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Author(s): David S. Jones

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Visions of a Cure

Visualization, Clinical Trials, and Controversies in Cardiac Therapeutics, 1968–1998

By *David S. Jones**

ABSTRACT

In the early 1970s physicians engaged in fierce debates over the most appropriate method of evaluating the efficacy of coronary artery bypass grafting (CABG). With millions of patients and billions of dollars at stake, CABG sparked fierce controversy. Skeptics demanded that randomized controlled trials (RCTs) be performed, while enthusiasts argued that they already had visual proof of CABG's efficacy. When RCTs appeared, they did not settle the controversy. Participants simply reasserted their preconceptions, defending a trial's strengths or exploiting its flaws. The debate centered on standards of knowledge for the evaluation of therapeutic efficacy. Specifically, cardiologists and cardiac surgeons struggled to assess the relevance of different measures of therapeutic success: physiological or clinical, visual or statistical. Many factors contributed to participants' decisions, including disciplinary affiliation, traditions of research, personal experience with angiography, and assessments of the history of cardiac therapeutics. Physicians had to decide whether angiography provided a meaningful representation of the disease and its treatment or whether demonstrations of therapeutic success could come only from long-term statistical evaluation of mortality data.

IN THE EARLY 1970s physicians struggled to determine the efficacy of coronary artery bypass grafting (CABG), a new surgical treatment for coronary artery disease. The debate polarized both cardiology and cardiac surgery. Some surgeons believed that the efficacy of CABG could be shown only "by a large-scale, prospective randomized study of a homogenous group of patients with a definable syndrome of symptomatic coronary artery disease." The cardiologist Eugene Braunwald argued that such randomized clinical

* Department of the History of Science, Science Center 235, Harvard University, Cambridge, Massachusetts 02138.

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trials (RCTs) had to be done before CABG, like a genie escaped from its bottle, became an uncontrollable force. Others, such as the pioneering cardiac surgeon Michael DeBakey, disagreed: “The insistence on the use of prospective randomized studies for the evaluation of surgical diagnostic and therapeutic techniques reflects a naive obsession with this research tool.” René Favaloro, the “father” of CABG, warned against the “almost religious sanctification” of the ideology of RCTs: “If relied on exclusively they may be dangerous.”¹

How could RCTs—a research methodology—be dangerous?² Powerful forces converged in the debates over the RCTs of CABG. This was a battle over fundamental questions of medical epistemology, a battle over the production of medical knowledge. In the 1960s RCTs had been established as the gold standard for evaluating the efficacy of new treatments. In theory, they would replace traditional, biased methods of evaluation, including both retrospective cases series and the vagaries of individual physicians’ clinical judgments. As CABG spread in the 1970s, many cardiologists and cardiac surgeons argued that only an RCT could prove its value. Against them stood the advocates of CABG, who argued that the physiological logic and the immediate, visible results of the operation proved, to them and to their patients, that the surgery had been a success. Underlying their hostility to RCTs was faith in the power of visualization. RCTs typically use statistical evidence of decreased mortality to demonstrate the efficacy of a therapy. But in the context of a model of coronary artery disease that identified the pathology as obstructed blood flow, there was an alternative method for demonstrating efficacy: visualization of restored blood flow, through the technique of coronary angiography.

Thus protagonists in the debate had to make choices about the relationships between definitions of a disease and definitions of a cure, about the comparative value of statistical and visual evidence. Did relief of symptoms, restoration of blood flow, or improved survival most meaningfully represent a successful treatment? Compelling arguments could be made for each case. This opened a space for judgment and preconception, grounded in tensions between cardiology and cardiac surgery, tensions within cardiology over the value of physiological and clinical research, and personal experiences with the reliability of angiography. Faith in angiography proved to be crucial, determining not only judgments about the relevance of visual evidence of revascularization but also physicians’ assessments of the legacy of past, failed treatments of coronary artery disease. Skeptics, citing the recurring cycle of therapeutic enthusiasm and disillusionment, demanded that the burden of proof for CABG be set very high. Enthusiasts, citing the ability of angiography to provide accurate diagnosis and postoperative assessment, argued that CABG deserved the benefit of the doubt.

The epistemological debates did not occur in a vacuum. The controversy over RCTs for

¹ Herbert N. Hultgren, Timothy Takaro, Noble Fowler, and Elizabeth G. Wright, “Evaluation of Surgery in Angina Pectoris,” *American Journal of Medicine*, 1974, 56:1–3, on p. 2; Eugene Braunwald, “Direct Coronary Revascularization . . . A Plea Not to Let the Genie Escape from the Bottle,” *Hospital Practice*, 1971, 6:9–10, on p. 9; Michael E. DeBakey and Gerald M. Lawrie, “Aortocoronary-Artery Bypass,” *Journal of the American Medical Association*, 1978, 239:837–839, on p. 838; and René G. Favaloro, “Critical Analysis of Coronary Artery Bypass Graft Surgery: A Thirty-Year Journey,” *Journal of the American College of Cardiology*, 1998, 31(4 [Suppl. B]):1B–63B, on pp. 37B–38B. The operation has been known by many names: direct myocardial revascularization, saphenous vein autograph replacement, coronary artery bypass surgery, and many variations on these themes. I use coronary artery bypass grafting (the current usage) throughout.

² This episode was an opening salvo in a continuing debate between advocates of RCTs (whose view is now embodied in the outcomes movement of evidence-based medicine) and those who see such probabilistic methods as a threat to physician knowledge, judgment, and authority. See Sandra J. Tanenbaum, “Evidence and Expertise: The Challenge of the Outcomes Movement to Medical Professionalism,” *Academic Medicine*, 1999, 74:757–763.

CABG was also a battle for professional authority and financial resources. After all, CABG had the potential to transform the treatment of coronary artery disease, one of the most prevalent diseases in the United States and the leading cause of death.³ Uncertainty about its ability to increase the life expectancy of its recipients had enormous stakes: CABG involved millions of patients and billions of dollars. Powerful groups—cardiologists, cardiac surgeons, patients, and insurers—all had interests in the process of evaluating the efficacy of the operation. Moreover, these concerns have not been confined to CABG in the 1970s. Instead, the tensions between visual and statistical evidence reemerged in cardiology and cardiac surgery during debates over the efficacy of angioplasty, minimally invasive bypass surgery, and gene therapy. This is not to imply that cardiac therapeutics has been plagued by hostile confrontation. Instead, as Peter Galison's notion of the disunity of science would suggest, there has been a productive tension between competing traditions of therapeutic evaluation.

TRIALS' TRIBULATIONS

Since the pioneering work of Bruno Latour, analysis of knowledge production has been a major interest in social studies of science. One leading area of investigation has been randomized controlled trials (RCTs). In an RCT, clinical investigators evaluate the efficacy of a new treatment by randomly assigning patients to receive either the new treatment or the existing, established treatment. Ideally, the trial is double-blinded: neither the patients nor the researchers know which treatment a patient received until after the results have been analyzed. Done properly, RCTs can provide unbiased results. This contrasts to traditional methods of clinical evaluation, such as retrospective case series, in which researchers compare the results of a new treatment against existing results with the old treatment. For medical researchers, RCTs have become the route to objective, rigorous knowledge of therapeutic efficacy. For historians, they are a crucial window into the practices and values of modern medicine.

