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NEW TECHNOLOGY

Stenting of Coronary Arteries: Has a Modern Pandora's Box Been Opened?

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Interventional cardiology has recently witnessed the growth of several alternatives to percutaneous transluminal angioplasty, including coronary stenting. Although stenting appears to be useful in treating abrupt closure after coronary angioplasty, its effectiveness in limiting the complex processes responsible for late restenosis is much less certain. Pathologic examination of stented human saphenous bypass grafts shows extensive deposits of platelets, fibrin and leukocytes along the stent wires within the 1st week and formation of a neointima of variable thickness after 3 months without evidence of foreign body reaction. The long-term effects of continuous barotrauma induced by the expanded stent remain unknown. It is difficult to assess the relative merits of the new devices, but stenting has several theoretic advantages. It seems less disruptive to the underlying architecture of the vessel wall and enjoys favorable theoretic and effective expansion ratios. Widespread clinical acceptance for stenting will depend on demonstrating that its safety, efficacy and cost efficiency are superior to those of balloon angioplasty.

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The introduction of coronary balloon angioplasty by Andreas Gruentzig (1) in 1977 provided the stimulus for rapid technologic growth in the field of interventional cardiology. This development has produced several new devices designed to ablate coronary artery narrowings, recanalize occluded vessels and prevent restenosis. It is difficult to evaluate the relative merits of each intervention and to define their roles in clinical cardiology. In applying this new technology, cardiologists have limited their concern to the technical and procedural aspects, while sometimes overlooking the complex biologic and physiologic mechanisms of atherosclerosis, and in particular of the restenosis process. In achieving the perceived benefit of therapeutic intervention with these devices, the vessel wall is subjected to thermal and mechanical insults that may have hidden long-term consequences. An example is the restenosis process, which has been iatrogenically induced in tens of thousands of patients.

One of these newer developments has been the use of endoluminal vascular prostheses, although the original concept of intravascular stenting precedes the introduction of coronary artery interventional cardiology by many years. Since the original description of Dotter's tubular coil spring stent (2), many variants of the original concept have been introduced, including thermal shape memory alloy stents (3–6), steel spirals (7), stainless steel mesh stents (8–11), slotted stainless steel tubes (12–15), zigzag stents (16–18), U-configuration bends (19), interdigitating coils (20–22), tantalum helical coil stents (23), knitted tantalum wire stents (24,25), removable, metallic mesh stents (26) and synthetic polymeric and biodegradable stents (27). These various devices differ greatly in their fundamental geometry (tube, mesh or single wire), composition (metal or plastic) and mechanical behavior (active or passive expansion). Furthermore, there are a variety of subtle differences that may be important in themselves, such as thickness of filaments, alloy composition, electrostatic behavior and biocompatible or therapeutic coatings.

More than 7 years have passed since the first clinical report (8) of successful coronary stent implantations. Although the current world experience has now exceeded 1,000 stent implantations, the clinical indications and applications of this prosthesis remain undetermined and even experienced investigators are uncertain on these issues. The current status of the coronary stent parallels that of other recently introduced technologic advances, including laser angioplasty and atherectomy (directional and nondirectional types). This raises a fundamental question: have we been unable to realize the full potential of these newer devices because of our limited understanding of the underlying biologic interactions, particularly those responsible for restenosis? In this review, we address several relevant issues based on our experience in the evaluation of various coronary stents.

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Rationale for Stenting an Atherosclerotic Stenosis During or After Balloon Dilation

Short-term consideration: abrupt closure. Abrupt vessel closure after angioplasty occurs in 2% to 11% of procedures (28–31). Intimal flaps induced by the arterial injury can disrupt flow by partially or completely occluding the lumen. Sluggish anterograde flow and the exposure of media to procoagulant blood-borne elements are potent thrombogenic stimuli that further contribute to the process. The coronary stent, by acting as a splint, can physically contain the protruding obstructive flap and maintain flow as well as possibly prevent distal embolization of macroscopic debris originating from the plaque or flap (32). This scaffolding function appears to be a property common to both balloon and self-expanding stenting prostheses. Angiographic studies (10) after stent implantation have shown that the self-expanding Wallstent has a smoothing effect that reduces calculated poiseuille and turbulent contributions to flow resistance. Several reports have documented successful deployment of the various types of stents in the "bail-out" situation when the presence of intimal dissection has led to a poor and even critical hemodynamic result (33,34).

Long-term considerations: restenosis. Restenosis remains the major limitation of coronary angioplasty. Despite a lack of uniformity of definition, several angiographic follow-up studies have documented a 20% to 40% incidence in the 1st 6 months after angioplasty (35–38). Restenosis has been defined angiographically as a significant deterioration in the luminal diameter of a lesion that had previously been successfully dilated, and does not necessarily indicate a common pathologic substrate. Diverse histologic processes may be responsible for restenosis depending on the time interval since angioplasty.

Early restenosis. Restenosis has been documented in up to 11% of lesions as early as 1 to 4 days after coronary angioplasty (38–40). It is believed that the early cases of angiographic worsening are a result of several processes, including elastic recoil, vasospasm or platelet-fibrin thrombi, or combinations. This time interval is too brief for significant fibrointimal hyperplasia to have occurred, for several reasons. Pathologic studies (41–43) of vessels retrieved <10 days after angioplasty have not shown any significant intimal hyperplasia. Animal experiments (44,45) in carotid arteries of rats have demonstrated that smooth muscle cell migration into the intima begins only at 4 days and maximal intimal smooth muscle cell proliferation is not noted before 7 days after balloon endothelial denudation. Furthermore, cell cultures of medial smooth muscle cells (46) have shown that the modulation of phenotype from the quiescent, contractile state (typical of normal medial smooth muscle cells) to a metabolically active, synthetic state occurs only after 6 to 7 days. Smooth muscle cells obtained from intimal thickenings phenotypically resemble these synthetic-type smooth muscle cells observed in culture and share a common cytoskeleton protein profile that differs from typical medial smooth muscle cells (47,48).

The stent and elastic recoil. The significance of elastic recoil has been demonstrated acutely during angioplasty. In a study of 151 dilated segments, the minimal luminal cross-sectional area before angioplasty was 1.1 ± 0.9 mm^2 (49). Immediately after the procedure the cross-sectional area of the dilated vessel was 2.8 ± 1.4 mm^2. Elastic recoil, defined as the difference between the balloon cross-sectional area (5.2 ± 1.6 mm^2) and the vessel area after angioplasty, was calculated to be 2.4 ± 1.4 mm^2, which is almost 50% of the cross-sectional area of the fully inflated balloon. In an angiographic study of the initial 117 stent implants, we demonstrated that the self-expanding Wallstent mitigates the effects of elastic recoil. Stenting immediately improved the minimal cross-sectional area from 3.0 ± 1.2 mm^2 after angioplasty to 5.5 ± 2.7 mm^2. In a subgroup of patients with angiography 24 hours later, the stent continued to expand and increased the cross-sectional area to 6.8 ± 4.4 mm^2 (Serruys et al., unpublished observations).

Late restenosis. Two processes have been implicated in the development of late restenosis. In some cases it has been attributed to the organization and fibrous conversion of platelet-fibrin thrombi that form at the site of intimal damage. However, a more important mechanism appears to be marked cellular proliferation within the vessel wall that is stimulated by complex interactions between platelets adherent to the damaged intima, macrophages, endothelial cells and medial smooth muscle cells. Pathologically, late restenosis is characterized by an aggressive proliferation of smooth muscle cells that presumably have migrated from the media into the intima, resulting in a variable degree of luminal narrowing (43,50). Immunoperoxidase staining of the cellular component of this fibrointimal tissue has identified the characteristic cytoskeleton proteins of medial smooth muscle cells—alpha actin, desmin and vimentin—confirming the origin of the cells responsible for this growth.

What Causes Smooth Muscle Cell Proliferation?

Abnormal smooth muscle cell proliferation is an intricate process that is only partially understood. Animal models have revealed that balloon denudation in arteries will stimulate a sequence of events if either of two conditions is present: 1) extensive endothelial denudation, or 2) significant medial smooth muscle cell injury.

