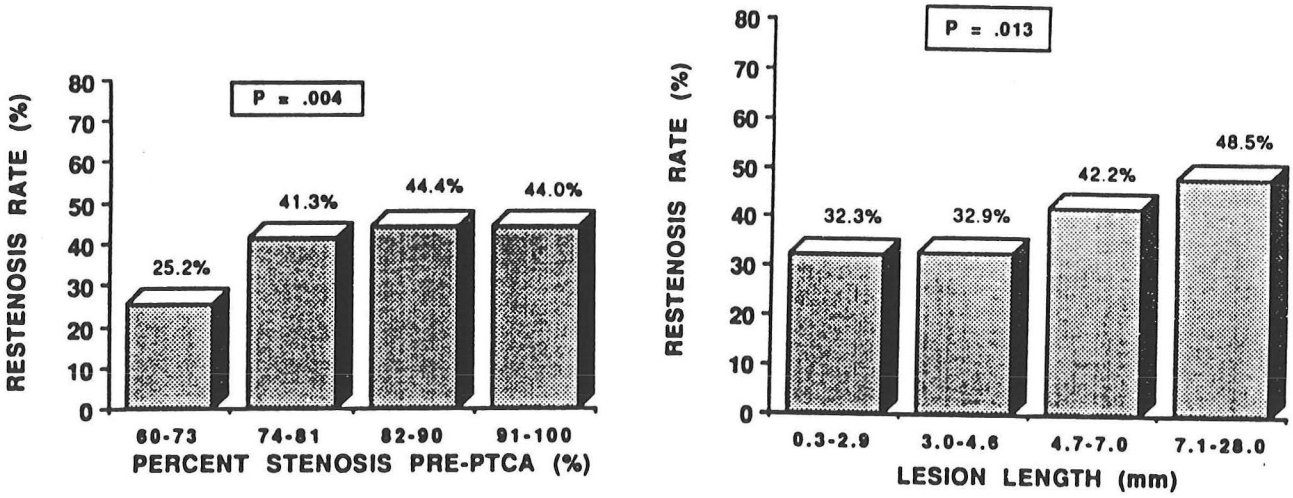


Higher restenosis rates are also noted when angioplasty is performed in saphenous vein grafts. Restenosis rates of 50 to 60% have been reported for angioplasty of lesions in the proximal portion or body of the graft. In contradistinction, the restenosis rate is approximately 20% for distal anastomotic dilatation [73,75-80].

The incidence of restenosis also increases as the severity of the preangioplasty narrowing worsens (Figure 6), as measured either angiographically (in terms of the percentage of luminal diameter narrowing) or hemodynamically (in terms of the transstenotic pressure gradient), with the highest incidence in vessels that have been chronically occluded [9,10,59,73,81-84].

Several reports on relatively small numbers of patients have suggested that the incidence of restenosis is increased in patients whose coronary stenotic lesions are eccentric, calcified, or long (> 10-15 mm)(Figure 6), but other studies - including the largest ones [8,11] - have failed to show that these factors exert an influence.

**FIGURE 6. EFFECT OF PRE-PTCA STENOSIS AND LESION LENGTH ON CORONARY RESTENOSIS RATE (from ref 73)**




**Procedural Variables.** Finally, certain procedural factors contribute to the occurrence of restenosis (Table 9). If the result of the angioplasty is suboptimal - there is a postangioplasty stenosis ≥30 percent or a transstenotic pressure gradient ≥15 to 20 mm Hg - restenosis is more likely to occur [9,11,67,68]. Not surprisingly, dilatation with a balloon that is undersized or oversized is more likely to lead to recurrence of the stenosis [62,73,85]. An undersized balloon yields a suboptimal postangioplasty result, and an oversized balloon creates an extensive dissection. Other procedural variables, such as inflation pressure and number of balloon inflations, do not appear to influence the incidence of restenosis [9,11].

