JULY 31, 1987

The American Journal of CARDIOLOGY®

A Symposium:
Restenosis After Percutaneous Transluminal Coronary Angioplasty

Editor:
Spencer B. King III, MD

A YORKE MEDICAL JOURNAL

The American Journal of
CARDIOLOGY®

A Symposium: Restenosis After Percutaneous Transluminal Coronary Angioplasty

Editor:
Spencer B. King III, MD
Professor of Medicine (Cardiology) and Radiology
Director, Interventional Cardiology
Andreas Gruentzig Cardiovascular Center of Emory University
Emory University Hospital
Atlanta, Georgia

This symposium was held June 7, 1986, at Emory University School of Medicine, Andreas Gruentzig Cardiovascular Center, Atlanta, Georgia, and was supported by an educational grant from USCI, Division of C. R. Bard.

THE AMERICAN JOURNAL OF CARDIOLOGY® (ISSN 0002-9149) July 31, 1987, Vol. 60, No. 3, (USPS: 505-750).

Member, American Business Press, Inc. and Audit Bureau of Circulations. Published once in August, October and December, 2 times in February, March, September and November, 3 times in January, May, June and July, and 4 times in April, by The Cahners Publishing Company, A Division of Reed Publishing USA, 275 Washington Street, Newton, Massachusetts 02158-1630. William M. Platt, President; Terrence M. McDermott, Executive Vice President; Carroll V. Dowden, Group Vice President; Jerry D. Neth, Vice President/Publishing Operations; J. J. Walsh, Financial Vice President/Magazine Division; Thomas J. Dellamaria, Vice President/Production and Manufacturing.

SUBSCRIPTIONS: Solicited only from cardiologists and other physicians. Publisher reserves the right to refuse unqualified subscribers. Subscribers agree that no article or any part thereof published in any editions of the American Journal of Cardiology received under this subscription agreement may be copied, recorded or reproduced in any form or by any means, electronic or mechanical, including, among other things, photocopying or the storing of part or all of such articles on any information retrieval system, without the written permission of the Publisher. Address correspondence regarding subscriptions and changes of address to: THE AMERICAN JOURNAL OF CARDIOLOGY, 44 Cook Street, Denver, Colorado 80206-5191. Please include your zip code and, in case of change of address, copy of old address label. Changes of address must reach the Journal one month preceding month of issue. Single copy price: Regular issues $10.00; Symposium and special issues $12.00. Subscription rate for individuals in field of publication: United States 1 year $66, 2 years $111, 3 years $150; Canada 1 year $83, 2 years $140; 3 years $190; Foreign 1 year $88 (additional $134 air mail), 2 years $150, 3 years $202. Residents, Interns, Medical Students: United States $40, Canada $74, Foreign $80. U.S. institutions 1 year $70, 2 years $119, 3 years $161. The Journal is not responsible for replacing missing issues unless the Circulation Department is notified of non-receipt within 3 months of issue date.

Second class postage paid at New York, New York 10001 and at additional mailing office. Printed in U. S. A. Trademark™ in U. S. Patent Office.

MANUSCRIPTS: Address all manuscripts to William C. Roberts, MD, Editor-in-Chief, The American Journal of Cardiology, 7960 Old Georgetown Road, Suite 2C, Bethesda, Maryland 20814.

POSTMASTER: Send address changes to The American Journal of Cardiology, 44 Cook Street, Denver, Colorado 80206-5191.

Mechanism of Angioplasty and Its Relation to Restenosis

DAVID P. FAXON, MD, TIMOTHY A. SANBORN, MD, and CHRISTIAN C. HAUDENSCHILD, MD

Balloon angioplasty enlarges atherosclerotic narrowings in the vast majority of patients in whom it is attempted at an acceptably low complication rate. Experimental and human pathologic studies have confirmed that angioplasty enlarges the lumen by stretching the vessel wall. Often this stretching process causes plaque fracture due to inelastic components of the atheroma. Denudation of the endothelium is also a consistent observation. While enlarging the lumen, this vascular trauma promotes marked platelet adhesion and aggregation that is dependent on the degree of vascular damage. Most platelets accumulate early within the first few hours. Subsequently, thrombus formation and smooth muscle cell proliferation can occur with the formation of a new fibrocellular occlusive process. Experimentally, antiplatelet therapy can significantly reduce platelet deposition and can reduce the incidence of restenosis. Although restenosis is a multifactoral process, prevention seems possible when platelet accumulation, thrombus formation and smooth muscle cell proliferation can be inhibited through drug or mechanical means.