The pioneering work of Reidy et al. (44,45) showed that significant intimal hyperplasia occurred after balloon injury in rat carotid arteries that resulted in the loss of up to 25% of the vessel wall deoxyribonucleic acid (DNA). This loss reflects widespread medial smooth muscle cell injury, since endothelial cell loss alone could not account for such a major change in DNA content. Later, more sophisticated techniques of vessel wall injury were used (51), which localized

damage to the endothelium, sparing the subendothelium and medial layers. Subsequently, intimal thickenings developed only in regions of the vessels that were not re-covered with endothelium after 7 days. These studies suggested that smooth muscle cell proliferation and migration are separately controlled processes, because some areas of rapid endothelial regrowth contained increased numbers of medial smooth muscle cells without a corresponding increase in intimal thickness. A separate series of autoradiographic experiments (52,53) showed that only 50% of intimal smooth muscle cells are capable of proliferation, supporting this concept.

Platelet-derived growth factor. Several mitogens have been implicated in the stimulation of smooth muscle cells. Platelet-derived growth factor, the most intensively studied factor, is a dimer compound composed of two homologous polypeptide chains (A and B) that are disulfide bonded (54). Although platelet-derived growth factor was originally isolated from platelets, further study has confirmed that it is released from several different cells, including vascular endothelium, macrophages and even activated smooth muscle cells, perhaps explaining why smooth muscle cells continue to proliferate long after the initial platelet-vessel wall interaction (55–58).

The binding of platelet-derived growth factor to its receptor initiates a complex cascade of signal transduction within the cytoplasm and ultimately into the nucleus of the smooth muscle cell, resulting in cell division and protein synthesis. Although these pathways have not been elucidated fully, important steps include the platelet-derived growth factor receptor-mediated phosphorylation of tyrosine kinase and activation of phospholipase C, which subsequently generates two important second messengers, diacylglycerol and inositol triphosphate (59,60). The platelet-derived growth factor receptor and both its chains have been sequenced and it is now possible to clone platelet-derived growth factor with recombinant technology. Monoclonal antibodies against both chains of platelet-derived growth factor and its receptor have also been produced. The gene that codes for the B chain mRNA of platelet-derived growth factor is c-sis, which is the cellular counterpart to the v-sis gene of the simian sarcoma virus. An intriguing connection between neoplasia and atherosclerotic lesions is the demonstration of an active human oncogene in atherosclerotic plaques (61). Cultured mouse fibroblast NIH 3T3 cells have been transformed with transfected DNA from these plaques (61). These transformed cells have established slow-growing tumors in "nude" mice.

Other growth factors. Other important growth factors that have been related to restenosis include interleukin-1 (IL-1), fibroblast growth factor, colony stimulating factor, epidermal growth factor, insulin-like growth factor (somatomedins), endothelin and serotonin. The relative influence of the individual factors and possible interactions are largely unknown and indicate our limited understanding of the entire process.

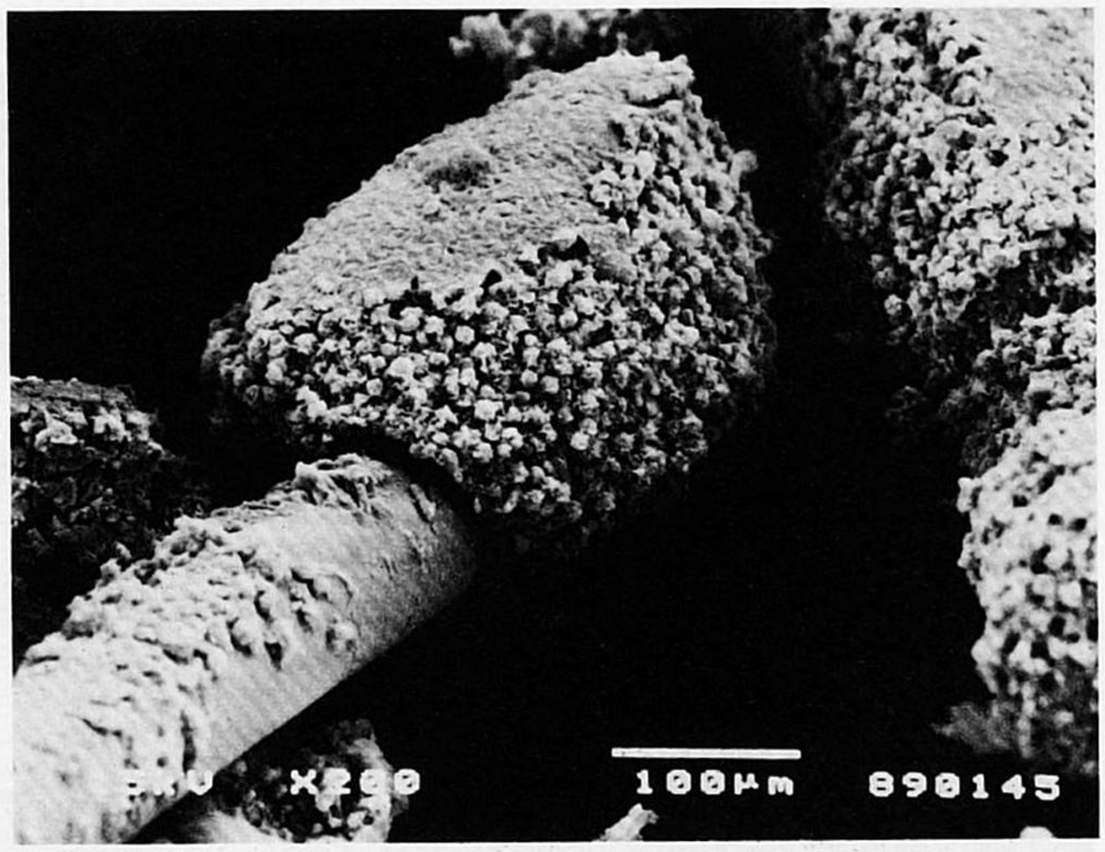

Figure 1. Scanning electron micrograph of a stented human saphenous vein bypass graft removed 3 days after implantation. Extensive deposits of platelets, leukocytes and fibrin are evident on this detail of the stent filaments.

Pathology of Restenosis: After Coronary Angioplasty and Coronary Stenting

Although autopsy reports of late follow-up angioplasty cases (3 to 20 months) are limited, the general consensus is that the characteristic features of restenosis are smooth muscle cell hyperplasia and a variable amount of extracellular matrix and fibrosis depending on the time elapsed since angioplasty. In addition to data from chronic animal studies, stented venous bypass grafts have been retrieved from several patients for analysis. Although the extent of intimal hyperplasia is similar after stenting to postangioplasty examination, several histologic features appeared to be unique to coronary stents.

Pathologic and histologic features. In human saphenous vein bypass grafts and porcine coronary arteries retrieved 3 to 7 days after stent implantation, extensive deposits of platelets, fibrin and leukocytes are observed along the stent wires (Fig. 1). In the pig, the stent wires become embedded in the vessel wall and are covered with a neointima within 7 days. This neointima consists of organizing thrombus directly adjacent to the wire and several layers of smooth muscle cells along the luminal surface (Fig. 2). Scanning electron microscopy has confirmed complete endothelialization.

At 4 weeks in porcine coronary arteries, few traces remain of the initial platelet-fibrin thrombus, which is represented by a few erythrocytes, leukocytes and lipid-laden foam cells that are interspersed in a disorganized fibrocellular layer (Fig. 3). At the luminal side two distinct layers of smooth muscle cells are present, one in a circular orientation immediately below the endothelium and a deeper layer in a longitudinal orientation.