As Harry Marks notes, RCTs emerged during the contingencies of antibiotic research during World War II. By 1970 the Food and Drug Administration required evidence not only of drug safety but also of efficacy, acquired through "well-controlled investigations" with "appropriate statistical methods." This requirement had been implemented as the expectation of double-blind testing and RCTs. Researchers hoped that RCTs would "neutralize the investigators' belief about the value of novel therapies" and create an "impersonal standard of scientific integrity."⁴

However, RCTs have not fulfilled these high expectations. As early as the mid 1970s, Marks and other observers of medicine became fascinated by the failure of RCTs to resolve therapeutic uncertainty. They have analyzed the failure of RCTs to change the conventional

³ In 1968, diseases of the heart were the leading cause of death in the United States, responsible for 38.6 percent (1,040,292) of all deaths; 65 percent of these deaths were from ischemic heart disease: U.S. Department of Health and Human Services, *Vital Statistics of the United States, 1968*, Vol. 2: *Mortality* (Hyattsville, Md.: Center for Health Statistics, 1972), Tables 1-5, 1-26.

⁴ Harry Marks, *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900–1990* (Cambridge: Cambridge Univ. Press, 1997), pp. 126, 3, 144. On the requirements of the Food and Drug Administration see Henk J. H. W. Bodewitz, Henk Buurma, and Gerard H. de Vries, "Regulatory Science and the Social Management of Trust in Medicine," in *The Social Construction of Technological Systems*, ed. Wiebe E. Bijker, Thomas P. Hughes, and Trevor J. Pinch (Cambridge, Mass.: MIT Press, 1987), pp. 243–259, on pp. 252–253; Marks, *Progress of Experiment*, pp. 11, 129, 133; and Steven Epstein, *Impure Science: AIDS, Activism, and the Politics of Knowledge* (Berkeley: Univ. California Press, 1996), pp. 185, 196.

wisdom about the value of low-fat diets, the refusal of researchers to pursue RCTs of vitamin C as a treatment for cancer, and the ability of politically empowered research populations to shape the conduct of RCTs for treatments of AIDS. RCTs are not an uncomplicated, objective technique but a social and political process, “the product of a negotiated social order.” They “cannot be pried apart from the vested interests and social objectives which they embody.” RCTs have such “interpretative flexibility” that, “rather than settling controversies, [they] may instead reflect and propel them.” In sum, they are part of broader processes of the “social management of trust.”⁵

The debates over CABG provide an opportunity to extend this analysis of RCTs to the field of surgery, where their role has been fiercely contested. RCTs of CABG have already attracted some analysis, as examples of the process of therapeutic evaluation, of the success of this process, and of obstacles to this process. For instance, Jochen Schaefer has argued that by the time surgeons had perfected CABG enough to allow a meaningful RCT, the “cardiological and cardiosurgical industry” was too committed to the procedure to perform such an “exact and critical analysis of its own work.” These analyses leave crucial questions unanswered. An examination of the debates that followed the early RCTs of CABG shows that concerns with the technical details of the trials were far less important than the preconceptions held by protagonists.⁶ The presence of a substantial debate before the RCTs were published allows an analysis of the origins of these preconceptions. This essay will explain these preconceptions and trace their impact on the ensuing debates. It will show how disciplinary tensions, disciplinary histories, and traditions of physiological and clinical research all shaped the evaluation of cardiac therapeutics. It will demonstrate how visual validation of CABG provided an alternative to the statistical ideal of RCTs.

NOTORIOUS TREATMENTS OF CORONARY ARTERY DISEASE

To understand the ferocity of the debates that surrounded coronary artery bypass surgery, it is necessary to appreciate the magnitude of the problem surgeons sought to treat. During the 1970s coronary artery disease (also known as ischemic heart disease) affected millions of people in the United States. By various estimates, it killed over 600,000 people each year, incapacitating another 3.5 to 5.0 million people. Leading cardiologists, such as Harvard Medical School’s Eugene Braunwald, considered coronary artery disease “to be the greatest scourge of Western man.” Its burden of suffering, disability, and deaths “dwarfs all of the other critical problems that face us in this turbulent era.” Donald Effler, the chief

⁵ Marks, *Progress of Experiment*, pp. 8, 240, 134 (“negotiated social order”); Evelleen Richards, “The Politics of Therapeutic Evaluation: The Vitamin C and Cancer Controversy,” *Social Studies of Science*, 1988, 18:653–701, on p. 685 (“vested interests and social objectives”) (see also Richards, *Vitamin C and Cancer: Medicine or Politics?* [London: Macmillan, 1991], pp. 216–217); Epstein, *Impure Science*, p. 33 (“interpretative flexibility”); Steven Epstein, “Activism, Drug Regulation, and the Politics of Therapeutic Evaluation in the AIDS Era,” *Soc. Stud. Sci.*, 1997, 27:691–726, on p. 716 (relation to controversies); and Bodewitz *et al.*, “Regulatory Science and the Social Management of Trust,” p. 257.

⁶ Jochen Schaefer, “The Case against Coronary Artery Surgery: A Paradigm for Studying the Nature of a So-Called Scientific Controversy in the Field of Cardiology,” *Metamedicine*, 1980, 1:155–176, on p. 162. On the process see John B. McKinlay, “From ‘Promising Report’ to ‘Standard Procedure’: Seven Stages in the Career of a Medical Innovation,” *Millbank Memorial Fund Quarterly*, 1981, 59:233–270, esp. p. 250; on its successes see J. C. Baldwin, M. J. Reardon, and R. J. Bing, “Coronary Artery Surgery,” in *Cardiology: The Evolution of the Science and the Art*, ed. Bing, 2nd ed. (New Brunswick, N.J.: Rutgers Univ. Press, 1999), pp. 166–182, esp. pp. 160–161; on its obstacles see Walsh McDermott, “Evaluating the Physician and His Technology,” *Daedalus*, Winter 1977, pp. 135–157, esp. p. 151. Marks and Epstein have addressed the impact of preconceptions in their own studies: Marks, *Progress of Experiment*, pp. 193–194; and Epstein, *Impure Science*, p. 343.

of cardiac surgery at the Cleveland Clinic, emphasized how coronary artery disease struck down “the most active and responsible” members of society: it was “so common among professional people, executives and men in public office” that it could “cripple the nation.” It was “so prevalent and ominous that heroic measures to deal with it seem not only appropriate but essential.”⁷

Unfortunately, through the 1960s doctors had found no satisfactory treatments. The work of James Herrick in the early twentieth century had provided a simple model for coronary artery disease.⁸ The coronary arteries supply blood flow to the muscles of the heart (see Figure 1). If flow through these vessels is obstructed, by atherosclerosis or spasm, the demand of the muscle for oxygenated blood exceeds the supply. This imbalance initially produces angina pectoris, “the wailing of an anguished heart during that period of stress when it is getting inadequate perfusion.” If the imbalance is severe enough the muscle cells start to die, producing a myocardial infarction, or heart attack.⁹

With this understanding of coronary artery disease, physicians recognized two treatment strategies: increase the supply of blood or reduce the demand for it. Many creative techniques had been tried along both lines.¹⁰ Early efforts to reduce demand, such as operations in the 1930s to remove the thyroid gland to slow the heart’s rhythm, were abandoned because of unacceptable complications. Efforts to increase supply showed more promise. Sympathectomy, first performed in 1916, cut the sympathetic nerves to dilate coronary arteries. While it did not actually improve blood flow, it inadvertently eased the symptoms of angina by interrupting sensory transmission from the heart. In the 1930s the Cleveland Clinic surgeon Claude Beck developed many techniques to provide alternative blood supplies for the heart. He connected a variety of noncardiac tissues—including pericardium, fat, muscle, skin, lung, omentum, stomach, intestines, liver, and spleen—to the heart, hoping that blood would flow from the donor tissue to the cardiac muscle. Other researchers

⁷ Braunwald, “Direct Coronary Revascularization” (cit. n. 1), p. 9; and Donald B. Effler, “Surgery for Coronary Disease,” *Scientific American*, Oct. 1968, 210:36–43, on p. 43. For the figures see note 3, above. See also F. C. Spencer, O. W. Isom, E. Glassman, A. D. Boyd, R. M. Engelman, G. E. Reed, B. S. Pasternak, and J. M. Dembrow, “The Long-Term Influence of Coronary Bypass Grafts on Myocardial Infarction and Survival,” *Annals of Surgery*, 1974, 180:439–451, esp. p. 451; and Effler, “Surgery for Coronary Disease,” p. 36.