(Am J Cardiol 1987;60:5B–9B)

In 1964, Dotter and Judkins[1] described the nonoperative technique of transluminal angioplasty to treat patients with severe femoral and popliteal atherosclerotic obstructions. They envisioned that angioplasty worked by remodeling and compressing the atheroma because initial pathologic studies revealed little intimal destruction and no evidence of dissection. However, subsequent pathologic studies did not confirm these observations; in fact, they suggested that marked vessel damage occurred after balloon angioplasty with neointimal tears and occasional perforation.[2,3] Castenada-Zuniga et al[4] reported vessel stretching, cracking of the intima and separation between the intima and media in human postmortem studies.

The results of postmortem studies have not been uniformly accepted because of variability in findings and inherent differences between viable atherosclerotic tissue and postmortem pathologic specimens. Studies in normal canine arteries showed that balloon dilatation caused marked intimal damage with extensive endothelial desquamation.[5] However, normal vascular tissue is not likely to respond to injury in the same way as atherosclerotic plaque. In order to circumvent this problem, we[6] and others[7] adapted a rabbit model of atherosclerosis in which significant focal iliac atherosclerotic lesions could be developed that were suitable for the study of the effect of angioplasty. Atherosclerotic lesions were induced in 3 kg white New Zealand male rabbits by balloon deendothelization of both iliac vessels followed by 6 weeks of a 2% cholesterol diet.[6] Cholesterol levels on this diet averaged 1,000 to 1,500 mg/dl. Angiography disclosed significant focal midiliac stenosis ranging from 50% to 90% in severity (Fig. 1).

Angioplasty was performed retrograde from the femoral artery using a 2 to 2.5 mm balloon catheter. Repeat angioplasty disclosed angiographic improvement in all animals. The animals were then killed and perfused at 80 mm Hg to permit histologic examination. Nondilated segments showed concentric foam cell lesions with a fibrous cap typical of this model. Using an indwelling catheter technique fibrocellular eccentric lesions could also be developed.[6] Histologic changes at the angioplasty site included vessel stretching when eccentric lesions were present and neointi-

From the Evans Memorial Department of Clinical Research and the Department of Medicine, University Hospital, Boston University Medical Center, and Mallory Institute of Pathology, Boston, Massachusetts. This study was aided in part by grant 85-1028 from the American Heart Association, Dallas, Texas.

Address for reprints: David P. Faxon, MD, Section of Cardiology, University Hospital, 75 East Newton Street, Boston, Massachusetts 02118.