After 3 months, a more extensive neointima forms in the

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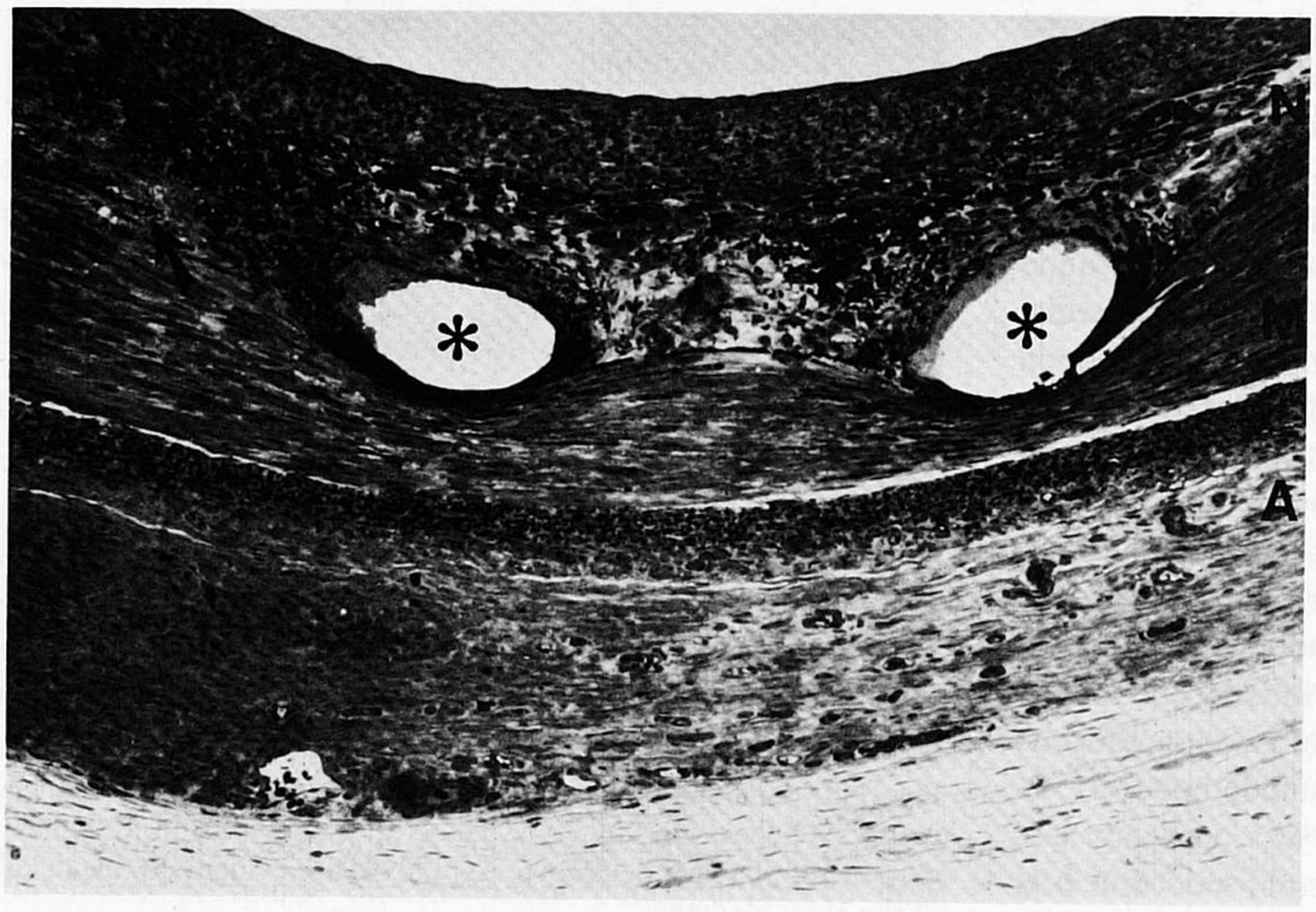
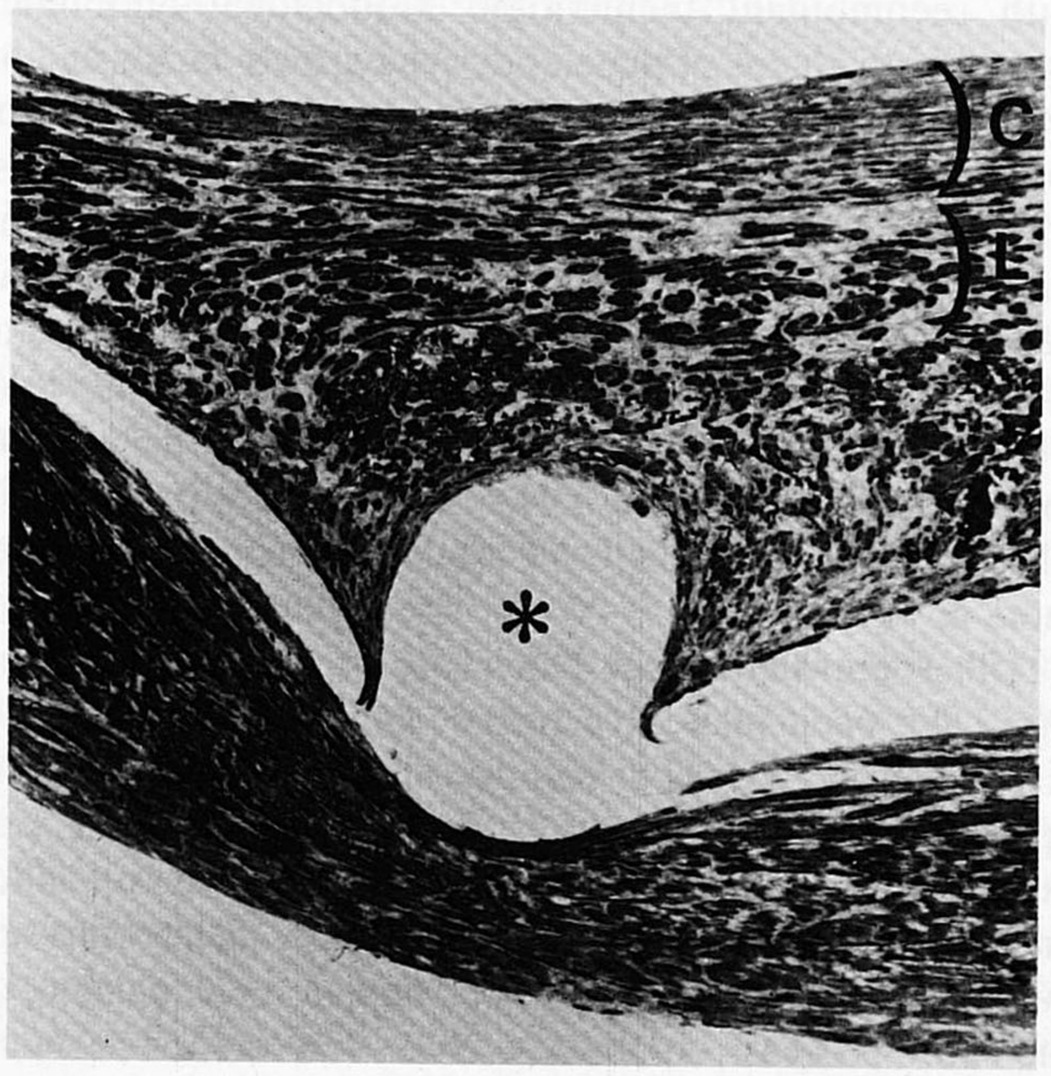


Figure 2. Light micrograph of a stented porcine femoral artery 7 days after implantation. The voids (*) represent the sites of the 70 μm diameter stent wires, which have been removed. There is a disorganized layer of neointima (N) on the luminal aspect of the stent wire, containing smooth muscle cells, trapped red blood cells and fibrin. Above the disorganized layer is an organized neointima that contains smooth muscle cells covered by endothelium. The internal elastic lamina is interrupted at the left (**arrow**). A = adventitia; M = media.

porcine coronary artery with only a small area adjacent to the stent wire containing leukocytes and cellular debris (the so-called "Bermuda triangle") (Fig. 4). In human saphenous vein bypass grafts removed 3 to 10 months after the stenting procedure, the amount of neointima which develops is comparable with the amount of neointima in the porcine coronary artery, but the neointima in humans borders on the old atherosclerotic plaque (Fig. 5). At the junction between old plaque and recent neointima, abundant foam cells and extracellular lipid deposits are found within the new neointima in addition to extensive extracellular matrix production (Fig. 6).

Mechanisms. The causes and possible relations between these early and late histologic features are unknown. Two factors may be important. First, the regenerated endothelium that covers the stented segment may be dysfunctional and thus permit abnormal and excessive lipid infiltration and macrophage penetration across the endothelial barrier. Scanning electron microscopy of the endothelial lining has indicated an irregular, raised endothelial surface in lieu of the normal smooth covering (Fig. 7) although no permeability to Evan's blue dye was demonstrated in stented porcine arteries after 3 months (Van der Giessen et al., unpublished observations). Second, important chemotactic substances may be released by the cellular debris trapped in the tissue adjacent to the stent wires. This area appears to persist late after stenting for several reasons, including continued damage from direct pressure necrosis and its deeper location in the vessel wall, which isolates it from laminar flow patterns predominating on the luminal aspect of the stent wires. Striking similarities exist between the biology of stented vessels at 3 months and chronic atherosclerotic lesions, namely, proliferation of smooth muscle cells, large amounts of connective tissue matrix including collagen, elastin and proteoglycans, and lipid accumulation in the form of foam cells (smooth muscle cells and macrophages), and extracellular deposits. The natural history of these post-stent lesions has not yet been determined.

