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EDITORIAL REVIEW

The Restenosis Paradigm Revisited: An Alternative Proposal for Cellular Mechanisms

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Coronary restenosis is a reparative response to arterial injury during angioplasty, and remains a major clinical problem. The reasons for treatment failures likely stem from our incomplete understanding of the cellular mechanisms in restenotic neointimal formation.

Restenosis is thought to result from migration and replication of medial smooth muscle cells to form an obstructive neointima, a concept neither observed nor demonstrated in humans. An alternative hypothesis for restenosis is based on observations in the porcine coronary injury model. In this model, there are three cellular stages in neointimal formation: thrombotic (stage I), cellular recruitment (stage II) and proliferative (stage III). The thrombotic stage occurs early and consists of platelets, fibrin and red blood cells accumulating at the vessel injury site. In the recruitment stage, the mural thrombus itself develops an endothelium, followed by a mononuclear leukocytic infiltrate beginning on the lumen side of the vessel. In the proliferative stage, a "cap" of actin-positive cells forms on the lumen surface and progressively thickens. These cells do not arise from media at the injury site. Extracellular matrix secretion and additional recruitment likely add to neointimal volume during this phase.

Thrombus assumes a major role in restenosis by providing an absorbable matrix into which smooth muscle cells proliferate. Further studies are needed to validate or modify this hypothesis.

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Coronary artery restenosis remains a major limitation of balloon angioplasty and all other percutaneous revascularization procedures. It is the Achilles' heel of angioplasty, resulting in repeat procedures, increased morbidity and escalating medical costs. Although the incidence, timing, clinical and anatomic associations of restenosis have been studied in depth (1–5), no therapy consistently prevents this difficult problem.

None of the many theories explaining the mechanisms of restenosis has been scientifically validated either in humans or in animal models. A diverse array of failed therapies (pharmacologic and technologic) have been based on these theories. The purpose of this review is to examine the possible reasons for these treatment failures and to propose an alternative hypothesis for the cellular mechanisms of restenosis. This alternative hypothesis, if proved correct, may be useful in developing more effective therapies.

Why have we failed to solve the restenosis problem? Most pharmacologic agents (Table 1) have failed to reduce the restenosis rate in clinical trials. These drugs span a broad spectrum of pharmacologic action, representing many drug classes. Failure of these trials implies one of the following: 1) a truly effective agent has not yet been tested, 2) one or more potentially effective agents have been tested, but in incorrect dosage or timing, 3) more than a single agent is needed, or 4) the restenotic response cannot be effectively modified by systemic therapy at drug levels that are tolerable in humans. It is noteworthy that all pharmacologic trials to date have tested systemic treatment for a problem localized to a small coronary artery segment.

Prior pharmacologic trials against restenosis have been based on the plausible but largely unproved hypothesis that obstructive neointima results from uncontrolled medial smooth muscle cell proliferation at the arterial injury site. This concept is shown schematically in Figure 1 and has been summarized previously (28,29). In this theory, medial smooth muscle cells at the site of the injured artery respond by uncontrolled migration, proliferation and extracellular matrix synthesis. Mural thrombus caused by the injury may contribute cytokines, chemoattractants and growth factors that initiate and sustain the neointimal growth process (30). The final result of uncontrolled growth is a space-occupying lesion that impinges on the arterial lumen.

This hypothesis does not originate from direct observation; instead, it is inferred from isolated observations in humans and animal models. Because prior approaches to restenosis based on this hypothesis have failed, the validity of the hypothesis itself should be questioned. The individual

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Table 1. Pharmacologic Results in Human Restenosis Trials

Agent (study*)	Result
Aspirin	
Thornton, 1984 (6)	Negative
Ellis, 1987 (7)	Negative
Mufson, 1988 (8)	Negative
Aspirin/dipyridamole	
Schwartz, 1988 (9)	Negative
Thromboxane blockade	
Finci, 1989 (10)	Negative
Coumadin	
Thornton, 1984 (6)	Negative
Urban, 1988 (11)	Negative
Heparin	
Ellis, 1989 (12)	Negative
Corticosteroids	
Pepine, 1990 (13)	Negative
Fish oil	
Grigg, 1989 (14)	Negative
Dehmer, 1988 (15)	Effective
Reis, 1989, 1990 (16–18)	Negative
Milner, 1989 (19)	Negative
Nye, 1990 (20)	Effective
Olsson, 1989 (21)	Effective
Lipid lowering	
Hollman, 1989 (22)	Negative
Sahni, 1991 (23)	Effective
Calcium channel blockade	
Corcos, 1985 (24)	Negative
Whitworth, 1986 (25)	Negative
Prostacyclin	
Knudtson, 1990 (26)	Negative
Angiotensin-converting enzyme inhibitors	
Serruys, 1992 (27)	Negative

*Studies are identified by first author, year of publication (reference number).

components of this conventional hypothesis will thus be critically examined.