⁸ Christopher Lawrence, “Moderns and Ancients: The ‘New Cardiology’ in Britain, 1880–1930,” in *The Emergence of Modern Cardiology*, ed. W. F. Bynum, Lawrence, and Vivian Nutton (London: Wellcome Institute for the History of Medicine, 1985), pp. 1–33, esp. pp. 26–27; Joel D. Howell, “Concepts of Heart-Related Diseases,” in *The Cambridge World History of Disease*, ed. Kenneth F. Kiple (Cambridge: Cambridge Univ. Press, 1993), pp. 91–102, on p. 91; Robert A. Aronowitz, “From the Patient’s Angina to the Cardiologist’s Coronary Heart Disease,” in *Making Sense of Illness: Science, Society, and Disease* (Cambridge: Cambridge Univ. Press, 1998), pp. 84–110; R. J. Bing, “Arteriosclerosis,” in *Cardiology*, ed. Bing (cit. n. 6), pp. 118–132; and O. Paul and Bing, “Coronary Artery Disease,” *ibid.*, pp. 133–153.

⁹ René G. Favaloro, Donald B. Effler, Laurence K. Groves, F. Mason Sones, and David J. G. Ferguson, “Myocardial Revascularization by Internal Mammary Artery Implant Procedures: Clinical Experience,” *Journal of Thoracic and Cardiovascular Surgery*, 1967, 54:359–370, on p. 370. On coronary artery disease more generally see Michael Lesch, Richard S. Ross, and Eugene Braunwald, “Ischemic Heart Disease,” in *Harrison’s Principles of Internal Medicine*, 8th ed., ed. George W. Thorn, Raymond D. Adams, Braunwald, Kurt J. Isselbacher, and Robert G. Petersdorf (New York: McGraw-Hill, 1977), pp. 1261–1271, on pp. 1264, 1262; and Effler, “Surgery for Coronary Disease” (cit. n. 7), p. 36.

¹⁰ J. Hilario Murray, R. Porcheron, and W. Roschlau, “Surgery of Coronary Heart Disease,” *Angiology*, 1953, 4:526–530; John H. Vansant and William H. Muller, “Surgical Procedures to Revascularize the Heart: A Review of the Literature,” *Circulation*, 1960, 100:572–578; David C. Sabiston, “Role of Surgery in the Management of Myocardial Ischemia,” *Modern Concepts of Cardiovascular Disease*, 1966, 35:123–127, esp. p. 123; Herbert N. Hultgren and Edward J. Hurley, “Surgery in Obstructive Coronary Artery Disease,” *Advances in Internal Medicine*, 1968, 14:107–150, esp. pp. 107–108; Norman V. Richards, *Heart to Heart: A Cleveland Clinic Guide to Understanding Heart Disease and Open Heart Surgery* (New York: Atheneum, 1987), p. 107; and Baldwin et al., “Coronary Artery Surgery” (cit. n. 6), pp. 154–157.

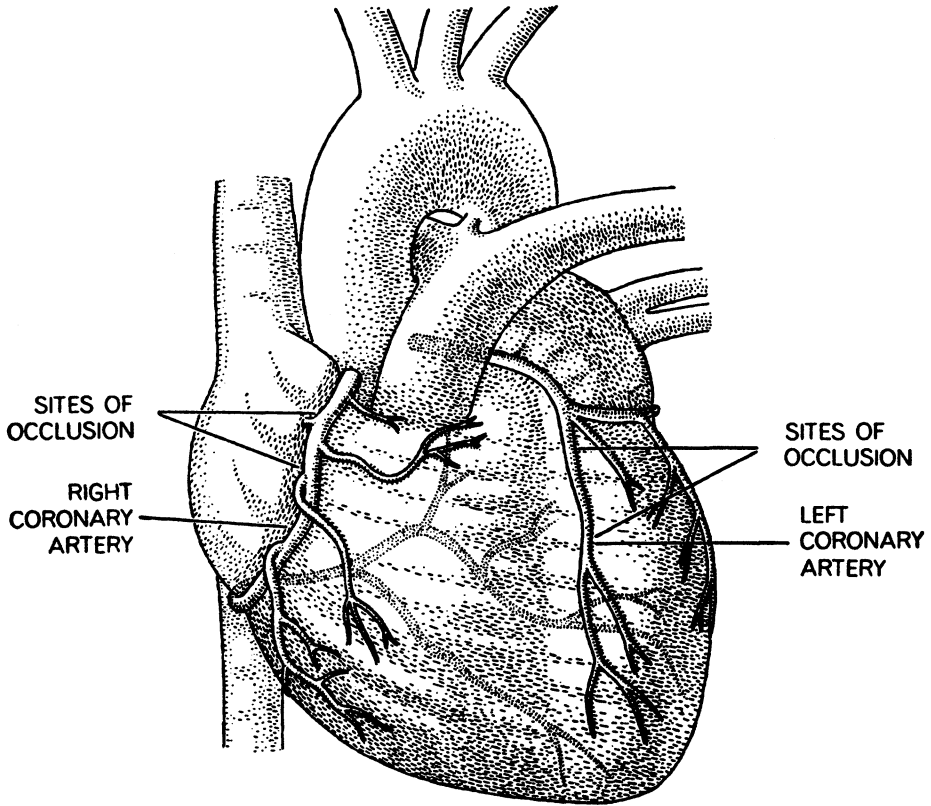


Figure 1. *The heart and its coronary arteries. Reprinted with permission from the estate of Eric Mose. (From Donald B. Effler, "Surgery for Coronary Disease," Scientific American, October 1968, 210:36–43, on page 38.)*

attempted direct manipulation of blood vessels. In 1939 Italian surgeons claimed to increase coronary blood flow by ligating (tying off) the internal mammary artery, a vessel that carries blood to the rib cage. In 1946 the Quebec surgeon Arthur Vineberg began to implant the cut end of arteries—the subclavian, intercostal, carotid, or splenic—directly into the wall of the heart. Meanwhile, Beck connected the coronary veins to the aorta, reversing their flow of blood, turning veins into arteries to bring new blood to heart. Across this range of techniques, surgeons typically reported success—relief of pain and ability to return to work—in 80 to 90 percent of patients.