Figure 3. Light micrograph of a porcine coronary artery 4 weeks after implantation, showing the remnants of the initial thrombus, which now contains a few erythrocytes, leukocytes and lipid-laden foam cells that are interspersed in a disorganized fibrocellular layer. At the luminal side, two distinct layers of smooth muscle cells are present, one in a circular orientation (C) immediately below the endothelium, and the other a deeper layer in a longitudinal orientation (L). (*) = void representing the site of a removed 127 μm diameter stent wire.



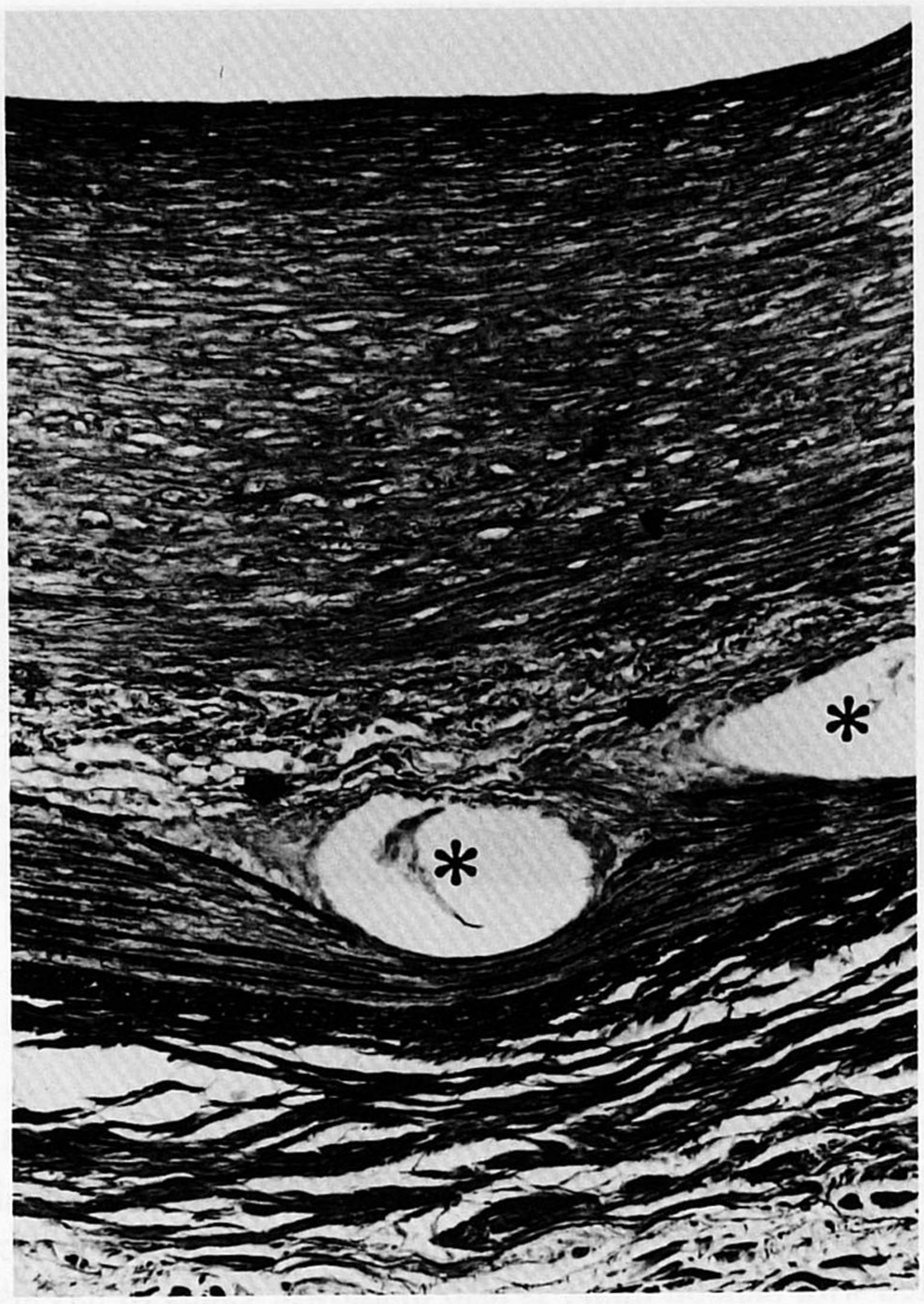


Figure 4. Light micrograph of a stented porcine artery 3 months after implantation. A more extensive neointima has formed, with only two small areas adjacent to the stent wire containing leukocytes and cellular debris (**arrows**). (*) = void representing the site of a removed 70 μm diameter stent wire.

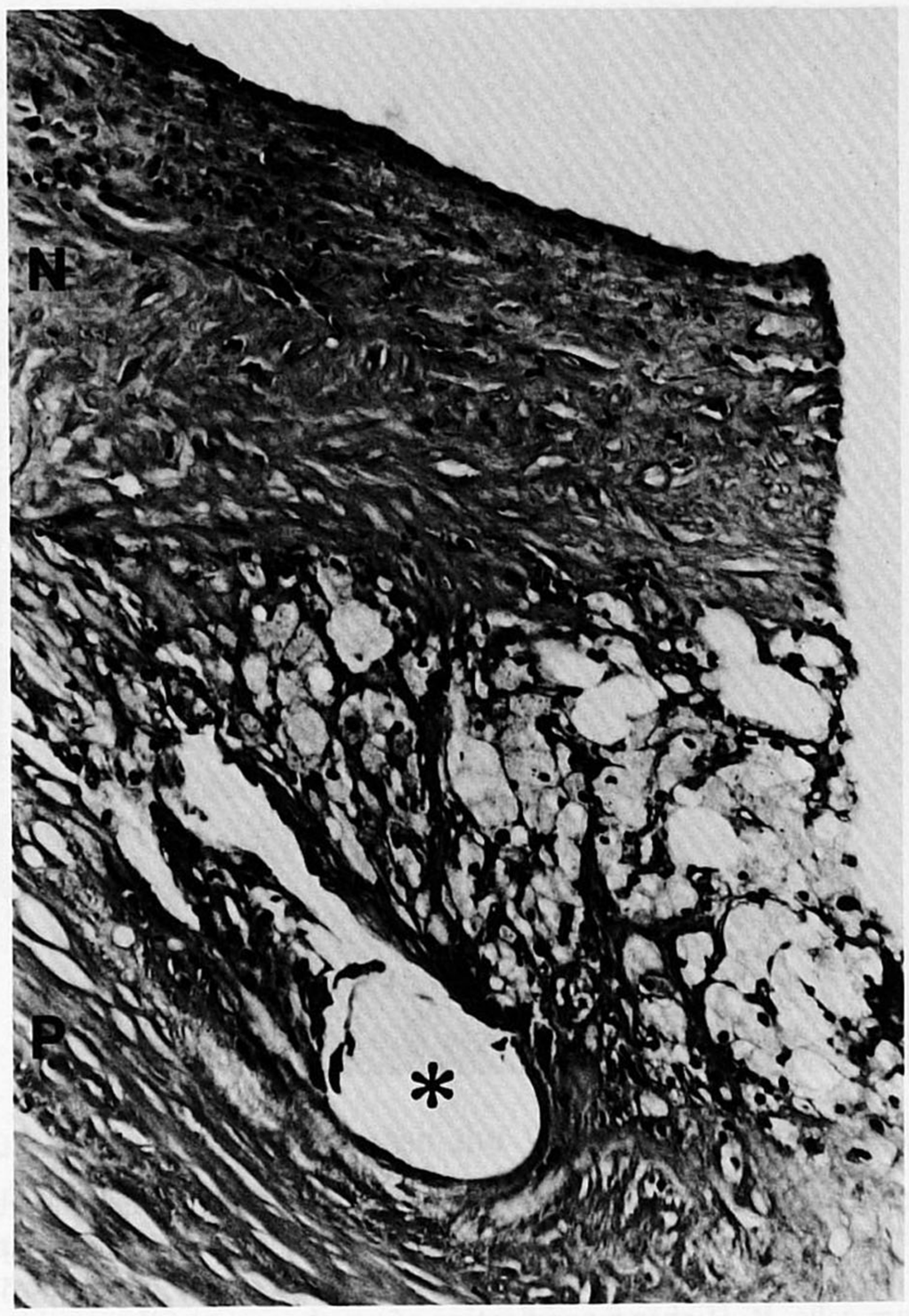


Figure 5. Light micrograph of a human saphenous vein bypass graft removed 10 months after stent implantation. A prominent neointima (N) has formed and borders on the old atherosclerotic plaque (P). At the junction between the old plaque and the recent neointima, abundant foam cells are found in the new neointima. (*) = void representing the site of a removed 70 μm diameter stent wire.