Proposed Mechanisms of Restenosis

Thrombus at the injury site. Thrombus has long been implicated in the formation of neointima (31–37). At sites of acute arterial injury, large aggregations of platelets ("white thrombus") and fibrin with entrapped red blood cells are routinely found (36,38). These thrombi contain attractants and mitogens for smooth muscle cells. Because the relative importance of platelets, thrombin and fibrin to restenosis is unclear, therapeutic approaches based on any one thrombus component may not be sufficient to successfully limit neointimal formation. Furthermore, the quantitative relation between thrombus volume and ultimate neointimal volume is unknown, and the relative contribution of thrombus to neointimal volume has not been addressed. That clinical trials of anticoagulants (aspirin, dipyridamole, heparin and coumadin) have failed may not be surprising in view of their

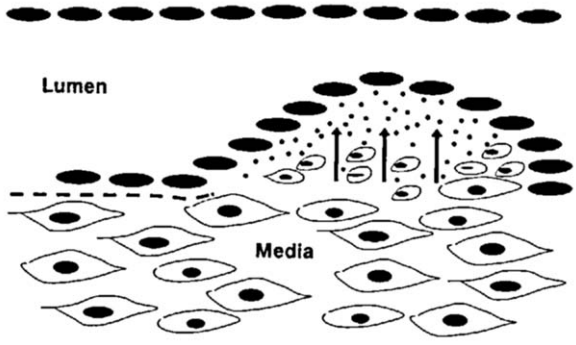


Figure 1. Current paradigm for neointimal formation. The current theory holds that smooth muscle cells of the injured media migrate and proliferate into a mass of tissue that subsequently causes vessel stenosis. In the schematized concept shown here, stenosis occurs at sites where the internal elastic lamina has been ruptured.

comparatively weak and nonspecific activity at the dosages used. Patients with clinically therapeutic anticoagulation must maintain some thrombotic capability (39) so that mural thrombus is probably present at the angioplasty site even in such patients.

The relation of platelets, thrombin and other components of the thrombotic process to neointimal formation should be better understood before substantial time and money are invested in new clinical trials. More potent agents (for example, hirudin, platelet fibrinogen receptor antagonists, factor Xa inhibitors) will shortly be available and will undoubtedly be subjected to extensive investigation (40,41).

One important question regarding thrombus and restenosis is whether the volume of mural thrombus relates to the ultimate volume of healed neointima. Liu et al. (28) suggested that thrombus volume may *not* be a major source of neointimal volume, but there is little direct histopathologic evidence to answer this question. Does a proportionality exist so that reduction of platelets and fibrin will correspondingly reduce neointima, or must *all* thrombus be eliminated to limit neointimal formation? Is a monolayer of platelets sufficient to cause a clinically significant restenotic lesion, as suggested by others (42)? These questions hold substantial implications for treatment because complete local elimination of thrombus may be neither feasible nor safe when achieved through systemic anticoagulation.

Growth factors. Biochemical growth factors are often implicated in the rapid formation of neointimal hyperplasia after arterial injury (43,44). Although many growth factors have been characterized (Table 2), little is known of their direct role in the genesis of restenotic neointima. Which growth factors have major, and which have minor effects? Do undiscovered growth factors play a key role in restenosis? Will it be necessary to inhibit more than one factor to reduce neointima? Although the principle of growth factors inciting smooth muscle cell replication enjoys widespread acceptance, it entails assumptions that have not been observed or confirmed in any in vivo system. Better under-

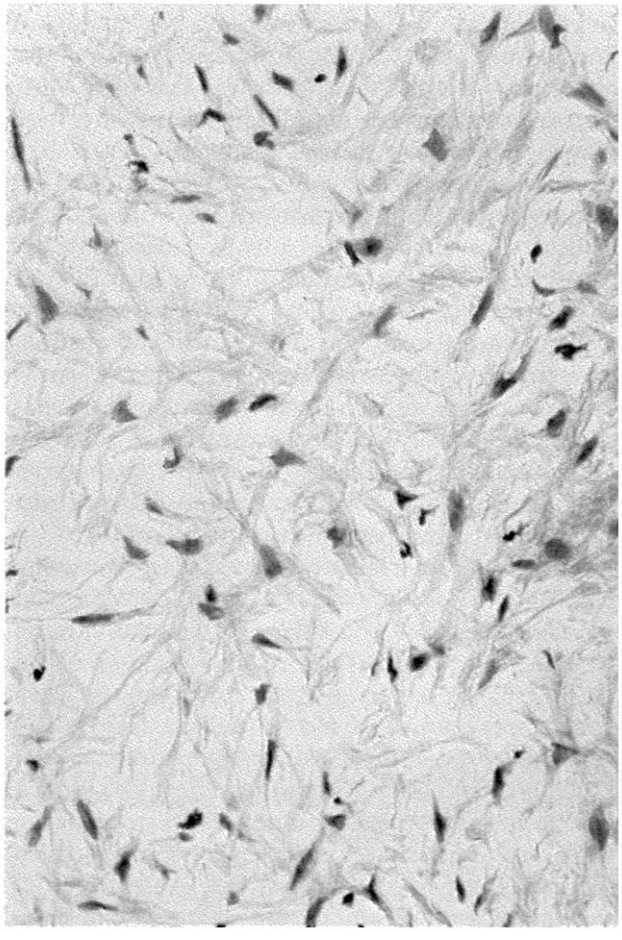
Table 2. Growth Factors and Cytokines Implicated in Restenosis