**TABLE 9. PROCEDURAL VARIABLES ASSOCIATED WITH AN INCREASED INCIDENCE OF RESTENOSIS FOLLOWING SUCCESSFUL PTCA**

1. Undersized balloon
2. Extensive dissection
3. Severity of post-PTCA stenosis
    a. Residual stenosis $\geq$30%
    b. Transstenotic pressure gradient >15 mm Hg

## STRATEGIES FOR THE PREVENTION OF RESTENOSIS: PHARMACOLOGIC APPROACHES

### Antiplatelet therapy

*Aspirin* (acetylsalicylic acid) blocks the synthesis of thromboxane $A_2$ - a potent vasoconstrictor and promoter of platelet aggregation - within platelets by irreversibly blocking the enzyme cyclooxygenase, which is responsible for the conversion of arachidonic acid to thromboxane $A_2$. In the animal model, aspirin is effective in reducing platelet deposition and restenosis following angioplasty [46,86].

Antiplatelet therapy is routinely used in patients undergoing angioplasty. Although such therapy has been shown to decrease the incidence of acute coronary thrombosis after angioplasty [87-89], 3 randomized, placebo-controlled studies have demonstrated that it is ineffective in preventing restenosis [89-91].

In the largest of these studies [89], - the Montreal Heart Institute Study - 376 patients were randomly assigned to receive placebo or aspirin (990 mg daily) and dipyridamole (225 mg) beginning the day prior to PTCA and continuing throughout the 4 to 7 month follow-up period. Repeat coronary arteriography demonstrated restenosis in 39% of the patients who received placebo and 38% of those who received antiplatelet therapy (p=NS).

Subsequent studies that have compared low dose aspirin (80 or 100 mg daily) to high dose aspirin (1000 or 1500 mg daily) have found equivalent restenosis rates between the two regimens [92,93]. *Ticlopidine*, another potent platelet inhibitor, was also ineffective in preventing restenosis after successful coronary angioplasty in a well conducted, multicenter trial [91].

In contrast, preliminary evidence in a small number of patients suggests that selective inhibition of thromboxane synthetase may be effective in preventing restenosis [94]. This may be mediated, in part, by preserving synthesis of the potent vasodilator prostacyclin. In comparison to a placebo treated group, those who received a selective *inhibitor of thromboxane synthetase* 5 days prior to angioplasty until follow-up angiography at > 3 months had a lower incidence of restenosis (22% vs 53%, $p<0.10$). This encouraging data has prompted a prospective, randomized, placebo-controlled European trial of a thromboxane synthetase inhibitor (Coronary Artery Restenosis Prevention on Repeated Thromboxane Antagonism) in more than 700 patients undergoing PTCA.

*Prostacyclin* is a potent platelet inhibitor and vasodilator produced by endothelium. When administered just prior to PTCA and continued for 48 hours, intravenous prostacyclin infusion did not significantly lower the incidence of restenosis in comparison to placebo treatment (27% vs 32%, respectively; p=NS) in a study of 270 patients [95]. Similarly, short-term administration of *ciprostene*, an analogue of prostacyclin, had no effect on the angiographic incidence of restenosis following coronary angioplasty [96].

## Antithrombotic Therapy

Pathologic and atherectomy specimens have demonstrated deposition and organization of thrombin at the site of angioplasty-induced arterial injury. Thrombin and its derivative products are known to activate smooth muscle cell mitogenesis and migration. In vitro experiments have demonstrated that heparin inhibits smooth muscle cell proliferation [97-99]. Accordingly, there has been considerable interest in the use of anticoagulants and antithrombotic agents to prevent restenosis.

*Heparin* is uniformly given to patients during PTCA and in the ensuing hours to prevent acute coronary thrombosis. A preliminary report of a large multicenter study in progress [100] suggested that prolonged heparin administration (18-24 hrs) following coronary angioplasty heparin may prevent restenosis. However, the completed study did not confirm the preliminary report [73]. In a randomized trial conducted at Emory University, 416 patients received placebo or 18 to 24 hours of intravenous heparin after PTCA. Those who received heparin had more bleeding complications and a similar rate of restenosis as those who received placebo [101].