Stenting and Hyperplasia

Role of stenting in hyperplasia. Several possible theories have been advanced to support the role of stenting in limiting intimal hyperplasia (32,63,64). However, there is minimal experimental evidence to justify this position, and available animal and clinical studies confirm that significant hyperplasia occurs within the stented segment. The extent and characteristics of this hyperplasia are illustrated by the case of a 67 year old man who had recurrence of angina 3 months after stenting in a bypass graft. Angiography revealed a severe narrowing within the stent that was treated by combined balloon angioplasty and atherectomy (Fig. 8). The tissue specimen removed by the atherectomy device is shown in Figure 9. The microscopic evaluation shows abundant extracellular collagenous matrix and areas of marked cellularity that stain positively for two smooth muscle cell cytoskeleton proteins, alpha actin and vimentin (Fig. 10).

Although hyperplasia is a consequence of stenting, the functional significance of this growth may be diminished. This is explained by the intrinsic dilating property of the self-expanding stent, which initially improves luminal area 50% more than angioplasty by itself and in many patients more than compensates for the late proliferation. Unfortunately, the ideal ratio of stent size to vessel size that will result in optimal dilation with minimal compensatory hyperplasia remains unknown. The importance of this relation to the final outcome was illustrated recently by a Mayo Clinic study (65) in which a model for restenosis was developed by implanting stainless steel and tantalum coils with markedly oversized angioplasty balloons inflated to high pressures up to 14 atm.

Confounding Aspects of Stenting

There are three additional aspects of stenting that further confound our understanding of the processes occurring in the vessel wall after injury.

1. Foreign body interactions with the vessel wall. In contrast to brief, transient balloon-induced injury, nonbiodegradable stents are permanent foreign bodies with potentially important interactions due to type of metal, electrostatic charges, and possible physical irritation from individual filaments. Whether the continued presence of a

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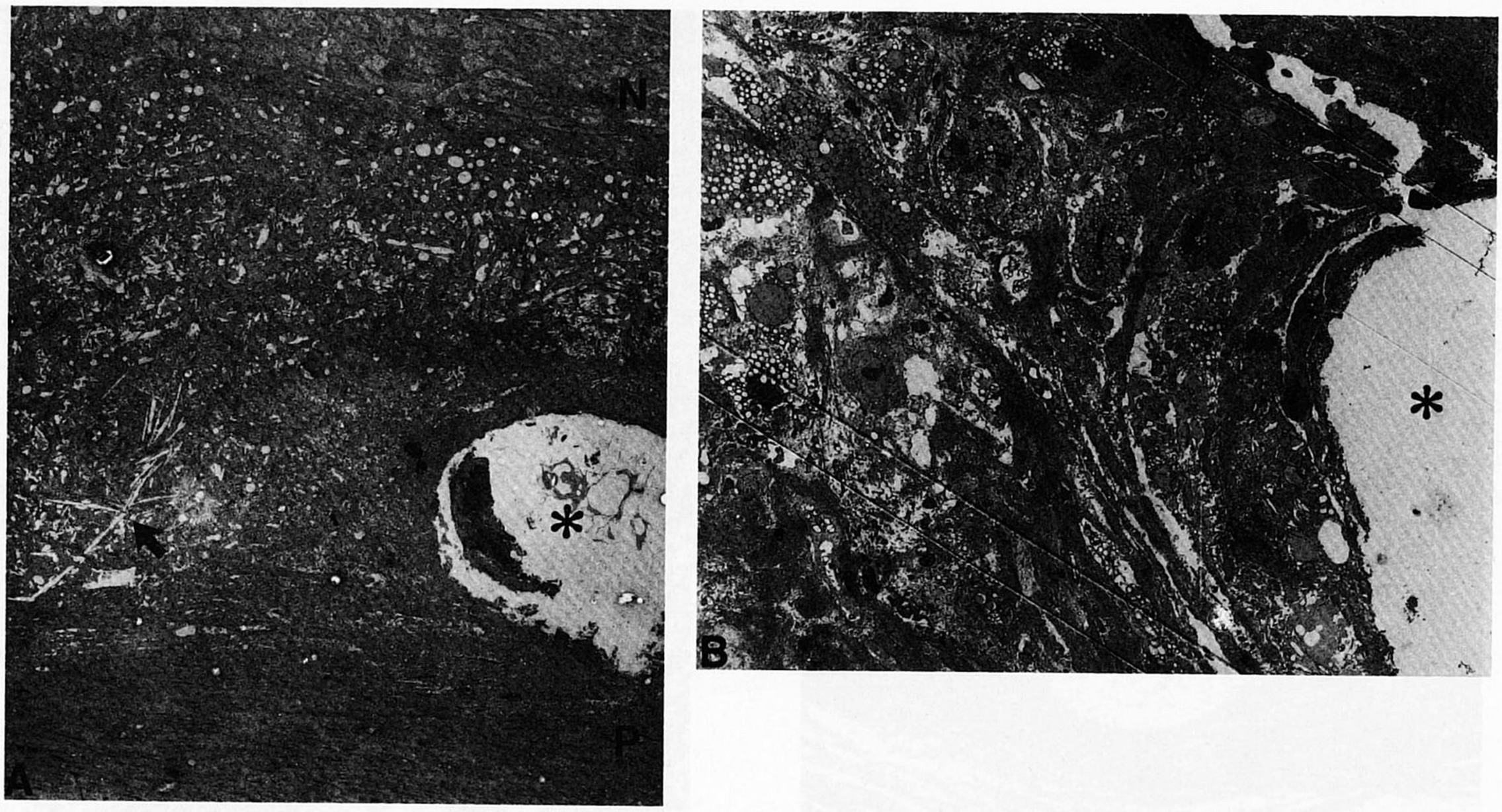

Figure 6. **A**, Transmission electron micrograph of saphenous vein bypass graft 6 months after stent implantation. Extracellular lipid deposits and cholesterol clefts (arrow) are evident alongside the foam cells. **B**, Higher magnification of another part of the section in **A**. An abundant number of foam cells can be seen. The diagonal lines are artifacts produced by the ultramicrotome. (*) = void representing the site of a removed 70 μm diameter stent wire. Abbreviations as in Figure 5.

Figure 7. Scanning electron micrograph of the endothelial lining shows an irregular, raised endothelial surface. Two leukocytes are adherent to the endothelium (bar = 5 μm).

foreign body in the vascular wall will continue to stimulate fibrointimal hyperplasia after the 6 months usually associated with balloon injury is also unknown. Concern has also been expressed as to whether the stent can trigger an allergic response, particularly in individuals who are hypersensitive to the individual metals that make up the device. Although there have been reports of transient inflammatory infiltrates in the adventitia after stent implantation, it is reassuring that there have been no reports of foreign body cells in the immediate vicinity of the implanted device in the experimen-

Figure 8. Coronary angiogram from a 67 year old patient who underwent stent implantation for a severe narrowing in the shaft of a 10 year old saphenous vein bypass graft. Three months later he was treated with atherectomy for restenosis within the stent.