	Reference No.
Platelet-derived growth factor	43,45,46
Basic fibroblast growth factor	47,48
Insulin-like growth factor	49–52
Transforming growth factors $-\beta_1$ and $-\beta_2$	53–55
Interleukin-1, interleukin-4, interleukin-6	56–61
Heparin binding growth factor-1	62

standing of growth factors and their role in restenosis (45) may permit the design of specific therapies, but a complete understanding of all growth factors prominent in restenosis is not likely in the near future.

Extracellular matrix. The importance of extracellular matrix in the restenotic process may be inferred from direct examination of neointima. Neointima is generally hypocellular fibrous tissue, predominantly glycosaminoglycans and various forms of collagen. Figure 2 shows an example of restenotic neointima. Measurements of human neointima in our laboratory show an average of 715 cells in a volume of 3.28×10^{-3} mm^3, or 2.18×10^5 cells/mm^3. Typically, the volume of one neointimal cell (nucleus plus cytoplasm) is approximately 512 μm^3. Thus in 1 mm^3 of neointima, the volume actually comprising cells is only 2.18×10^5 cells $\times$ 512 μm^3/cell, or 0.111 mm^3. Thus, cellular components constitute only about 11% of neointimal volume, and the remainder is extracellular matrix.

Figure 2. Human neointima is mostly extracellular matrix (see calculations in text). Hematoxylin-eosin ×300, reduced by 25%.



Given the abundance of extracellular matrix in restenotic lesions, one restenosis treatment strategy may be to reduce the matrix volume surrounding each cell. A substantial reduction in neointimal volume might be obtained even if the absolute number of cells secreting matrix were unchanged. A net decrease in stenosis would result without the need to inhibit smooth muscle cell migration or proliferation. Growth factor inhibition may contribute to this strategy because some growth factors (49,53) have been implicated in matrix synthesis.

The smooth muscle cell. Both secretory and contractile smooth muscle cell phenotypes are considered to play the central role in restenosis. Most therapies under consideration involve inhibition of smooth muscle cell function. These strategies propose to reduce migration, proliferation or matrix synthesis by the smooth muscle cell and are briefly described later.

Angiotensin-converting enzyme inhibition and restenosis. Reports by Powell et al. (63) and others (64–66) demonstrated a substantial reduction of neointimal thickness in balloon-injured rat carotid arteries by angiotensin-converting enzyme inhibition. The arterial wall contains proteases capable of the conversion of angiotensin I to angiotensin II. Angiotensin II is not a known mitogen, but it does stimulate protein synthesis (64). Inhibition of extracellular matrix formation by angiotensin-converting enzyme inhibitors may be one reason for the successful use of these agents in the rat model.

Great interest after early reports led to several clinical trials of angiotensin-converting enzyme inhibitors. However, data from the European MERCATOR trial with oral cilazapril suggest little benefit at the dosing and schedules used (27).

Lipids and restenosis. The importance of serum cholesterol and other lipids in restenosis remains unclear. Results of several lipid-lowering restenosis trials have been conflicting. No definitive evidence yet exists for the efficacy of lipid lowering after percutaneous transluminal coronary angioplasty to prevent restenosis (15,16,20,23). At least two large randomized trials are in progress using the 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitor lovastatin. It is unclear how serum lipid reduction might prevent restenosis, although toxicity of lipids to endothelium is one possibility.

Antimetabolites and antimitotic agents. Pharmacologic prevention of smooth muscle cell proliferation has been the rationale for using antimetabolite agents in restenosis. Methotrexate and azathioprine were unsuccessful in animal models (67,68). Anecdotal data on unsuccessful experiences with

Table 3. Animal Restenosis Models

Species	Vessel	Reference No.
Rat	Carotid	(42,74,75,78)
Rabbit	Iliac	(40,79,80)
Rabbit	Ear	(81)
Pig	Coronary	(82)
Pig	Carotid	(33,83)

methotrexate in humans also exist (Hinohara, personal communication, November 1991). Other potent toxins are under active consideration (69), as are growth inhibitors such as somatostatin analogues (70–73).

Current concepts of restenotic cellular mechanisms thus focus on hypotheses in which arterial smooth muscle cells at the medial injury site migrate to intima, proliferate and synthesize extracellular matrix in an uncontrolled manner. This sequence of events has not been observed in humans; thus, animal models have assumed paramount importance in the study of restenosis (74–77).