Evaluation of these new techniques was complicated by the elusive nature of angina pectoris. Observers had long recognized that “symptoms of cardiac ischemia may come and go in a random fashion, seemingly unrelated to therapeutic interventions.” As a result, skeptics argued that relief of angina did not equal therapeutic success: “the notorious unreliability of such data should preclude any important inferences.” Even surgeons agreed: “Relief of angina pectoris by an operative procedure is not a certain index of surgical success.” Long experience had also taught physicians that angina was remarkably susceptible to placebo effects. In a classic study, Henry Beecher showed that angina—

and many other symptoms—responded to irrelevant treatments, consistently improving in 35.2 percent of patients.¹¹

Placebo effects of surgery had been strikingly demonstrated in the case of internal mammary artery ligation. Many observers, noting that the internal mammary artery had no connections to the heart, could not believe surgeons' claims of success. Two groups conducted controlled studies in which thirty-five unwitting patients were assigned to receive either ligation or a sham operation. Remarkably, patients in both groups reported increased exercise tolerance and reduced need for pain-relieving medication. Struggling to explain this dramatic demonstration of the power of surgical placebos, the researchers credited the many aspects of cardiac surgery that contributed to the perceived effects: "The frightened, poorly informed man with angina, winding himself tighter and tighter, sensitizing himself to every twinge of chest discomfort, who then comes into the environment of a great medical center and a powerful positive personality and sees and hears the results to be anticipated from the suggested therapy is not the same total patient who leaves the institution with the trademark scar."¹²

By the late 1960s these experiences had left physicians frustrated. New drugs showed promise for reducing cardiac oxygen consumption, but the cardiologists Edward Orgain and Henry McIntosh feared that these would fail because of complications that included heart failure, shock, and death. Cardiologists frequently confessed their impotence. For instance, in 1972 David Spodick, from Tufts University School of Medicine, concluded that medical management "had failed." Surgeons were quick to criticize, with Donald Effler characterizing cardiologists' efforts as "not terribly impressive, either to the patient or to the cardiac surgeon." But surgeons themselves had little to celebrate. Effler admitted that by the early 1960s coronary artery surgery had fallen into "virtual disrepute": "papers on this subject were viewed with frank skepticism and the authors looked upon with suspicion." The cardiologist Mason Sones saw promise in Effler's work but nonetheless chastised his surgical colleagues: "Gentleman, I suggest you surgeons get with it!"¹³

¹¹ Irwin J. Schatz, "Commentary on 1971 Reflection of 1970 Statistics," *Chest*, 1972, 61:477–479, on p. 478; Favaloro *et al.*, "Myocardial Revascularization by Internal Mammary Artery Implant Procedures" (cit. n. 9), p. 367 (surgeons' view); and Henry K. Beecher, "The Powerful Placebo," *J. Amer. Med. Assoc.*, 1955, 199:1602–1606, on p. 1606.

¹² E. Grey Dimond, C. Frederick Kittle, and James E. Crockett, "Comparison of Internal Mammary Artery Ligation and Sham Operation for Angina Pectoris," *American Journal of Cardiology*, 1960, 5:483–486, on p. 486. On placebo effects of internal mammary artery ligation see Henry K. Beecher, "Surgery as Placebo: A Quantitative Study of Bias," *J. Amer. Med. Assoc.*, 1961, 176:1102–1107; and Ernest M. Barsamian, "The Rise and Fall of Internal Mammary Artery Ligation in the Treatment of Angina Pectoris and the Lessons Learned," in *Costs, Risks, and Benefits of Surgery*, ed. John P. Bunker, Benjamin A. Barnes, and Frederick Mosteller (New York: Oxford Univ. Press, 1977), pp. 213–220. For the controlled studies see Leonard A. Cobb, George I. Thomas, David D. Dillard, K. Alvin Merendino, and Robert A. Bruce, "An Evaluation of Internal-Mammary-Artery Ligation by a Double-Blind Technique," *New England Journal of Medicine*, 1959, 260:1115–1118; and Dimond *et al.*, "Comparison of Internal Mammary Artery Ligation and Sham Operation for Angina Pectoris."

¹³ Edward S. Orgain and Harry D. McIntosh, "Editorial: Coronary Artery Disease: Physiological Aspects and Surgical Therapy," *Circulation*, 1967, 35:1–2, on p. 2; David H. Spodick, "Letter: Surgery in Coronary Artery Disease—I," *Amer. J. Cardiol.*, 1972, 29:581–582, on p. 582; Favaloro *et al.*, "Myocardial Revascularization by Internal Mammary Artery Implant Procedures" (cit. n. 9), p. 370 (quoting Effler, "not terribly impressive"); Donald B. Effler, Laurence K. Groves, F. Mason Sones, and Earl K. Shirey, "Increased Myocardial Perfusion by Internal Mammary Artery Implant: Vineberg's Operation," *Ann. Surg.*, 1963, 158:526–536, on p. 526 ("virtual disrepute") (see also W. Bruce Fye, *American Cardiology: The History of a Specialty and Its College* [Baltimore: Johns Hopkins Univ. Press, 1996], p. 257); René G. Favaloro, Effler, Groves, Mehdi Razavi, and Tail Lieberman, "Combined Simultaneous Procedures in the Surgical Treatment of Coronary Artery Disease," *Annals of Thoracic Surgery*, 1969, 8:20–29, on p. 29 (skepticism and suspicion); and Sones, quoted in Effler, Sones, Favaloro, and Groves, "Coronary Endarterectomy with Patch-Graft Reconstruction," *Ann. Surg.*, 1965, 162:590–601, on p. 601.

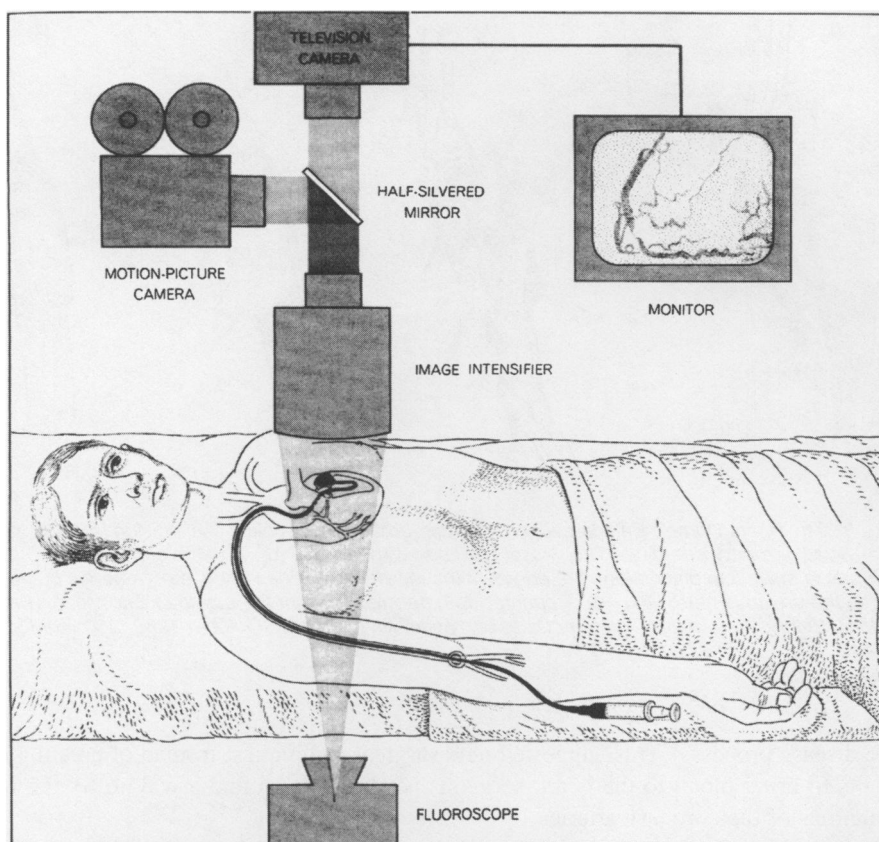


Figure 2. "Visual diagnosis of coronary artery disease." Angiography uses a flexible catheter, threaded through a peripheral vein and into a coronary artery, to inject a radio-opaque dye, which is then visualized with fluoroscopy. The technique "makes possible diagnosis with an unprecedented degree of accuracy." Reprinted with permission from the estate of Eric Mose. (From Donald B. Effler, "Surgery for Coronary Disease," *Scientific American*, October 1968, 210:36-43, on page 39.)