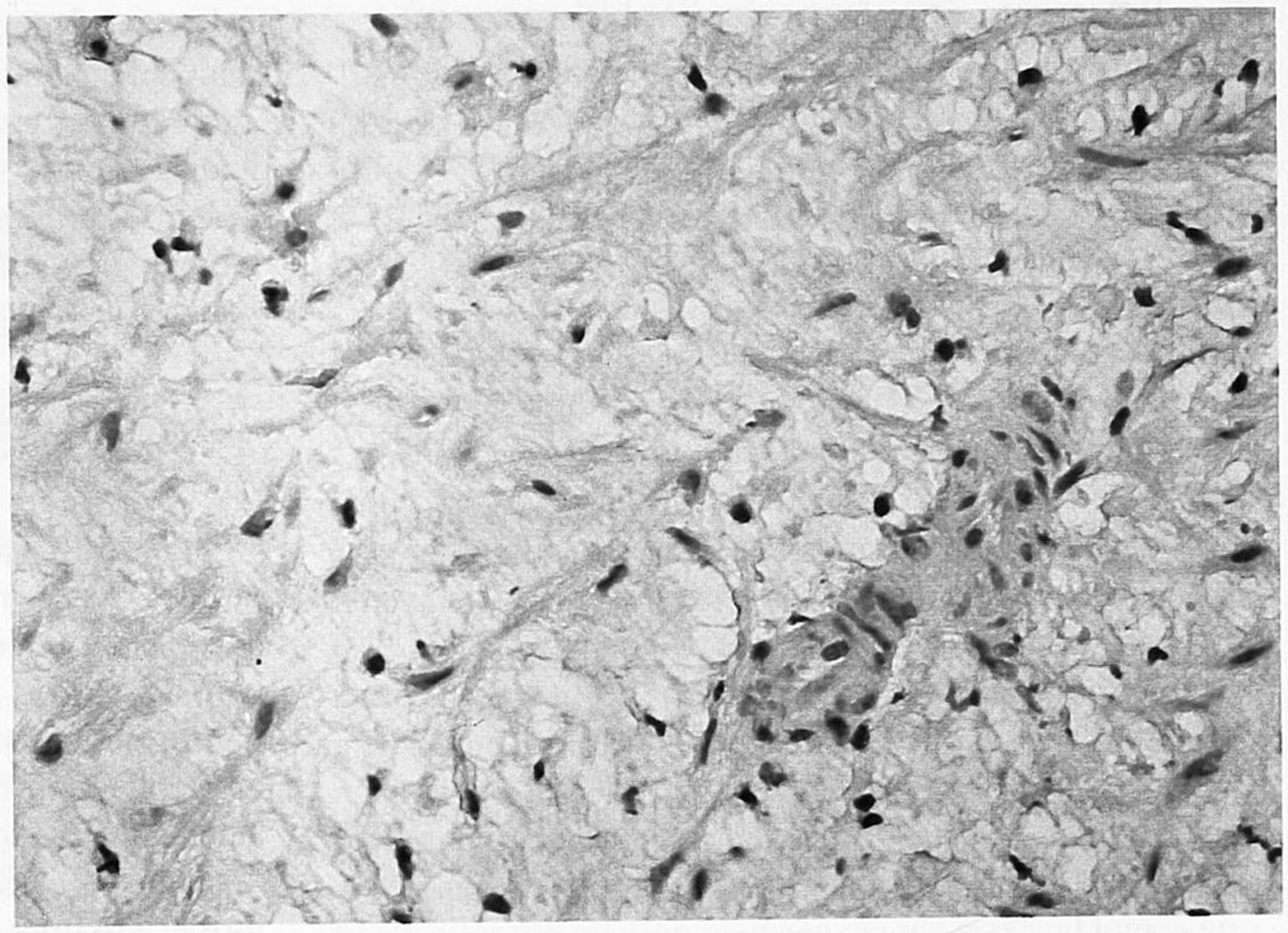

Figure 9. Light micrograph of hyperplastic tissue removed by atherectomy from the narrowed stent in Fig. 8. The specimen contains abundant smooth muscle cells and loose extracellular matrix. (Hematoxylin-eosin stain.)

tal animal model (14,15). This has been confirmed in limited experience in retrieved human stented coronary bypass grafts. In vitro attempts (Van der Giessen et al., unpublished observations) to identify endothelial membrane lipid peroxidation by free radicals formed in the presence of metallic stent elements have been unsuccessful, although the theoretic possibility exists.

2. Long-term effects of continuous barotrauma: role of exerted radial pressure. The chronic effects of continuous barotrauma induced by the expanded stent may have important ramifications. Because the Wallstent's properties are analogous to those of any spring, it tries to assume its equilibrium configuration, defined as the unconstrained diameter where net radial force is zero. If it is stretched beyond or constricted below this equilibrium, it generates forces to return to this configuration. We have studied the in vitro force-length relationship of the Wallstent stent (Fig. 11). These measurements have yielded calculations of the radial pressures exerted by this stent, both globally and locally at the site of the individual filaments if the stent is

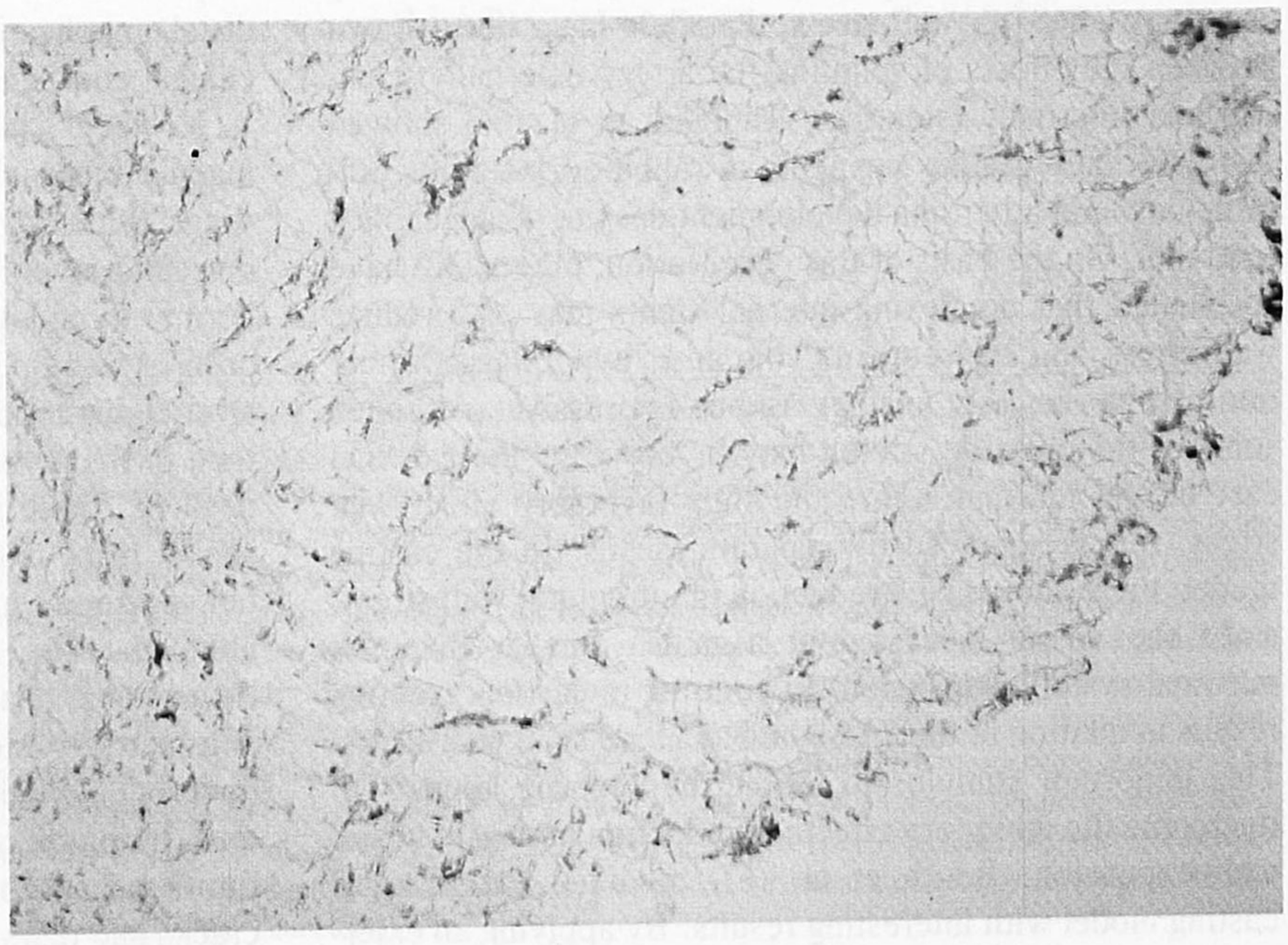

Figure 10. Smooth muscle cells are identified in the restenosis tissue obtained at atherectomy by the dark brown staining. An antibody specific for smooth muscle alpha actin has been coupled to a peroxidase reaction and is responsible for the dark color.