Similarly, long term (6 months) use of *coumadin* after PTCA has no effect on the incidence of restenosis [102,103].

## Antispasm Medications

Coronary spasm is frequently observed following angioplasty, and coronary vasoconstriction from elastic "recoil" is known to contribute to restenosis. It is also known that patients with vasospastic angina have a high incidence of restenosis, Thus, it has been hypothesized that drugs that inhibit coronary vasospasm (i.e., calcium channel blockers) may reduce the incidence of restenosis. Although animal studies examining the influence of calcium channel blockers on restenosis were promising, human studies have shown that neither *nifedipine* or *diltiazem* administered for 3 to 6 months after PTCA affected restenosis [104-107].

## Antiproliferative Agents

As previously discussed, overexuberant smooth muscle cell proliferation in response to vessel wall injury and inflammation is important in the restenosis process. As a result, antiinflammatory agents, growth factor antagonists, and antimitogenic drugs have been used to prevent restenosis in patients undergoing PTCA .

In animals, *corticosteroids* inhibit vascular smooth muscle proliferation after balloon-induced endothelial injury [108]. Three studies [109-112] have evaluated the use of short-term, high dose steroids administered prior to angioplasty to prevent restenosis. In none of the studies were steroids useful in reducing the rate of restenosis (Table 10).

**TABLE 10. STUDIES USING CORTICOSTEROIDS TO PREVENT RESTENOSIS**

| Study | n | Steroid dose | Timing | Restenosis Pl | Restenosis Ster |
|---|---|---|---|---|---|
| Stone [109] | 102 | 125mg IMx1, 240mg/d po | 1 day before, 7 days after | 36% | 40% |
| Rose [110] | 66 | 48mg/d | 12 hrs before 5 days after | 33% | 33% |
| Pepine [111] | 915 | 1000 mg IV | 2-24 hrs before | 39% | 40% |

Abbreviations: Pl=placebo, Ster=steroids

*Colchicine* binds to tubulin, the subunit protein of microtubules, interfering with microtubule-dependent cell functions such as cell division, secretion of chemotactant factors, synthesis and secretion of collagen, and lysosome degranulation after phagocytosis. Furthermore, colchicine increases collagenase activity, and inhibits platelet aggregation [112]. These actions account for its antiinflammatory and antifibrotic effects and its use in the treatment of conditions such as acute gouty arthritis, malignancy, and cirrhosis.

In animals, colchicine inhibits the development of atherosclerotic plaques, reduces the severity of intimal fibrous proliferation in those with established atherosclerosis, and prevents intimal thickening after balloon intimal thickening [113].

A randomized, placebo-controlled trial of colchicine therapy in humans is currently underway. Subjects (n=197) receive colchicine (0.6 mg twice daily) or placebo commencing the day before coronary angioplasty and continuing throughout the 6 month follow-up period. Preliminary analysis of data from the first 145 subjects who have completed the study show a significant incidence of side effects in the treated group (7% discontinued colchicine) but no reduction in the incidence of restenosis (colchicine treated patients, 46%; placebo group, 47%) [114].

## Lipid-Lowering Therapy

*Omega-3 fatty acids* (fish oils) lower serum lipid levels, inhibit platelet aggregation, and have antimitogenic effects. The effects of fish oil preparations on restenosis following PTCA has been examined in 6 randomized studies [115-120] (Table 11). Four demonstrate a lower rate of restenosis in patients who received omega-3 fatty acids, whereas the remaining two did not. In one of the two negative studies [118], the fish oil was administered in a form (ethyl ester form) that is poorly absorbed. In the other negative study [117], the pretreatment time period may not have been sufficiently long (<24 hrs) to permit incorporation of the fish oils into cell membranes. If fish oils are to be maximally effective in preventing restenosis, they should probably be administered in high doses (3 to 6 gms of omega-3 fatty acids), and therapy should begin at least one week before PTCA. This obviously limits their usefulness in patients with unstable angina pectoris who are unable to defer PTCA to a later time.