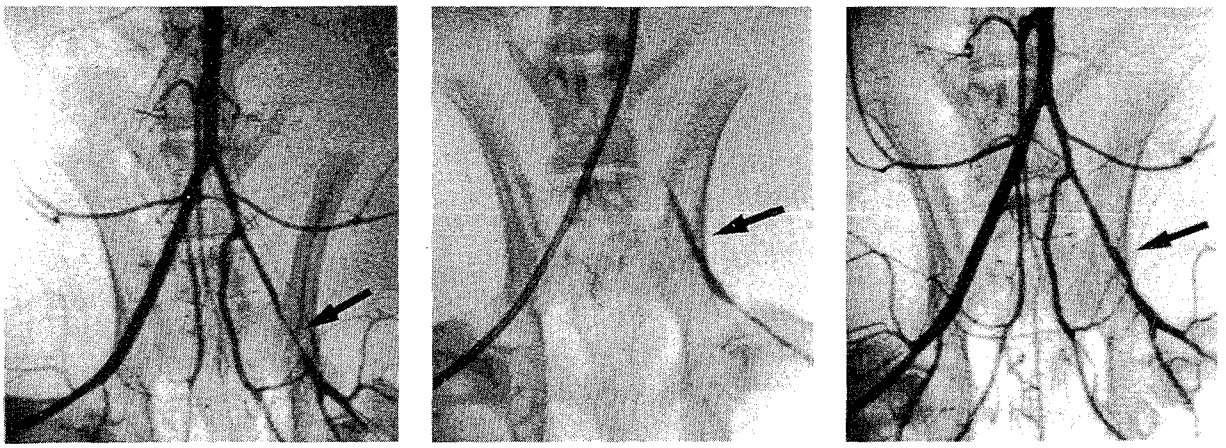

FIGURE 1. Significant iliac stenosis is evident in the left iliac artery of a rabbit after balloon deendothelization and a 2% cholesterol diet for 6 weeks. *Middle* panel shows a 2.5 mm angioplasty balloon catheter inflated in the stenosis with angiographic improvement evident after angioplasty in the *right* panel. Reproduced with permission from Atherosclerosis.[6]

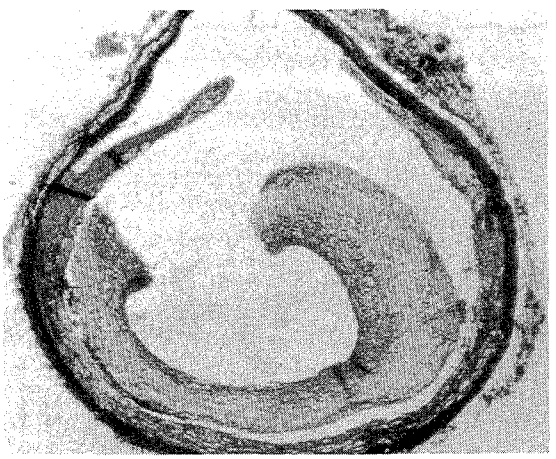

FIGURE 2. An example of histological changes seen immediately after angioplasty. Marked neointimal fracture is evident with the creation of neointimal flaps extending into the vessel lumen. Reproduced with permission from Circulation.[9]

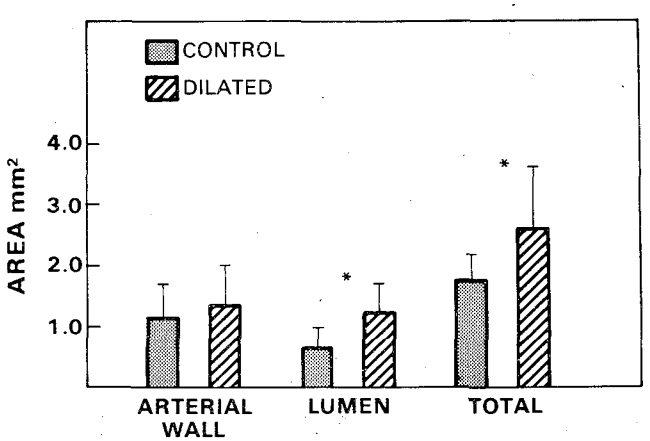

FIGURE 3. Morphometric analysis of serial histologic sections through the angioplasty site and control segments show enlargement of the lumen and vessel area without change in the area of the arterial wall (intima and media). This finding is consistent with vessel stretching without compression of the atheroma. *p ≤0.05. Reproduced with permission from Circulation.[8]

mal fracture and localized dissection when concentric lesions were present[6] (Fig. 2). Further studies from our group verified that the increase in luminal diameter after percutaneous transluminal coronary angioplasty (PTCA) was primarily due to vessel stretching, as morphometric analyses showed no change in vessel wall area (Fig. 3).[8] In addition, studies in this rabbit model have also revealed that dislodgement of atherosclerotic material does not occur. Sanborn et al[9] reported no evidence of embolization of atherosclerotic material or cholesterol using an in vivo perfusion system.