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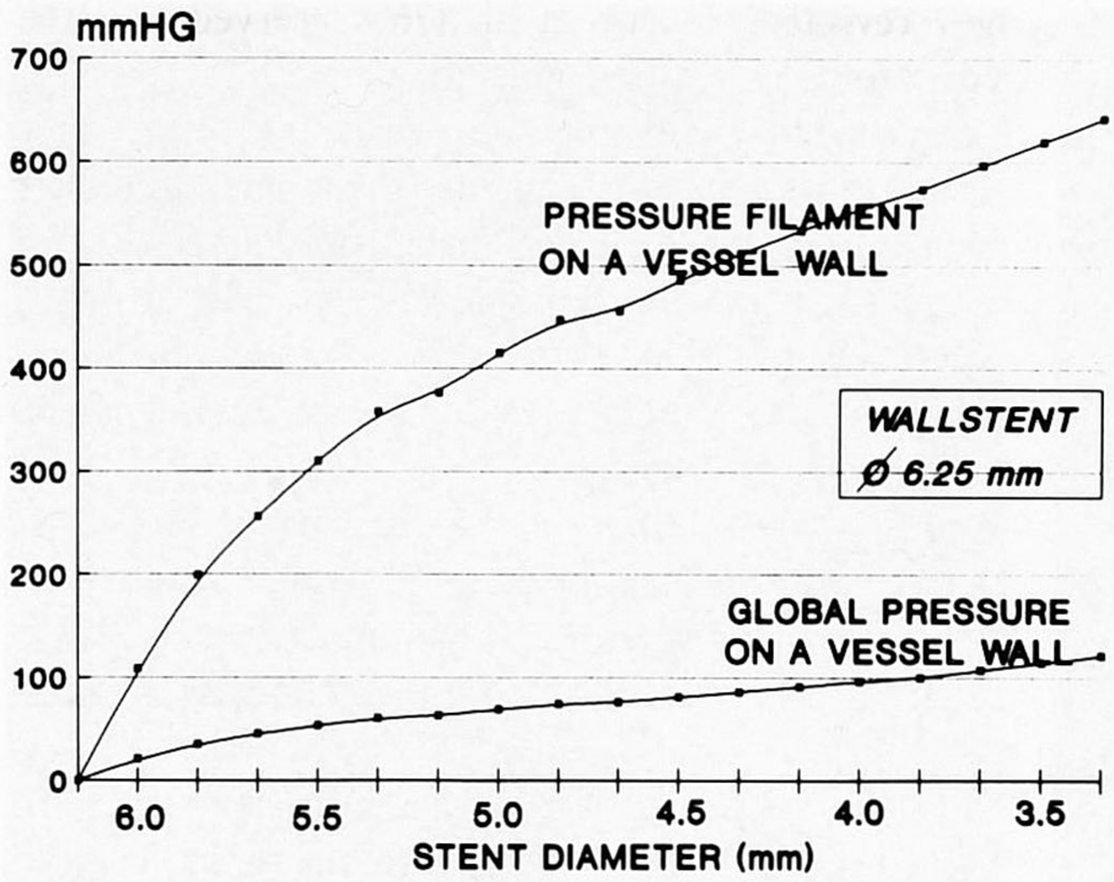

Figure 11. Radial pressures of the individual stent filament and the global pressure on the vessel wall of a self-expanding Wallstent (unconstrained diameter 6.25 mm) at varying degrees of expansion.

maintained at a diameter less than that of the unconstrained diameter. Significant pressures are generated by the stent (as in any spring-loaded device) to return it to its unconstrained size. For example, an unconstrained 6.25 mm diameter stent generates a radial global pressure of 50 mm Hg and a radial local pressure of about 300 mm Hg at the stent filament if it is maintained at 5.5 mm. This increases to 90 mm globally and 500 mm locally at 4.5 mm diameter. These pressure calculations would be additive to the mean arterial pressure and could have an important impact in situations where oversized Wallstents are implanted. In fact, localized areas of necrosis adjacent to the stent wires have been seen, which are probably the result of a pressure phenomenon.

3. Splinting the artery externally (casting) versus internally (stenting): effect on wall stress. Parallels have been drawn between the effects of splinting the artery externally (casting) and internally (stenting). Thubikar et al. (66) showed that externally casting segments of rabbit aortas limits pulsatile flow and atheroma development despite a high cholesterol diet. On the basis of this observation, others (32) have speculated that nonflexing internal stents may also reduce wall stress and consequently diminish hyperplasia formation. However, this analogy is not impressive. Although some of the pulsatile stretch may be borne by the external cast or the internal stent, and thus favorably affect wall stress, this is achieved by separate means. In the casting model, there should be a reduction in intramural wall stress, since the vessel is casted at a radius smaller than the maximal systolic expansion. In contrast to casting, stenting results in dilation of the artery and an increase in wall stress. This important stimulus to intimal hyperplasia appears to overcome the inhibitory effects of reduction in phasic vessel wall expansion. Booth et al. (67) modified the external casting model with interesting results. By applying an external nonoccluding Silastic collar on a rabbit carotid artery that did not affect end-systolic dimensions, they demonstrated that focal hyperplastic lesions rapidly develop. This finding supports the concept that external casting must decrease the vessel radius in order to achieve inhibition of intimal hyperplasia.

The State of Interventional Cardiology in 1990: Debulking Versus Dilating

Interventional cardiology has moved in two directions: devices that primarily dilate coronary narrowings (balloon angioplasty and stenting) and devices that physically debulk coronary tissue by extraction, liquefaction or vaporization (laser, directional and rotational atherectomy and spark erosion). At present, it is difficult to make comparisons among the various devices. However, there are several fundamental differences that may be important and merit further discussion.

Comparison of the various techniques. The ideal coronary intervention should selectively reduce the effect of the atheromatous lesion with minimal alteration of the normal vessel wall components and architecture. None of the currently available techniques completely satisfy these requirements. Balloon angioplasty, atherectomy (rotational and directional) and laser devices all cause extensive traumatic changes within the plaque and usually major alterations to the vessel wall architecture as well. Balloon angioplasty, the earliest intervention, has been shown to create tears and dissections within and at the edges of atherosclerotic plaques and frequently disrupts the internal elastic membrane and medial layers (68–71). Theoretically, these disruptions may be advantageous since the liberation of lipid and debris from the atheromatous lesions, a sort of debridement, may favorably affect the long-term biologic growth and behavior (if distal embolization of this material does not cause immediate clinical consequences) (72–74).

However, more important considerations may be the manner in which the healing process ensues in a damaged vessel with frayed, ragged membrane edges and separated muscular layers and the inherent problems of restoring the normal three-layered architecture of the arterial wall in an orderly fashion after such injury. Moreover, the extent of arterial disruption from angioplasty appears to be much less than in the actual removal of coronary tissue by debulking devices. Directional atherectomy in particular has been shown to be extremely effective in removing the atheroma but specimens include adventitia in up to 30% of cases (75), although there is no evidence to date that the rate of restenosis is related to the depth of the vessel wall extracted. Alternatively, stenting seems to be the least disruptive to the underlying architecture, although the underlying atheromatous lesion persists in the stented vessel with unknown future consequences. Stenting is able to "tack back" the cracks and tears induced by balloon angioplasty, which may

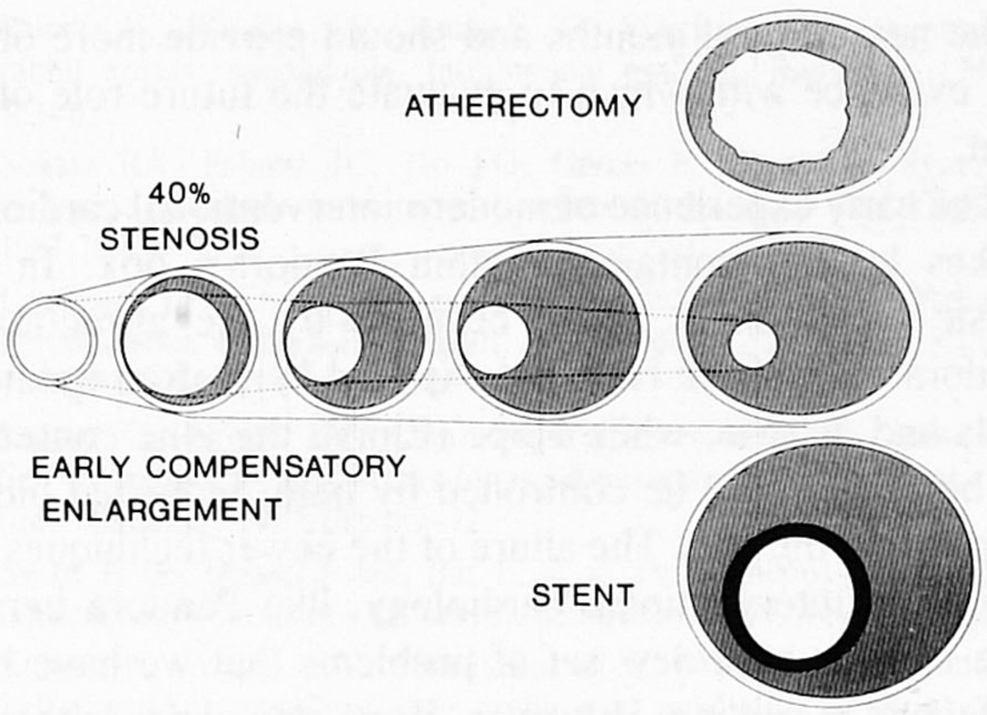

Figure 12. The natural progression of coronary artery disease as suggested by Glagov et al. (76) is illustrated in the **center row** by the early compensatory enlargement and the late luminal narrowing of progressive atherosclerosis. The differential effects of stenting and atherectomy in restoring the vessel diameter are shown. Stenting (**below**) restores the early compensatory enlargement in the vessel while it maintains the basic architecture of the vessel wall. By extracting vascular tissue, atherectomy (**above**) disrupts the underlying architecture of the wall. Modified from Glagov S et al. (76) with permission.

diminish the stimulus for fibrosis in much the same way that a properly closed wound minimizes fibrotic scar in the healing phase.