**TABLE 11. STUDIES USING FISH OILS FOR THE PREVENTION OF RESTENOSIS AFTER CORONARY ANGIOPLASTY**

| Author | n | Dose of n-3s(gm) | Therapy Started | Endpoint | Restenosis Rx | Restenosis Pl |
|---|---|---|---|---|---|---|
| Dehmer [115] | 103 | 5.4 | 7 days prior | angio | 16% | 36%* |
| Slack [116] | 113 | 2.7 | at PTCA | ETT | 16% | 33%* |
| Grigg [117] | 108 | 3 | <24 hrs prior | angio | 29% | 31% |
| Reis [118] | 133 | 6 | 5±3 days prior | clin | 32% | 28% |
| Milner [119] | 142 | 4.5 | immed after | clin | 20% | 37%* |
| Roy [120] | 205 | 4.5 | 3 wks prior | angio | 31% | 48%* |

* $p<0.05$

Abbreviations; angio = angiography; clin = clinical (clinical evaluation with stress test in most patients and angiography if restenosis suspected); ETT = exercise stress test; n-3s = omega-3 fatty acids; n = number of patients; Pl = placebo group; Rx = treatment group.

Lipid modification plays an important role in primary and secondary prevention of coronary artery disease. Recent animal data showed that *lovastatin* reduces intimal hyperplasia in hypercholesterolemic rabbits. Two human trials of lovastatin in postangioplasty patients have yielded conflicting results.

In the first trial [121], 157 patients were randomized to receive lovastatin (20 or 40 mg) or placebo beginning on the day of coronary angioplasty. Unfortunately, only 50% of the patients underwent follow-up angiography an average of 4 months after PTCA. In these patients, restenosis occurred in 14% of those receiving lovastatin and 47% of

those receiving placebo. In the second trial [122], aggressive therapy to lower serum cholesterol (diet, colestipol, and lovastatin) was initiated the day of PTCA in 55 patients. Serum cholesterol level fell by about 50% in the group, and repeat coronary angiography was available in 44 of the patients. There was no difference in cholesterol levels between patients with and without restenosis.

## STRATEGIES FOR THE PREVENTION OF RESTENOSIS: NONPHARMACOLOGIC APPROACHES

New interventional techniques have been employed with the hope that a more "controlled injury" of the arterial wall or removal of the underlying atheroma - mechanically or thermally - would decrease the incidence of restenosis. These newer interventional technologies include the following; *autoperfusion devices* that allow prolonged (15-30 min) balloon inflation times; *atherectomy catheters* that shave and extract atheromatous plaques; *laser angioplasty* catheters; and, *coronary stents*.

All currently available interventional techniques cause arterial wall trauma and evoke neointimal proliferation. While each of these interventional techniques may have a specialized application, none has proven effective in preventing restenosis. This underscores the fact that smooth muscle cell proliferation and intimal thickening are a nonspecific response to arterial wall injury and may occur with balloon dilatation or any other intervention that damages the arterial wall.

## NEW PHARMACOLOGIC APPROACHES

### Growth Factor Inhibitors

Since growth factors released by circulating cells and local tissues are known to play an important role in regulating smooth muscle proliferation and migration, inhibition of these mitogens may be useful in arresting the cellular proliferation that accompanies angioplasty-induced vessel injury. In this regard, *trapidil* (triazolopyrimidine), a platelet-derived growth factor antagonist, inhibits cellular proliferation in cell culture and initimal thickening in damaged carotid arteries in animals [123]. Clinical studies in man are in progress.

Plasma and local concentrations of insulin-like growth factor-1 (somatomedin c) are directly regulated by hypophyseal growth hormone. Local concentrations of insulin-like growth factor-1 increase with administration of growth hormone and fall when pituitary release of growth hormone is inhibited by somatostatin administration [124]. *Angiopeptin*, a somatostatin analogue, inhibits intimal

hyperproliferation in rodent and primate models of restenosis [125]. Clinical trials of angiopeptin for the prevention of restenosis in humans are currently in progress.