Human autopsy studies of patients who died shortly after angioplasty have shown similar findings to those reported in animal models.[10] Block et al[11] examined the histopathology of 3 patients who died 2 hours to 9 days after angioplasty. Histologic sections revealed intimal splits with a dissecting hematoma in 1 patient. Other studies have also confirmed these observations.[11]

Based on these studies angioplasty appears to work by stretching the vessel with a fusiform dilatation or localized aneurysm formation (Fig. 4).[8] Plaque fracture appears to depend on the histopathology of the lesion with the most compliant portion of the vessel wall stretching. If the lesion is eccentric, then the most nondiseased portion of the vessel wall will stretch. If the lesion is concentric, then the nonelastic atheroma will fracture and split, creating a variety of histopathologic changes.[12] However, 2 features remain constant after balloon angioplasty: desquamation of the endothelium and stretching of the vessel wall.

Restenosis

Restenosis, the phenomenon of renarrowing of the vessel early after PTCA, has been reported to occur in 25% to 50% of patients, averaging 33%.[13] The incidence of restenosis has changed little since PTCA was first introduced nearly 10 years ago. Restenosis is an early phenomenon with the vast majority of patients requiring repeat procedures within 6 months. However, repeat angioplasty is highly successful and can result in long-term patency in the majority of pa-

tients.[14] While clinical, angiographic and procedural factors can predict a higher incidence of restenosis, the most likely cause of restenosis is the response of the vascular tissue to the often dramatic injury that can occur after PTCA. Vascular injury of the type seen after angioplasty would be expected to result in 4 separate but interactive processes: vasospasm, thrombosis, platelet adhesion and cellular perforation. In order to evaluate these potential mechanisms, we again used the atherosclerotic rabbit model. After induction of iliac atherosclerosis and successful angioplasty, animals were maintained on a high cholesterol diet for 4 weeks at which point they underwent repeat angiography. Angiographic evidence of restenosis was documented in all animals. Histologic studies also confirmed restenosis with evidence of organized thrombus and cellular proliferation (Fig. 5).[15]

Further studies were undertaken to evaluate the potential role of vasospasm as a contributing factor. In separate groups of animals with angiographically documented lesions, nifedipine or placebo was randomly administered. Angioplasty was performed and the animals followed for 4 weeks. Repeat angiography showed no significant differences between groups. Likewise histologic examination also showed no significant difference.[16] These findings have been verified by randomized clinical trials.[17] While calcium antagonists may not play a role in preventing restenosis in most patients, clinical studies would suggest that they are important in patients with variant angina.[18]

Although the injury hypothesis of atherosclerosis, popularized by Ross and Glomset, is not presumed to be a primary mechanism of de novo atherosclerosis, it is highly likely that it plays a prominent role in angioplasty.[19] This hypothesis states that repeated vascular injury results in endothelial denudation with platelet adhesion, thrombus formation and monocyte infiltration, which can lead to smooth muscle cell proliferation, in part due to stimulatory effects of platelet derived growth factor. Subsequently increased uptake of cholesterol within arterial wall and formation of atherosclerosis can occur. As previously mentioned, animal studies have demonstrated deendothelialization of the vessel wall after PTCA with a dense platelet "carpet" laid down immediately after the procedure. We[20] have recently quantified platelet accumulation at various time frames after experimental angioplasty in the rabbit model using chromium-51-labelled platelets (Fig. 6). The degree of platelet accumulation at the angioplasty site was significant and nearly 10-fold greater than that reported with milder forms of vascular injury. Of note was that platelet adhesion occurred principally within the first 2 hours after angioplasty. The degree of platelet accumulation was directly related to the degree of vascular damage quantified histologically. Efforts to reduce this marked platelet deposition have been somewhat unrewarding as the usual platelet regimens are only partially effective. Studies from our laboratory have demonstrated that intravenous aspirin and a thromboxane synthetase inhibitor significantly reduced platelet accumulation 30 minutes after angioplasty while oral aspirin and heparin were not effective.[21] Longer term experimental studies have demonstrated that aspirin and dipyridamole as well as sulfinpyrazone significantly reduce the occurrence of restenosis as determined angiographically; however, neither drug regimen was completely successful as one-third to one-half of the animals showed some degree of restenosis.[22] Histologic correlates have also confirmed the benefit of these agents in that less neointimal proliferation, and thrombus formation, occurred (Fig. 7). While platelet accumulation and thrombus formation are prominent features of experimental studies, cellular proliferation appears to be the most common and consistent finding. Human autopsy studies, although scant, have also demonstrated fibrocellular proliferation. In a report by Essed et al,[23] histo-