Animal Restenosis Models: Problems or Solutions?

At least five animal models of arterial injury restenosis are in current use (Table 3). Animal models have two roles in restenosis research. The first is to test potential therapies before human trials. In this context, these models have been disappointing because many therapies that proved effective in these models failed in human studies. Many possible reasons exist for these frustrating failures. First, the pathophysiologic response to arterial injury in an animal model may differ from that in humans. Cellular events in these models have not been correlated with comparable events in humans; thus, the limitations of these models at a cellular level remain unknown. Second, doses and drug effects from successful animal trials may not translate acceptably to humans. Third, many animal models utilize peripheral arteries such as the iliac or carotid arteries, which are elastic vessels, as opposed to the epicardial coronary arteries, which are muscular. Also, definitions for successful treatment in animal models frequently differ from those of treatment defined clinically. Histopathologic measurements of neointimal thickening in animal arteries, for example, are frequently statistically significant but would not be detectable if measured angiographically. Finally, human restenosis occurs on an atherosclerotic substrate, substantially different from the normal arteries used in most animal studies.

Animal models also may be used to understand the cellular and molecular events of restenosis. Fewer than 70 cases have been described in all published studies of pathologic findings after angioplasty in humans, including <10 cases in the critical early (1 to 4 weeks) time periods. The time course of human restenotic neointimal formation thus remains unknown because tissue has been obtained only from the very early (hours to days) or late stages of healing after dilation. Efforts should be directed toward better characterization of animal models to understand the formation of neointima.

In summary, current animal models of restenosis have not been sufficiently well characterized to understand their limitations and relevance when applied to human angioplasty. The discrepant data from human and animal trials highlight our incomplete understanding of the restenosis process itself at both cellular and molecular levels. Standardization of methodology in animal models is needed to better understand why these models fail to predict results of the same agents used in humans.

Questions about the current restenosis hypothesis. Because most therapies based on the classic smooth muscle cell proliferation hypothesis have failed, the validity of this hypothesis should be questioned. Recent studies (84) in a porcine coronary injury model suggest a different sequence of events in the restenotic process that may be closer to the pathophysiology of restenosis in humans.

Restenotic Neointimal Development: Stages in a Porcine Model

Severe mechanical injury to the normal porcine coronary artery causes arterial stenosis from neointima identical histopathologically to human restenotic tissue. Three distinct, sequential cellular healing phases occur in this injury-response model (Fig. 3 and 4).

Stage I: thrombotic phase (Fig. 4A). The immediate response to arterial injury in the porcine model is thrombus formation composed initially of aggregated platelets, fibrin and trapped erythrocytes. The platelet component ("white thrombus") occurs at the site of deep arterial injury. The fibrin and red cell component ("red thrombus") is attached to the densely aggregated platelets.

Stage II: Cellular recruitment phase (Fig. 4B). The next stage of healing comprises cellular recruitment into the thrombus itself. The first recruitment event is endothelialization of the lumen (blood) surface of the thrombus, which occurs by 3 to 4 days. Recruitment of mononuclear leukocytes follows endothelialization and consists of monocytes-macrophages and lymphocytes. These monocytes and lymphocytes line the *lumen* surface and are found migrating deep into the degenerating thrombus beneath the newly formed endothelium. The recruitment phase thus begins from the lumen (endothelial) surface of the thrombus mass rather than from deep medial regions of the injured vessel segment.

Macrophages and lymphocytes are commonly found within the thrombotic mass and often are surrounded by a clear, fibrin-free zone. The macrophages secrete fibrinolytic enzymes that are probably responsible for resorption of thrombus (85). The cellular infiltrate and the thrombus itself