THE ORIGIN AND SPREAD OF CORONARY ARTERY BYPASS GRAFTING

The situation changed dramatically in 1968, when a Cleveland Clinic team led by René Favaloro published their first report about coronary artery bypass grafting. Their enthusiasm quickly spread among physicians and patients, transforming the treatment of ischemic heart disease.

The Cleveland Clinic story began in 1958, with Mason Sones's accidental discovery of selective coronary arteriography (angiography). This technique, which used a catheter to inject contrast dye into coronary arteries, gave cardiologists their first opportunity to visualize these arteries, and their obstructions, in a living patient (see Figure 2). Visualization transformed their understanding of coronary artery disease. Instead of seeing the expected diffuse obstructions from coronary atherosclerosis, Sones found "remarkable localization"

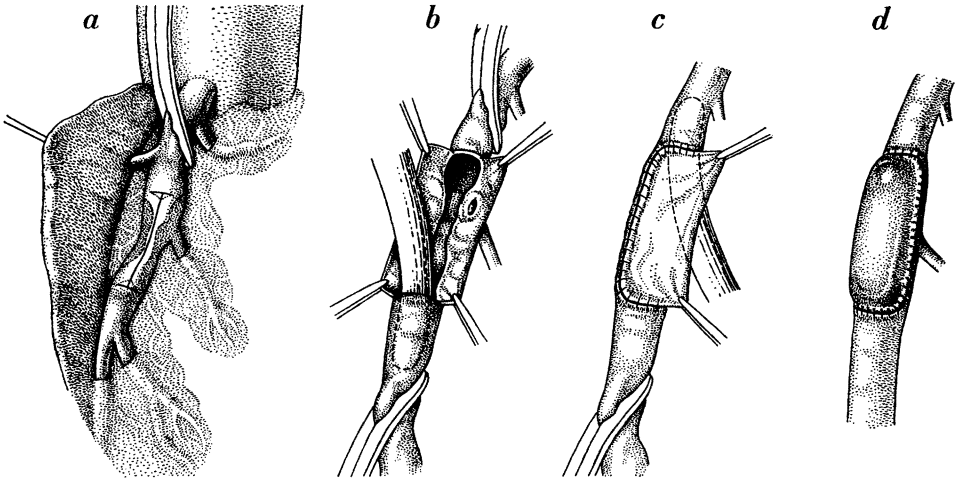


Figure 3. The "Vista Dome": Effler's pericardial patch-graft reconstruction. An incision is made into the narrowed coronary artery (a). The vessel is dilated with a probe (b). A patch of pericardial membrane is sewn into place along the edges of the incision (c). When complete, "a gentle bulge replaces the previous narrowing" (d). Reprinted with permission from the estate of Eric Mose. (From Donald B. Effler, "Surgery for Coronary Disease," *Scientific American*, October 1968, 210:36–43, on page 41.)

of the disease process.¹⁴ This suggested new surgical techniques: instead of creating new conduits to bring blood to the heart, surgeons needed only to find a way to fix the focal obstructions of the coronary arteries.

Effler and his team first tried endarterectomy, removing the obstructing plaque from the coronary artery. They abandoned this technique when they realized that fragments broke off the plaque and produced new obstructions further along the arterial tree. In 1962 Effler attempted a new operation: he left the plaque in place but used a patch of pericardium to expand the diameter of the coronary artery. This procedure, named the "Vista Dome" for its resemblance to the passenger cars of railroads, allowed blood to flow past the obstruction (see Figure 3). The operation, a "direct, surgical attack," provided "instant revascularization." Combining this direct approach with Vineberg's internal mammary artery implants allowed Effler's team to treat patients who had both focal and diffuse obstructions. Earlier beliefs that only a limited set of patients could benefit from surgery were "restrictive and unimaginative"; surgery could be "applicable to a rather wide group of coronary artery problems."¹⁵ The future seemed full of promise.

¹⁴ Claude Bernard first performed cardiac catheterization in an animal. Werner Forssmann performed the first human catheterization, on himself, in 1929. During the 1940s Richard Bing used catheterization of the coronary sinus to study cardiac metabolism and a group in Sweden performed nonselective coronary angiography (visualizing the coronary arteries with the aorta). Sones inadvertently performed the first selective coronary angiography in 1958 when the tip of his ventricular catheter slipped into a coronary artery. See D. Baim and R. J. Bing, "Cardiac Catheterization," in *Cardiology*, ed. Bing (cit. n. 6), pp. 1–15. The "remarkable localization" found by Sones is reported in Effler *et al.*, "Coronary Endarterotomy with Patch-Graft Reconstruction," p. 590.

¹⁵ On the problems with coronary endarterotomy see Effler, "Surgery for Coronary Disease" (cit. n. 7), p. 42. On the "Vista Dome" see Donald B. Effler, Laurence K. Groves, Ernesto L. Suarez, and René G. Favaloro, "Direct Coronary Artery Surgery with Endarterotomy and Patch-Graft Reconstruction," *J. Thorac. Cardiovasc. Surg.*, 1967, 53:93–101, on p. 99; and John E. Connolly, "The History of Coronary Artery Surgery," *ibid.*, 1978,



Figure 4. René Favaloro in the operating room, Cleveland Clinic, circa 1970. Reprinted with permission from the Cleveland Clinic Archives.

In this setting René Favaloro began his work at the Cleveland Clinic (see Figure 4). Favaloro had been a general surgeon in rural Argentina when, in 1962, he committed himself to becoming a heart surgeon and flew to Cleveland with only a letter of introduction. He arrived soon after Effler's first successful patch-graft repair and Sones's demonstration of blood flow through Vineberg implants. Although he shared in the excitement of Effler's early successes, Favaloro was not satisfied with the existing techniques. Impressed by the work of vascular surgeons, who used vein grafts to bypass obstructions in renal arteries, he adapted the bypass technique for the heart (see Figure 5). Favaloro's

76:733–744, on p. 739. See also Effler, "Surgical Treatment of Myocardial Ischemia," *Clinical Symposia*, 1969, 21:3–17, on p. 6 ("instant revascularization"); and Effler *et al.*, "Coronary Endarterectomy with Patch-Graft Reconstruction," p. 591.