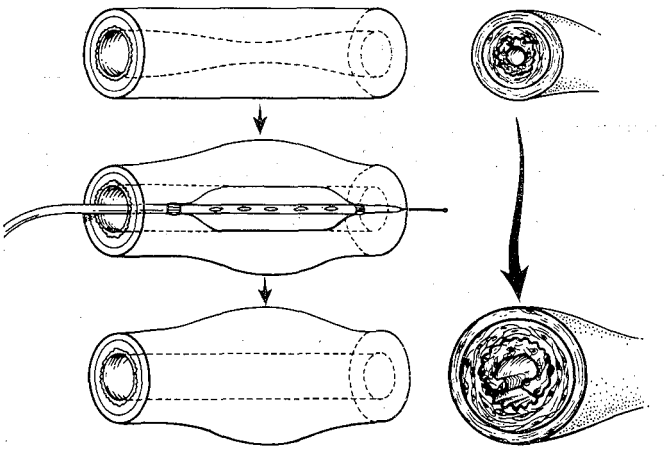

FIGURE 4. The mechanism of angioplasty appears to be vessel stretching with a fusiform dilatation at the angioplasty site. Neointimal fracture is a common consequence of this stretching process. Reproduced with permission from Circulation.[8]

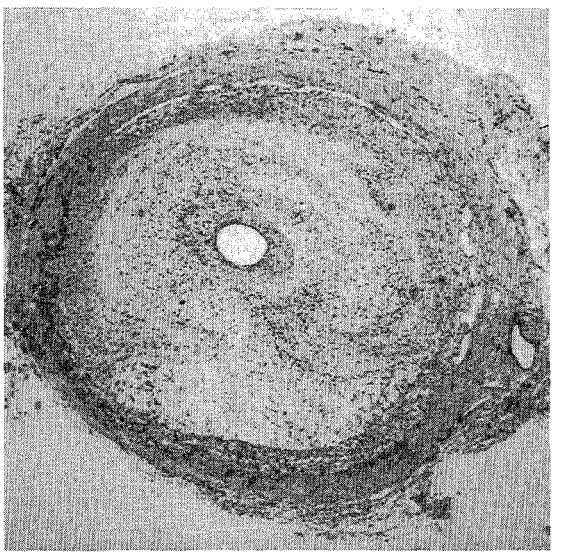

FIGURE 5. An example of restenosis showing marked neointimal proliferation with renarrowing of the lumen. Evidence of the original neointimal tear can be seen with a filling in of a new fibrocellular process. Reproduced with permission from Arteriosclerosis.[15]

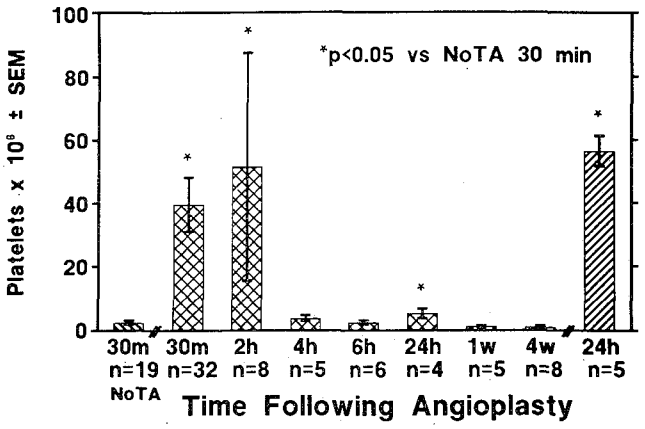

FIGURE 6. The time course of chromium-51 platelet aggregation after experimental angioplasty. Most platelet aggregation at the angioplasty site occurs within 2 hours. When compared with animals not receiving angioplasty (no TA), accumulation was 22 times greater.