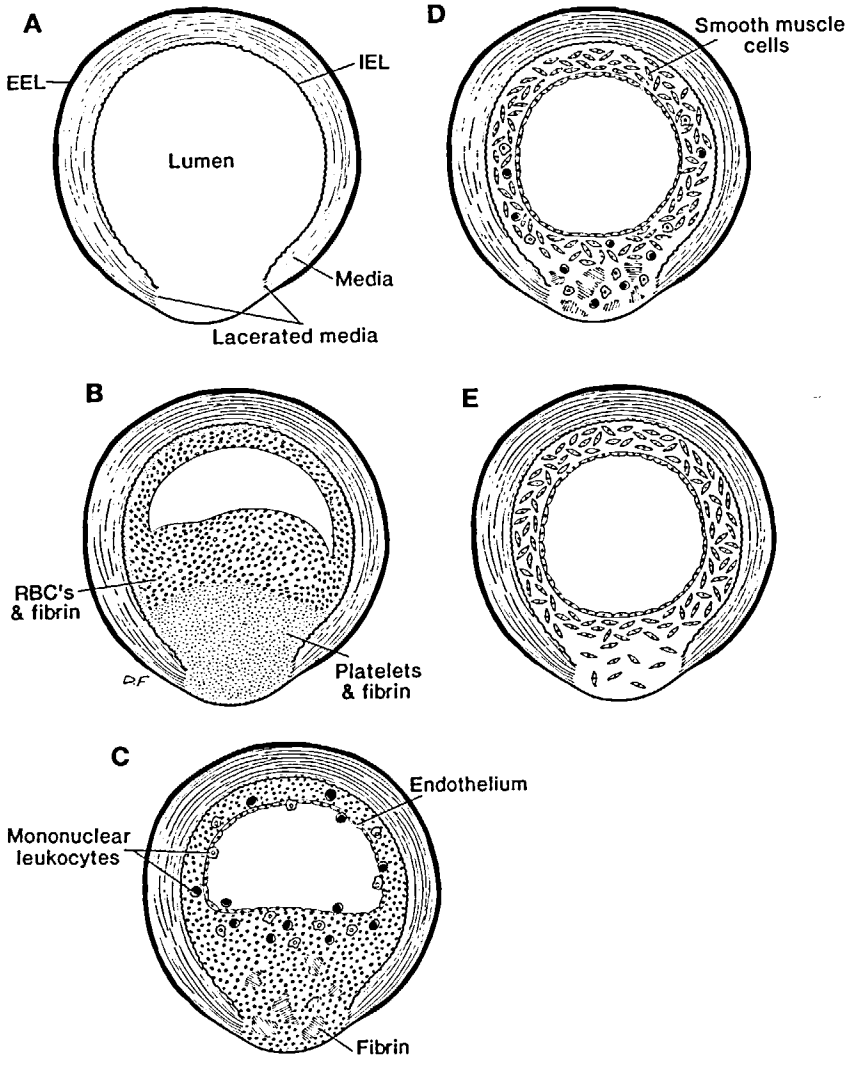


Figure 3. Schematic illustration of the formation of neointima in the porcine coronary model. **A,** Acute arterial injury. The internal elastic lamina (IEL) and media have been lacerated. **B,** Within minutes after injury, acute thrombosis occurs at the site of injury, and in many cases spreads to nearby arterial sites. The thrombus has a mixed appearance, consisting of platelet-rich and fibrin-rich regions. **C,** The thrombus becomes covered by a layer of endothelium at roughly 3 to 4 days. Shortly thereafter, there is infiltration of mononuclear cells (from the lumen side first), consisting of monocytes-macrophages and lymphocytes. Much fibrin and degenerating thrombus remain in the deeper regions. **D,** Smooth muscle cells begin to be seen roughly 6 days after injury. These cells stain positively for actin and appear first at the *lumen* surface to form a "cap" on the degenerating thrombotic mass that gradually thickens over time. Residual monocytes-macrophages and lymphocytes are still present in the deeper layers. **E,** The neointima is completely formed by about 21 days. Residual fibrin and thrombus have been resorbed. The cap of panel D has progressively thickened to complete the healing process. Extracellular matrix is probably being synthesized at this time, possibly increasing the severity of stenosis. EEL = external elastic lamina; RBC's = red blood cells.

may be an abundant source of growth factors and chemoattractant substances, facilitating and sustaining further cellular recruitment.

Stage III: proliferative phase (Fig. 4C). Cellular proliferation occurs in the final arterial healing stage of the porcine model, approximately 7 to 9 days after injury. Beginning again at the *lumen* surface, cells that stain for alpha actin (possibly smooth muscle cells or myofibroblasts) colonize the degenerating thrombus mass. These cells initially form in a thin "cap" on the lumen surface just beneath the endothelium. The cap thickens over time and appears to grow toward the site where medial injury initially occurred. Residual thrombus is resorbed as this cap thickens. Within the cap, the cellular architecture has the appearance of mature neointima. The healing process is complete when the all residual thrombus is resorbed and replaced by mature neointima. The mononuclear cell infiltration disappears at this late stage. Elaboration of extracellular matrix probably plays a role in this stage, increasing the neointimal volume through the amount of matrix produced.

An Alternative Hypothesis for Restenosis

A different mechanism for restenosis is suggested by this sequence of events in the pig. Prior work (31,86) implicating mural thrombus and neointima has not specifically implicated a relation between thrombus volume and eventual neointimal volume. The distinction between platelet-rich and fibrin-rich thrombus has not been previously emphasized. In the current model, early endothelialization of the fibrin-rich thrombus itself, with subsequent smooth muscle cell colonization of the thrombus from the lumen surface, strongly suggests that much of the neointimal volume relates to the early fibrin-rich mural thrombus. These observations clearly implicate the fibrin thrombus as playing a central role in restenosis, different from the current paradigm of smooth muscle cell proliferation to create arterial obstruction through a tumor-like growth.