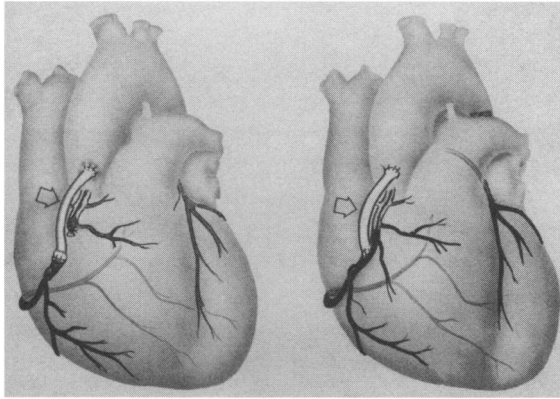


Figure 5. Favaloro's technique of saphenous vein bypass grafting (CABG), using a piece of saphenous vein as a conduit between the aorta and the right coronary artery: end-to-end anastomosis (left) and end-to-side anastomosis (right). Reprinted with permission from Mosby, Inc. (From Donald B. Effler, René G. Favaloro, and Laurence K. Groves, "Coronary Artery Surgery Utilizing Saphenous Vein Graft Techniques: Clinical Experience with 224 Operations," *Journal of Thoracic and Cardiovascular Surgery*, 1970, 59:147–154, on page 149.)

ideal candidate for his new operation arrived in May 1967: a fifty-one-year-old woman with an obstructed right coronary artery. Favaloro used a piece of saphenous vein to bypass the obstruction. He described the operation's immediate success: when the team removed the clamps, they saw that "blood flowed rapidly"; "we could see the branches of the right coronary artery fill with blood." Postoperative angiography showed "excellent function of the graft" (see Figure 6).¹⁶

Favaloro was immediately convinced of the value of the operation; only Sones's conservatism constrained his "Latin enthusiasm." They performed only a few bypass operations during the next months, waiting to see if the vein grafts would remain patent (i.e., open to blood flow during normal physiological conditions). Within a year, they had what they considered convincing evidence. Favaloro and his colleagues began to perform CABG with increasing frequency: 37 in 1967, nearly 200 in 1968, and 1,500 in 1969. The Cleveland Clinic team was full of enthusiasm. CABG "appeals to the imagination by its very simplicity": it provided a direct and immediate solution to the fundamental problem of obstructed flow. The team reported "complete symptomatic relief and excellent postoperative angiographic verification": the "majority of patients are fully recovered, enjoy a normal life, and work full time." Although they could not yet prove that CABG would prevent heart attacks and prolong life, by 1973 they claimed that "experience over the past 5 years in the Cleveland Clinic suggests that this is true."¹⁷

¹⁶ René G. Favaloro, *The Challenging Dream of Heart Surgery: From the Pampas to Cleveland* (New York: Little, Brown, 1994) (hereafter cited as **Favaloro, *Challenging Dream of Heart Surgery***), pp. 1–27, 70–86, 96 (quotations); and Favaloro, "Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion," *Ann. Thorac. Surg.*, 1968, 5:334–339, on p. 337 ("excellent function"). On the "ideal candidate" see Favaloro, "Critical Analysis of Coronary Artery Bypass Graft Surgery" (cit. n. 1), p. 2B. Favaloro's use of this technique was not based on animal experimentation but grew out of his experience with other coronary artery operations on hundreds of patients: Favaloro, *Challenging Dream of Heart Surgery*, p. 98. Favaloro's choice of a female patient is discussed later in this essay; see note 42, below.

¹⁷ Donald B. Effler, "Myocardial Revascularization—Direct or Indirect?" *J. Thorac. Cardiovasc. Surg.*, 1971, 61:498–500, on p. 498 (simplicity); René G. Favaloro, Effler, Laurence K. Groves, William C. Sheldon, and

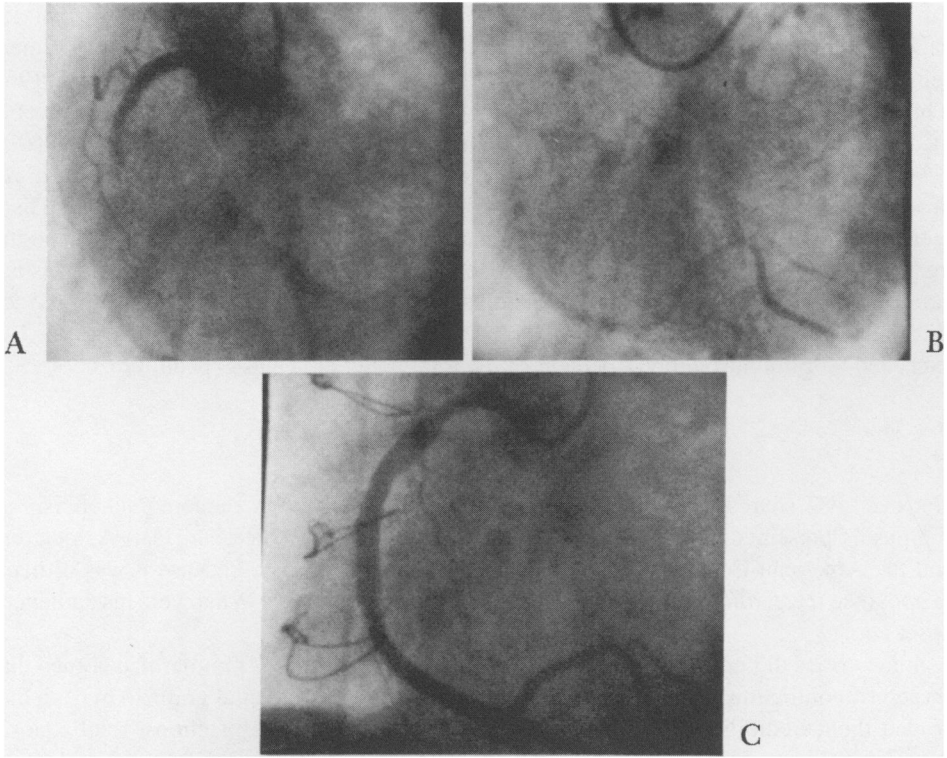


Figure 6. Visual proof of success? Coronary angiogram showing total occlusion of the right coronary artery (A), perfusion of the distal right coronary artery by collateral branches from the left coronary artery (B), and reconstruction of right coronary artery with a saphenous vein graft (C). Reprinted with permission from the Society of Thoracic Surgeons. (From René Favaloro, "Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion," *Annals of Thoracic Surgery*, 1968, 5:334–339, on page 338.)

Their enthusiasm quickly infected other groups of surgeons. Many vascular surgeons—especially those, like David Sabiston and Michael DeBakey, who had prior experience with bypass surgery—immediately recognized Favaloro's accomplishment.¹⁸ By 1972, the

Mohammed Riahi, "Direct Myocardial Revascularization with Saphenous Vein Autograft: Clinical Experience in 100 Cases," *Diseases of the Chest*, 1969, 56:279–283, on p. 282 (symptomatic relief); Favaloro, "Direct Myocardial Revascularization," *Surgical Clinics of North America*, 1971, 51:1035–1042, on p. 1042 (full recovery); and Sergio V. Moran, Robert C. Tarazi, Jorge U. Urzua, Favaloro, and Effler, "Effects of Aorto-Coronary Bypass on Myocardial Contractility," *J. Thorac. Cardiovasc. Surg.*, 1973, 65:335–342, on p. 335 (five years' experience). For the statistics see Baldwin *et al.*, "Coronary Artery Surgery" (cit. n. 6), p. 158; Favaloro, "The Present Era of Myocardial Revascularization—Some Historical Landmarks," *International Journal of Cardiology*, 1983, 4:331–344, esp. pp. 334–337; Katherine M. Detre, "Non-Randomized Studies of Coronary Artery Bypass Surgery," *Statistics in Medicine*, 1984, 3:389–398, esp. pp. 389–390; and Sheldon, Favaloro, F. Mason Sones, and Effler, "Reconstructive Coronary Artery Surgery: Venous Autograft Technique," *J. Amer. Med. Assoc.*, 1970, 213:78–82, esp. p. 78.