## Antineoplastic Agents

Antineoplastic agents (i.e., *vincristine, actinomycin D, methotrexate*) administered to animals with experimental arterial injury reduce the number subintimal smooth muscle cells and inhibit mitogenesis [126]. Obviously, the toxicity of these potent antimitogenic compounds prohibits their systemic administration to prevent restenosis in humans. However, recently developed coronary infusion catheters permit local delivery of agents directly into the arterial wall after balloon angioplasty with intramural drug concentrations 1000-fold greater than serum concentration [127]. Whether this therapy will have clinical application in man is not yet known.

## Angiotensin-Converting Enzyme Inhibitors

Recently, studies have demonstrated that the local angiotensin system may play an important role in regulating the vascular response to local injury. Besides being a potent vasoconstrictor, angiotensin II stimulates smooth muscle cell proliferation and matrix formation. In some animal models (rat carotid and rabbit iliac ), high dose *cilazapril* - an angiotensin converting enzyme inhibitor which blocks conversion of angiotensin I to angiotensin II - has been highly effective in inhibiting neointimal proliferation after balloon dilatation [128,129]. Interestingly, concomitant heparin therapy exerts a synergistic antiproliferative effect with cilazapril. In the near future, a large, multicenter clinical trial (Multicenter European Research Trial with Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis) will provide data on the clinical efficacy of angiotensin converting enzyme inhibition in preventing restenosis in humans.

## Gene Therapy

Major advances in our understanding of gene regulation and recombinant DNA technology may soon result in gene therapy of vascular cells in the prevention of restenosis. A variety of methods of *gene transfer* are already available, including physical methods (microinjection and electroporation), chemical methods (liposomes), and viral vectors (retrovirus, adenovirus, and DNA viruses). Various cell types may be appropriate targets for gene manipulation therapy, including platelets, endothelial cells, and smooth

muscle cells. Logical therapeutic targets may include anticoagulants, vasodilating agents, growth factors, growth-inhibiting factors, and cellular receptors for these various molecules.

In vitro modification of endothelial cells has already been accomplished with preservation of endothelial morphology and function [130-132]. To be clinically useful, the endothelial cells that have been genetically modified in vitro must be reimplanted into the vascular wall. This has been accomplished percutaneously with specially designed double balloon catheters and coronary stents lined with endothelium [132,133].

In vitro techniques are cumbersome and time consuming since they require establishment of a cell line from the same species prior to genetic modification. This may limit its clinical use. In vivo genetic modification is a more useful approach to modifying vascular cells. This has also been accomplished in animal models. Using specially designed catheters - double balloon catheters with central reservoirs and perforated balloon catheters - high concentrations of viral vectors have been successfully introduced locally into arterial segments [134,135].

In vivo gene modification of cardiac and vascular cells is currently an area of active research at our own institution. Taking this research from "the bench" to "the bedside" involves a cooperative effort of talented investigators in multiple disciplines including (but not limited to) molecular biology, physiology, biomedical engineering, and interventional cardiology.

## CONCLUSIONS

Despite significant advances in angioplasty technology and increased clinical success rates with PTCA, restenosis following successful coronary angioplasty continues to be a significant problem and remains the Achilles heel of PTCA. Pathologic examination of restenosis lesions has yielded considerable insight into the mechanism(s) of restenosis and has directed experimental studies and subsequent therapy. Although more than 50 experimental animal studies have suggested that at least nine different classes of pharmacologic agents are effective in preventing restenosis following angioplasty [136], none have reliably reduced the incidence of restenosis after coronary balloon angioplasty in humans. The future of restenosis prevention lies in the development of; (a) experimental models of restenosis that more closely mimic the human condition; (b) new and effective pharmacologic agents; (c) and in vivo gene transfer therapy.

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