If this same sequence also occurs in humans after angioplasty, novel conclusions and questions arise regarding possible therapy. Neointimal cells apparently *do not* come

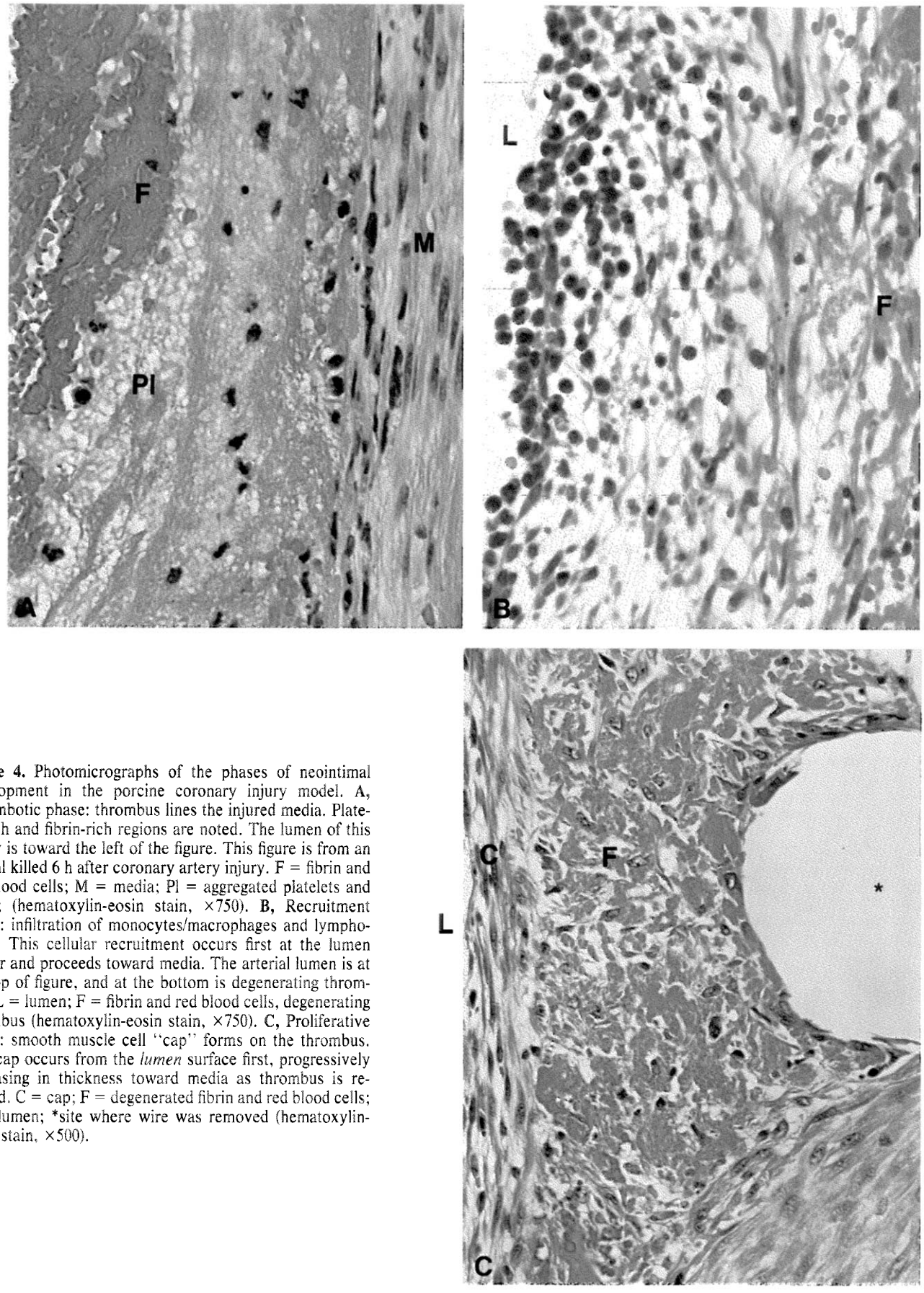


Figure 4. Photomicrographs of the phases of neointimal development in the porcine coronary injury model. **A,** Thrombotic phase: thrombus lines the injured media. Platelet-rich and fibrin-rich regions are noted. The lumen of this artery is toward the left of the figure. This figure is from an animal killed 6 h after coronary artery injury. F = fibrin and red blood cells; M = media; Pl = aggregated platelets and fibrin; (hematoxylin-eosin stain, ×750). **B,** Recruitment phase: infiltration of monocytes/macrophages and lymphocytes. This cellular recruitment occurs first at the lumen border and proceeds toward media. The arterial lumen is at the top of figure, and at the bottom is degenerating thrombus. L = lumen; F = fibrin and red blood cells, degenerating thrombus (hematoxylin-eosin stain, ×750). **C,** Proliferative phase: smooth muscle cell "cap" forms on the thrombus. This cap occurs from the *lumen* surface first, progressively increasing in thickness toward media as thrombus is resorbed. C = cap; F = degenerated fibrin and red blood cells; L = lumen; *site where wire was removed (hematoxylin-eosin stain, ×500).