¹⁸ Experiments with coronary bypass grafts in animals began in 1910 but were abandoned because of unacceptable operative mortality: Favaloro, "Present Era of Myocardial Revascularization," p. 340; Vansant and Muller, "Surgical Procedures to Revascularize the Heart" (cit. n. 10), p. 578; Lester R. Sauvage, Stephen J. Wood, Kenneth M. Eyer, Alexander H. Bill, and Robert E. Gross, "Experimental Coronary Artery Surgery: Preliminary Observations of Bypass Venous Grafts, Longitudinal Arteriotomies, and End-to-End Anastomoses,"

cardiologist Richard Ross believed that CABG might become “the most significant advance in the therapy of heart disease in our time.” Use of CABG spread to many medical centers and community hospitals. The range of its applications quickly expanded; by 1968 it had been used to treat patients during acute heart attacks. CABG received such favorable media publicity that many patients came to hospitals seeking the surgery. By 1974, 100,000 CABGs had been performed. Surgeons and cardiologists believed that the procedure relieved pain, prevented heart attacks, and prolonged lives. Effler was triumphant: “There seems to be little doubt today that the surgeon will continue to play a dominant role in the treatment of the patient who suffers from ischemic heart disease.”¹⁹ His forecast was accurate: by 1980 roughly 150,000 procedures were performed each year (see Figure 7). With a typical cost of \$15,000 to \$20,000 for each operation, the annual cost of CABG exceeded \$2 billion, roughly 1 percent of the total national health expenditure.²⁰

SKEPTICS’ CRITICISMS AND CALLS FOR TRIALS

Not everyone shared the excitement about CABG. Favaloro encountered skepticism as soon as he presented his results. His talks at meetings of the American Heart Association and the American College of Cardiology “produced a sour taste because it was difficult to convince the cardiologists in spite of the evidence available.”²¹ What were his audiences upset about?

Some critics did not trust the surgeons. The cardiologist Henry Zimmerman argued that surgeons’ conflicting advocacy of different techniques, from omental grafts to bypass, had eroded their credibility: coronary artery surgery was “in a state of almost total chaos.” Some wanted to see data, not optimism: “enthusiasm is not a substitute for evidence.” Specific data caused alarm. While teams at elite centers like the Cleveland Clinic achieved

J. Thorac. Cardiovasc. Surg., 1963, 46:826–836, on p. 835. David Sabiston performed the first human bypass in 1962; the patient died three days later. Sabiston did not attempt another such repair until after he had heard of Favaloro’s success. Edward D. Garrett and DeBakey performed a successful bypass in 1964, but they did not report their results until 1973: Connolly, “History of Coronary Artery Surgery” (cit. n. 15), pp. 738, 740; Michael E. DeBakey, “The Development of Vascular Surgery,” *American Journal of Surgery*, 1979, 137:697–738, on pp. 710–711; and Favaloro, *Challenging Dream of Heart Surgery*, pp. 154–155. A Russian team performed a bypass in 1965; this was reported in English in 1967 and commented on by Effler before Favaloro’s first attempt: Igor Konstantinov, “The First Coronary Artery Bypass Operation and Forgotten Pioneers,” *Ann. Thorac. Surg.*, 1997, 64:1522–1523. Favaloro was the first to apply the technique systematically and publicize his results.

¹⁹ Richard Ross, “Surgery for Coronary Artery Disease Placed in Perspective,” *Bulletin of the New York Academy of Medicine*, 1972, 48:1163–1178, on p. 1163; Favaloro, “Direct Myocardial Revascularization” (cit. n. 17), p. 1041 (range of applications) (see also note 85, below); Eugene Braunwald, “Editorial: Coronary-Artery Surgery at the Crossroads,” *New Engl. J. Med.*, 1977, 297:661–663, on p. 663 (patients seeking CABG); Edwin L. Alderman, Harvey J. Matlof, Lewis Wexler, Norman E. Shumway, and Donald C. Harrison, “Results of Direct Coronary-Artery Surgery for the Treatment of Angina Pectoris,” *ibid.*, 1973, 288:535–539, esp. p. 536 (surgeons’ and cardiologists’ views); and Donald B. Effler, comment following Spencer *et al.*, “Long-Term Influence of Coronary Bypass Grafts on Myocardial Infarction and Survival” (cit. n. 7), p. 449.

²⁰ Eldred D. Mundth and W. Gerald Austin, “Surgical Measures for Coronary Heart Disease,” *New Engl. J. Med.*, 1975, 293:13–19, 75–80, 124–130, esp. p. 128; Gina Kolata, “Coronary Bypass Surgery: Debate over Its Results,” *Science*, 1976, 194:1263–1265, on p. 1263; Eugene Braunwald, “Coronary Artery Bypass Surgery—An Assessment,” *Postgraduate Medical Journal*, 1976, 52:733–738, on p. 737; Braunwald, “Editorial: Coronary-Artery Surgery at the Crossroads,” p. 663; Henry D. McIntosh and Jorge A. Garcia, “The First Decade of Aortocoronary Bypass Grafting, 1967–1977: A Review,” *Circulation*, 1978, 57:405–431, on pp. 405–406; and McIntosh, “Commentaries on the Consensus Conference of Coronary Artery Bypass Surgery,” *Journal of the Florida Medical Association*, 1981, 68:833–835, on p. 835.

²¹ Favaloro, *Challenging Dream of Heart Surgery*, pp. 113–114. As one observer described, “You could virtually palpate his frustration”: Thomas J. Ryan, “Revascularization: Reflections of a Clinician,” *J. Amer. Coll. Cardiol.*, 1998, 31(4[Suppl. B]):89B–96B, on p. 89B.

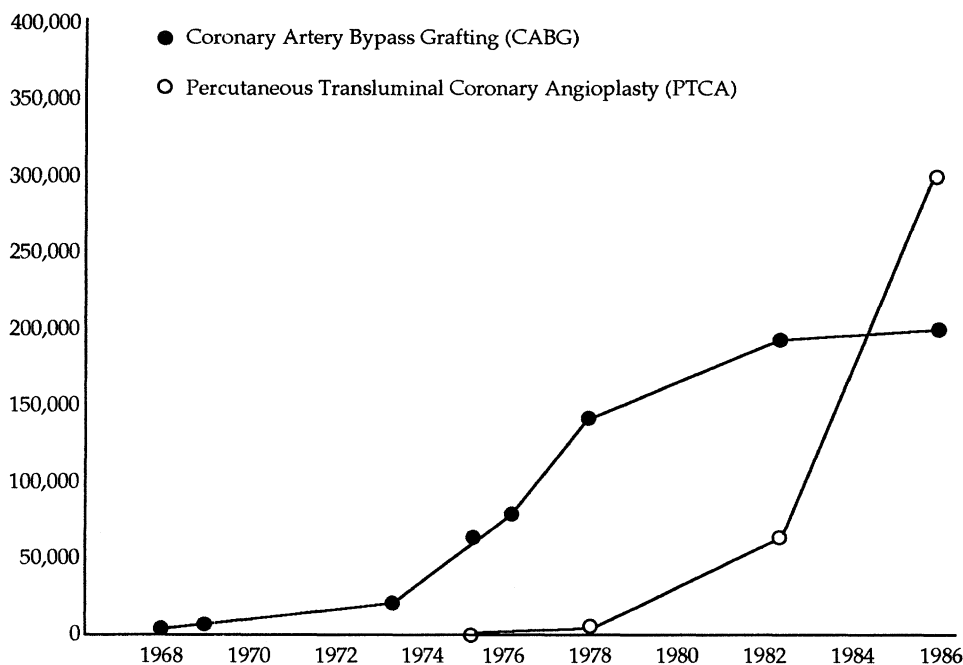


Figure 7. The spread of CABG and PTCA, 1968–1988; number of procedures performed each year. Data compiled from Henry D. McIntosh and Jorge A. Garcia, “The First Decade of Aortocoronary Bypass Grafting, 1967–1977: A Review,” *Circulation*, 1978, 57:405–431, on pages 405–406; Jay L. Hollman, “Myocardial Revascularization: Coronary Angioplasty and Bypass Surgery Indications,” *Medical Clinics of North America*, 1992, 76:1083–1097, on pages 1084–1085; and Charles Landau, Richard A. Lange, and L. David Hillis, “Percutaneous Transluminal Coronary Angioplasty,” *New England Journal of Medicine*, 1994, 330:981–993, on page 981.