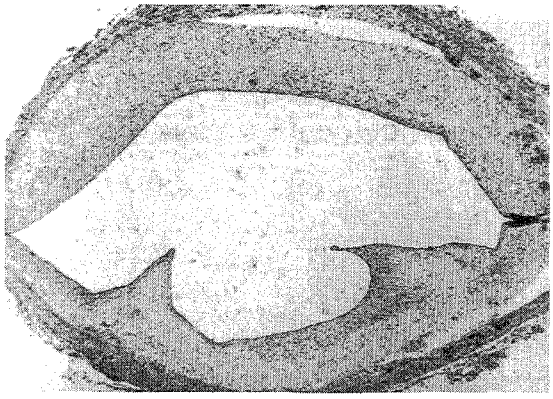

FIGURE 7. A histologic example of a sulfinpyrazone-treated animal 4 weeks after angioplasty shows no significant restenosis. The vessel wall also shows no evidence of neointimal tears.

logic studies of a patient who died 5 months after a left anterior descending PTCA demonstrated marked fibrocellular process with renarrowing of the vessel lumen. Reports by others[24,25] have also stressed the development of a fibrocellular process with histologic features that distinguish it from the underlying atherosclerosis.

Experimental studies from our laboratory in addition to human autopsy evidence strongly endorse the injury hypothesis as an important mechanism of restenosis. The evidence to date suggests that platelets may initiate this process. After vascular injury and removal of the endothelium, platelets adhere, aggregate and release vasoactive substances as well as platelet derived growth factor. Fibrin deposition with thrombus formation may also occur. Cellular proliferation stimulated in part by platelet derived growth factor or growth factors from other cellular elements such as monocytes seems likely. Our studies would suggest that the degree and type of vascular damage may be very important in the stimulation of restenosis. As we have shown, the degree of platelet aggregation is directly related to the degree of vascular damage. If greater platelet aggregation leads to a greater proliferative response as well as greater fibrin deposition, then the propensity for restenosis through either cellular proliferation or thrombus would be increased. This concept is supported by the observation that other forms of vascular damage such as the laser-heater probe causes less vascular damage and less restenosis than angioplasty in the same animal model.[26]

In summary, restenosis is a multifactoral process and while clinical, anatomical and procedural factors are important, it appears that the primary element is the response of the vascular wall to the acute injury. Prevention seems possible when platelet accumulation, thrombus formation and smooth cell proliferation can be inhibited through drug or mechanical means.