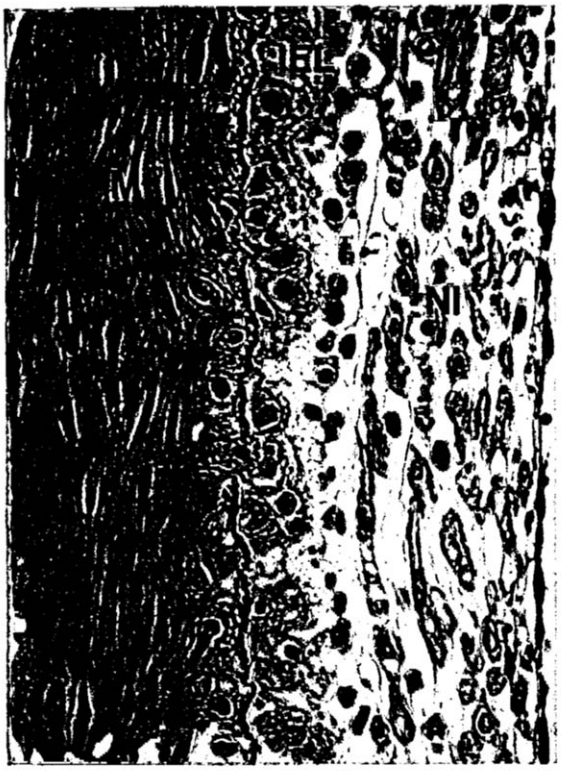
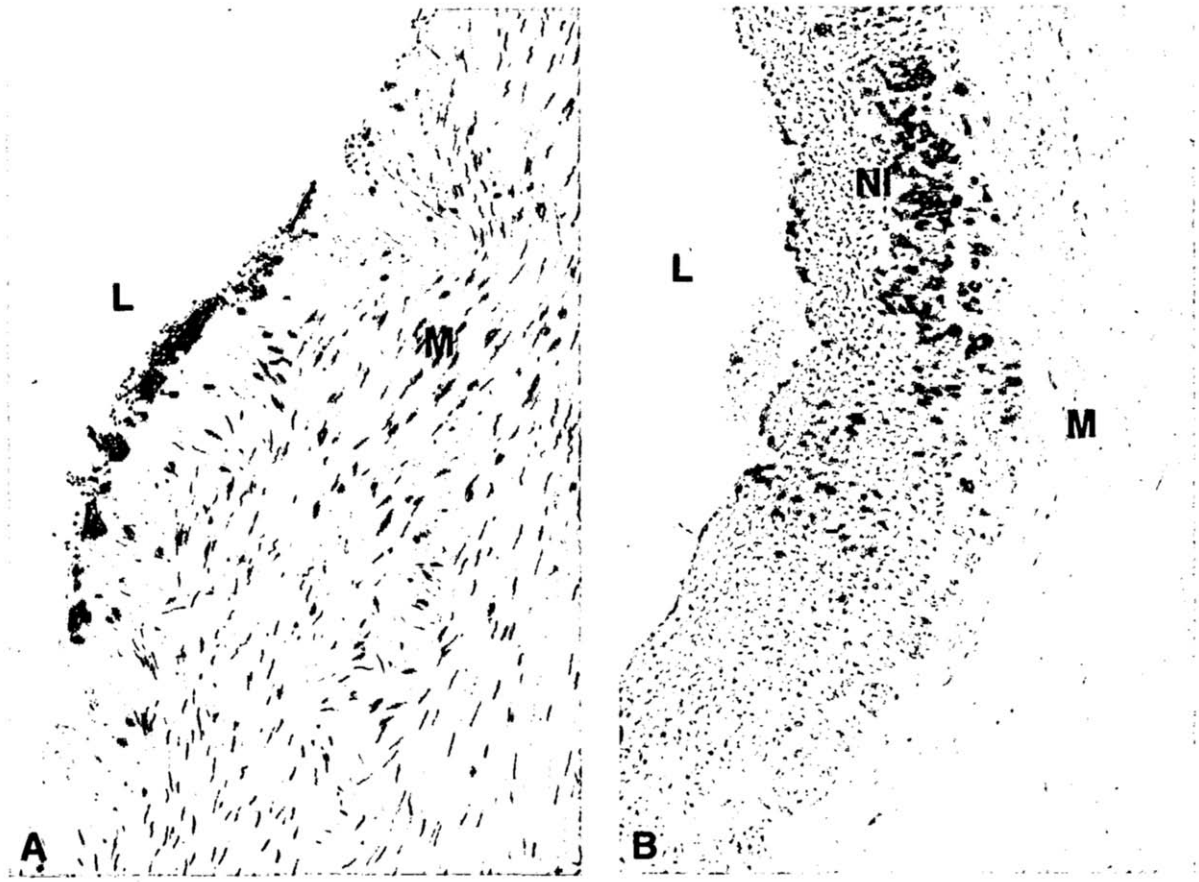