Glagov revisited. Glagov et al. (76) observed that the diseased coronary artery is able to adapt to progressive plaque expansion by enlarging the size of the vessel. This compensatory mechanism maintains the luminal area until the plaque lesion occupies 40% of the area inside the internal elastic lamina, beyond which progressive luminal narrowing occurs. In other words, significant atherosclerosis can coexist with normal or even enlarged luminal area until the limits of this adaptation are exceeded.

Striking similarities exist between the chronic process of atherosclerosis and the situation in the stented vessel wall. The stent is initially embedded in the intima, which results immediately in enlargement of the lumen and later in localized medial thinning at the site of the stent wires, a commonly observed pathologic feature of atherosclerosis. Stenting may be regarded as the invasive cardiologist's attempt to restore the aforementioned "Glagovian" balance between plaque and luminal area, but in vessels that contain plaques >40% of the internal elastic lamina (Fig. 12). Stents effectively alter the relation between plaque size and lumen area, resulting in a shift in the curve. Progressive vessel dilation by the stent can maintain adequate luminal area unless excessive fibrointimal hyperplasia upsets the new balance.

Expansion ratio. Expansion ratio is an important concept that relates the final effect on the arterial diameter to the size of the catheter required to deliver this effect (32) (Table 1). A

Table 1. Expansion Ratios With the Coronary Interventional Devices

Intervention	Procedures	Device Profile (mm)	Vessel Diameter Preprocedure (mm)	Maximal Achievable Diameter/(Range) (mm)	Postprocedure Diameter (mm)	Theoretic Expansion Ratio	Effective Expansion Ratio
Balloon angioplasty	443	0.7–1.3	1.1 ± 0.3	2.9 ± 0.4 (2.0–3.5)	1.8 ± 0.4	2.2–4.1	1.4–2.6
Stenting							
Self-expandable	357	1.6	1.3 ± 0.7	4.0 ± 0.7 (2.5–6.0)	2.6 ± 0.6	2.5 (1.6–3.8)	1.6
Balloon-expandable	27	1.4–1.6	1.0 ± 0.3	3.3 ± 0.3 (3.0–4.0)	2.4 ± 0.3	2.1–2.4	1.5–1.7
Atherectomy							
Directional	39	2.1–2.5	1.1 ± 0.4	3.3 ± 0.5* 2.0 ± 0.2†	2.5 ± 0.6	1.3–1.6	1.0–1.2
Rotational	52	1.5–2.0	0.9 ± 0.3	1.9 ± 0.3 (1.5–2.0)	1.7 ± 0.4	1.0	0.9–1.1
Excimer laser	55	1.4	0.5 ± 0.4	1.4	1.7 ± 0.5	1.0	1.2

*With balloon inflated; †with balloon deflated. This table compares the device profile and immediate angiographic results of several interventions. The profile of the device is based on data on 2.0 to 3.5 mm diameter balloon catheters (77), the Wallstent (Medinvent) self-expandable stent, Wiktor (Medtronic) balloon-expandable stent, Simpson Coronary Atherocath (DVI) directional atherectomy device, Rotablator (Heart Technology) rotational atherectomy device and the model Max-10 excimer laser (Technolas, Munich). The relation between the profile of the device and the maximal achievable diameter of the device is the theoretical expansion ratio. The maximal achievable diameter of the vessel is calculated according to the size of the device while it is operational in the coronary vessel. In the case of balloon angioplasty, balloon-expandable stent and directional atherectomy, the maximal achievable diameter corresponds to the diameter of the device while the balloon is inflated and to the unconstrained diameter of the self-expandable stent. The rotational atherectomy device and the excimer laser do not alter their diameter during the procedure. The postprocedure diameter is measured immediately after the procedure. The effective expansion ratio represents the ratio between the postprocedure result and the profile of the device and thus indicates not only the initial effect of the device but also the effect of elastic recoil, which is primarily responsible for the deterioration in the diameter from the maximal achievable diameter to the postprocedure diameter. The diameter values listed are the mean value ± SD of the different-sized devices from each interventional study; ranges are in parentheses. The preprocedure data, which may also affect the postprocedure result, were similar for all interventions (0.9 to 1.3 mm) except for the excimer laser, which may explain a somewhat lower postrecoil diameter and effective expansion ratio. The quantitative angiographic data for all devices except the rotational atherectomy device (Peterson K, unpublished observations) and the excimer laser (79), were collected at the Thoraxcenter.

favorable ratio is best exemplified by a small catheter delivery system that is able to pass severely narrowed segments and yet optimally dilate the stenosis. The maximal effect of the device may be partially lost because of the elastic recoil of the vessel. The current interventional devices may have differential effects in these two areas: the immediate result when the device is initially used, and then the partial loss of the initial gain after the device has been removed. An attempt has been made to separate these two effects by subdividing the expansion ratio into the theoretical expansion ratio (a measure of the effect while the device is operational) and the functional expansion ratio (which takes into account the elastic recoil phenomenon). For example, a 4 mm diameter balloon angioplasty catheter should achieve a vessel diameter of 4 mm at the time of balloon inflation but this is reduced immediately after deflation, primarily because of the elastic recoil of the vessel. Balloon angioplasty and stenting give extremely favorable theoretic and effective expansion ratios since they may be delivered on low profile catheters. The wide range for the theoretic and effective expansion ratios seen with balloon angioplasty is explained by the variation in the size of the balloons (2.0 to 3.5 mm) used in the study from which these data were obtained. The atherectomy devices are more limited by the profile of the device that is introduced into the coronary artery. The dimensions of the rotational atherectomy device and the excimer laser do not change while in operation and therefore both exhibit lower theoretic expansion ratios. However, by physically removing or vaporizing tissue, the potential elastic recoil effect is diminished by atherectomy and excimer laser devices.

Conclusion

Once again the question is asked: Can the promises of the new technology, and in particular the coronary stent, ever be realized?. Stenting will only achieve clinical acceptance when the safety, efficacy and cost efficiency are superior to those of balloon angioplasty alone. Safety remains the major limitation of stenting. In the initial 105 patients with an implanted Wallstent, 20% had documented occlusion within the 1st 14 days, usually resulting in myocardial infarction and in some cases necessitating emergency bypass surgery. With further experience this was reduced to 13% in the next 100 patients. Schatz et al. (15) recently reported a 3.6% subacute occlusion rate in contrast to a 16% rate in their early experience when warfarin treatment was omitted (78). However, the price of chronic anticoagulation therapy—bleeding complications, prolonged hospitalization to initiate therapy and effects on the quality of life—must also be considered. With the increasing importance of third party payment, the cost differential among competing therapies will also dictate medical policies. Finally, these devices must show beneficial effect on late restenosis in order to gain clinical acceptance. The late follow-up results of quantitative coronary angiography for two of the stents will be published in the next several months and should provide more objective evidence with which to evaluate the future role of the stent.

The early experience of modern interventional cardiology evokes lessons contained within Pandora's box. In this classic Greek myth, man, beguiled by the attraction of Pandora opened the box that exposed heretofore unknown perils and disease, while Hope (Elpis), the lone content of the box that could be controlled by man, remained hidden deep within the box. The allure of the newer techniques and devices in interventional cardiology, like Pandora herself, have brought us a new set of problems that we have been ineffectual in solving. However, Hope also exists within the modern Pandora's box and our capacity to realize hope will depend on a scientific approach to the problems of restenosis and neointimal hyperplasia in a mutual effort (in concert with industry) of interventional cardiologists, pathologists, molecular biologists, biochemists, pharmacologists and our patients, the general public.

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