References

1. Dotter CT, Judkins MP. *Transluminal treatment of atherosclerotic obstruction: description of a new technique and a preliminary report of its application. Circulation 1964;30:654–670.*
2. Lee G, Ikeda RM, Joye JA, Bogren HG, DeMaria AM, Mason DT. *Evaluation of transluminal angioplasty of chronic coronary stenosis, value and limitations assessed in fresh human cadaver hearts. Circulation 1980;61:77–83.*
3. Baughman KL, Pasternak RC, Fallon JT, Block PC. *Transluminal coronary angioplasty of postmortem human hearts (abstr). Am J Cardiol 1981;48:1044.*
4. Casteneda-Zuniga WR, Formanek A, Tadavarthy M, Vlodavar Z, Edwards JE, Zollikofer C, Amplatz K. *The mechanism of balloon angioplasty. Radiology 1980;135:565–571.*
5. Pasternak RC, Baughman KL, Fallon JT, Block PC. *Scanning electron microscopy after coronary transluminal angioplasty of normal canine coronary arteries. Am J Cardiol 1980;45:591–597.*
6. Faxon DP, Weber VJ, Haudenschild CC, Gottsman SB, McGovern WA, Ryan TJ. *Acute effects of transluminal angioplasty in three experimental models of atherosclerosis. Atherosclerosis 1982;2:125–133.*
7. Block PC, Baughman KL, Pasternak RC, Fallon JT. *Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. Circulation 1980;61:778–785.*
8. Sanborn TA, Faxon DP, Haudenschild CC, Gottsman SB, Ryan TJ. *The mechanism of transluminal angioplasty: evidence for aneurysm formation in experimental atherosclerosis. Circulation 1983;68:1136–1140.*
9. Sanborn TA, Faxon DP, Waugh D, Small DM, Haudenschild CC, Gottsman SB, Ryan TJ. *Transluminal angioplasty in experimental atherosclerosis: analysis for embolization using an in vivo perfusion system. Circulation 1982; 66:917–922.*
10. Block PC, Myler RK, Stertzer S, Fallon JT. *Morphology after transluminal angioplasty in human beings. N Engl J Med 1981;382–386.*
11. Waller BF, McManus BM, Garfinkel HJ, Kishel JC, Schmidt EC, Kent KM, Roberts WC. *Status of the major epicardial coronary arteries 80 to 150 days after percutaneous transluminal coronary angioplasty. Analysis of 3 necropsy patients. Am J Cardiol 1983;51:81.*
12. Faxon DP. *Pathophysiologic considerations of transluminal coronary angioplasty. In: Jang GD, ed. Angioplasty. New York: McGraw-Hill, 1986:409–416.*
13. Baim DS, Faxon DP. *Coronary angioplasty. In: Grossman W, ed. Cardiac Catheterization and Angiography. Philadelphia: Lea & Febiger, 1986:473–492.*
14. Meier B, King SB, Gruentzig AR, Douglas JS, Hullman J, Ischinger T, Galan K, Tankersley R. *Repeat coronary angioplasty. JACC 1984;4:463–466.*
15. Faxon DP, Sanborn TA, Weber VJ, Haudenschild CC, Gottsman SB, McGaem WA, Ryan TJ. *Restenosis following transluminal angioplasty in experimental atherosclerosis. Arteriosclerosis 1984;4:189–195.*
16. Faxon DP, Sanborn TA, Haudenschild CC, Gottsman SB, Ryan TJ. *The effect of nifedipine on restenosis following experimental angioplasty (abstr). Circulation 1984;70:II-175.*
17. Corcus T, David PR, Val PG, Renlan J, Pangoisse U, Rapold HG, Bourassa MG. *Failure of diltiazem to prevent restenosis after percutaneous transluminal coronary angioplasty. Am Heart J 1985;109:926–931.*
18. David PR, Waters DD, Scholl JM, Crepeau J, Ezlachcic J, Lesperance J, Huden G, Bourassa MG. *Percutaneous transluminal coronary angioplasty in patients with variant angina. Circulation 1985;66:695.*
19. Ross R. *Atherosclerosis: a problem of the biology of arterial wall cells and their interactions with blood components. Arteriosclerosis 1981;1:293–311.*
20. Wilentz JR, Sanborn TA, Haudenschild CC, Valeri CR, Ryan TJ, Faxon DP. *Platelet accumulation in experimental angioplasty: time course and relation to vascular damage. Circulation 1987;75:636–642.*
21. Sanborn TA, Ballelli LM, Faxon DP, Haudenschild CC, Valari R, Ryan TJ. *Inhibition of 51Cr-labeled platelet accumulation after balloon angioplasty in*

rabbits: comparison of heparin, aspirin, and CGS13080, a selective thromboxane synthetase inhibitor (abstr). JACC 1986;7:213A.

22. Faxon DP, Sanborn TA, Haudenschild CC, Ryan TJ. *Effect of antiplatelet drugs on restenosis following experimental angioplasty. Am J Cardiol 1984; 53:72C–76C.*

23. Essed CE, Van den Brand M, Becker AE. *Transluminal coronary angioplasty and early restenosis: fibrocellular occlusion after wall laceration. Br Heart J 1983;49:383.*

24. Waller BF. *Early and late morphologic changes in human coronary arteries after percutaneous transluminal coronary angioplasty. Clin Cardiol 1983;6:363–372.*

25. Austin GE, Ratlitt NB, Hollman J, Tabel S, Phillips DF. *Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. JACC 1985;6: 369–375.*

26. Sanborn TA, Haudenschild CC, Garber GR, Ryan TJ, Faxon DP. *Angiographic and histologic consequences of laser thermal angioplasty: comparison with balloon angioplasty. Circulation 1987;75:1281–1286.*