Figure 5 (left). Photomicrograph taken at an arterial site distant from stent injury. Note the thin, endothelialized neointima. Along the internal elastic lamina, medial cells seem to be transforming to a more rounded shape and migrating through breaks in the internal elastic lamina (**arrows**). The arterial lumen is at the right. E = endothelium; IEL = internal elastic lamina; M = media, NI = neointima. Hematoxylin-eosin ×750, reduced by 35%.

Figure 6 (below) A, Acute medial injury from microwave heating (see text) induced in a normal pig coronary artery 24 h before the animal's death. The endothelium is missing, probably because of heat and mechanical injury. Note the edematous media and pyknotic, corkscrew-shaped nuclei indicating severe damage. Very few of these cells are likely to survive. L = lumen, M = media. Hematoxylin-eosin ×380, reduced by 35%. **B,** Actin stain of a coronary artery site that underwent microwave heat injury 4 weeks before. The media is highly abnormal and quite hypocellular with very little actin affinity, probably because of the heat injury. Conversely, there is a thick neointima that avidly stains for actin. Such sections suggest that smooth muscle cells of the neointima may not originate at sites of arterial injury. In this case, the medial smooth muscle cells were severely damaged at the time of heating, and it is unlikely that they were responsible for forming the neointima. M = media (**arrows** show radial extent of the media); L = lumen, NI = neointima. Actin ×254, reduced by 35%.



from media located at the injury site; their origin remains elusive. Do they come from media at the borders of the injury site? Figure 5 suggests this possibility. It shows the medial-neointimal interface at an arterial site distant from the injury location. These cells seem to be changing shape (and possibly phenotype), migrating through the internal elastic lamina into the subintimal space. From there they may continue migration into the "cap" seen directly above the injury location.

Some of the neointimal cells may be myofibroblasts (87–91), cells known to heal injury in other tissues. From which cell line does the neointima arise, and what is its relation to the monocytes and lymphocytes present in the recruitment phase?

Contrary to current understanding, the neointimal cell may not be primarily responsible for the volume of the restenotic lesion. The smooth muscle cell may be guilty only of infiltrating a preexisting thrombotic matrix. Support for this concept comes from a recent experiment in which microwave energy was delivered to normal swine coronary arteries by a custom balloon and antenna (Fig. 6). Heat from the microwave energy (80°C, 30 s) rapidly killed most medial smooth muscle cells at the balloon site. Yet 28 days later, the heated arteries exhibited a thick neointima staining positively for alpha actin. The media was atrophic, hypocellular and no longer stained for actin. Neointimal cells could not have come from the microwave balloon site because they were killed very early by local heat. Early clinical reports of laser balloon angioplasty (92) suggested that heat might cause local medial smooth muscle cell death, thus preventing restenosis. Yet subsequent studies found increased restenosis rates in proportion to temperature.

To summarize this alternative hypothesis: 1) neointimal cells and "proliferation" are not primarily responsible for lumen obstruction but instead colonize a biodegradable fibrin matrix; 2) these cells do not necessarily arise from arterial media at the injury site; and 3) the neointimal cell heals the injury site from the lumen surface *toward* the adventitial surface.

Clinical Observations Supporting the Alternative Hypothesis

Support for this alternative hypothesis of restenosis mechanisms may be found in several clinical observations. Functional testing may predict patients who will develop restenosis (93–99). This phenomenon could be explained by the presence of early mural thrombus. Larger thrombus may cause early abnormal stress test or thallium results by stenoses at the angioplasty site.

Implications of this alternative hypothesis. The proposed alternative hypothesis implies that thrombus is important in restenosis because it provides volume into which smooth muscle cells proliferate. If a strong relation exists between early thrombus volume and final neointimal volume, then interventions to markedly limit mural thrombus after angioplasty might be an effective therapeutic strategy. One strategy would be to severely limit mural thrombus, to yield a thin rim of neointima rather than a bulky mass causing stenosis. Local thrombus size limitation might be required so that patient safety could be maintained. These strategies are currently under evaluation in animal models (40).

Conclusions. In summary, pharmacologic agents may have been ineffective against restenosis because the cellular and molecular events of restenosis remain poorly defined. An alternative hypothesis based on the porcine coronary injury model suggests that mural thrombus determines the volume of neointima early after angioplasty. Caution must be used before embarking on new, expensive and time-consuming human trials. Strategies that are successful in some animal models should be confirmed in other models and species. Ideally, new human trials should be based on solid scientific understanding of proved mechanisms rather than on unconfirmed hypotheses.

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