operative mortality rates as low as 1.4 percent, a 1970 survey found average rates between 7.2 and 11.8 percent. Other “disquieting facts” had appeared in the literature: between 8 and 30 percent of grafts obstructed and between 5 and 29 percent of post-CABG patients experienced myocardial infarctions within one year. One group of Veterans Administration physicians wondered whether CABG could prolong life and whether the improvement in quality of life counterbalanced the risks and costs of the surgery.²²

Other critics were concerned with financial issues. Surgeons collected one-quarter of the annual cost of CABG. Writing in 1972, Ross noted that there were “economic factors at work which make it difficult to be objective.” Such concerns captured the attention of the Senate, which held hearings about resource allocation and the uncertain benefits of CABG. Critics also cited an “even more insidious problem”: the growth of an industry of facilities and training programs with a “momentum and constituency of its own.” These

²² Henry A. Zimmerman, “Editorial: The Dilemma of Surgery in the Treatment of Coronary Artery Disease,” *American Heart Journal*, 1969, 77:577–578, on p. 577; Jerome Cornfield, “Approaches to Assessment of the Efficacy of Surgical Revascularization,” *Bull. N.Y. Acad. Med.*, 1972, 48:1126–1134, on p. 1126 (enthusiasm vs. evidence); Schatz, “Commentary on 1971 Reflection of 1970 Statistics” (cit. n. 11), pp. 477–478 (mortality rates); Eliot Corday, “Status of Coronary Bypass Surgery,” *J. Amer. Med. Assoc.*, 1975, 231:1245–1247, on p. 1245 (“disquieting facts”); and Hultgren *et al.*, “Evaluation of Surgery in Angina Pectoris” (cit. n. 1), p. 2.

factors led observers to conclude that “financial incentives for performing the operation are enormous, and there is no balancing economic disincentive to restrain the operation.”²³

These critics and skeptics were always quick to state that they did not oppose CABG—everyone hoped that it would work. Cardiologists had long struggled to provide relief to patients suffering from angina, and CABG brought the prospect that a cure might finally be at hand. Tufts cardiologist David Spodick, a leading skeptic, believed that CABG was “a quantum jump ahead of its predecessors in concept and execution”; he agreed “with Favaloro that bypass surgery holds the greatest promise for definitive management.” Braunwald held a similar position. The concern was not so much substantive as epistemological. Spodick stated this most clearly: “My criticism of the surgical enthusiasts is not that they are wrong (or even probably wrong), but rather that they have not attempted to really prove themselves right”; “the professional quality and technical skill of the disputants is not in question. The basis of their evidence and beliefs is.”²⁴

By identifying advocates of CABG as “enthusiasts,” Spodick implied that their trust in the procedure resembled religious faith, not scientific certainty.²⁵ Where had CABG enthusiasts gone wrong? Typically, surgical researchers compiled the results from several years of their own experience and compared them to previously published reports of medical treatments. Such case series abounded, with groups at Stanford, New York, Boston, and Houston reporting up to five-year follow-up results on thousands of patients showing that their CABG patients had better survival rates than medically treated groups. Such retrospective studies dominated the field: by 1977, 250,000–300,000 patients had received CABG; fewer than 1,300 had been enrolled in randomized trials.²⁶

Unfortunately for CABG advocates, many physicians in the early 1970s considered retrospective case series to be a “time-dishonored approach” that produces “misleading results and is clearly wasteful of time, resources—and lives.” Spodick dismissed case series as “peep-show reports of a handful of chosen survivors.” Audiences at national meetings were “beguiled by beautiful slides and motion pictures.” Case series were so problematic because many surgical groups compared their results with those in a group of

²³ McIntosh and Garcia, “First Decade of Aortocoronary Bypass Grafting” (cit. n. 20), p. 406 (surgeons’ share); Ross, “Surgery for Coronary Artery Disease Placed in Perspective” (cit. n. 19), p. 1170; Fye, *American Cardiology* (cit. n. 13), p. 259 (Senate hearings); Braunwald, “Editorial: Coronary-Artery Surgery at the Crossroads” (cit. n. 19), p. 663 (growth of an “industry”); and Thomas A. Preston, “The Hazards of Poorly Controlled Studies in the Evaluation of Coronary Artery Surgery,” *Chest*, 1978, 73:441–442, on p. 441.

²⁴ David H. Spodick, “Letter: Coronary Bypass Operations,” *New Engl. J. Med.*, 1971, 285:55–56; Spodick, “Letter: Surgery in Coronary Artery Disease—I” (cit. n. 13), p. 582; Braunwald, “Direct Coronary Revascularization” (cit. n. 1), p. 9; Spodick, “Letter: Need for Controlled Study,” *J. Amer. Med. Assoc.*, 1970, 213:1344; and Spodick, “Editorial: Revascularization of the Heart—Numerators in Search of Denominators,” *Amer. Heart J.*, 1971, 81:149–157, on p. 156.

²⁵ Marks has noted that “enthusiasts” was a term frequently used by therapeutic reformers and RCT advocates after World War II: Marks, *Progress of Experiment* (cit. n. 4), pp. 149–150. Spodick might have had this meaning of “enthusiast” in mind. However, he made the claim about religion explicitly. When Effler offered to open the doors of his operating room to anyone who wanted to come learn his techniques, Spodick responded derisively: “Apparently none can become members of the Elect until they make the prescribed pilgrimage (Mecca; Lourdes?)”: Donald B. Effler, “Myocardial Revascularization,” *Chest*, 1973, 63:79–80, on p. 79; and David H. Spodick, “Aortocoronary Bypass,” *ibid.*, pp. 80–81, on p. 81. See also note 38, below.

²⁶ For retrospective studies see Alderman *et al.*, “Results of Direct Coronary-Artery Surgery for the Treatment of Angina Pectoris” (cit. n. 19); Spencer *et al.*, “Long-Term Influence of Coronary Bypass Grafts on Myocardial Infarction and Survival” (cit. n. 7); Lawrence H. Cohn, Caryl M. Boyden, and John J. Collins, “Improved Long-Term Survival after Aortocoronary Bypass for Advanced Coronary Artery Disease,” *Amer. J. Surg.*, 1975, 129:380–385; and George J. Reul, Denton A. Cooley, Don C. Wukasch, E. Ross Kyger, Frank M. Sandiford, Grady L. Hallman, and John C. Norman, “Long-Term Survival Following Coronary Artery Bypass: Analysis of 4,522 Consecutive Patients,” *Archives of Surgery*, 1975, 110:1419–1424. For the statistics see McIntosh and Garcia, “First Decade of Aortocoronary Bypass Grafting” (cit. n. 20), p. 412.

medically treated patients from the Cleveland Clinic in the 1960s, patients treated before the advent of cardiac care units and many valuable drugs, “at a chronologically different and therapeutically not comparable time.” Without data from RCTs, the CABG debates were “a battle of wits between unarmed opponents.”²⁷

Moreover, the retrospective case series generally relied on unconvincing assessments of therapeutic efficacy. Surgeons celebrated the extent to which CABG could relieve angina. As noted earlier, however, angina was well known to be susceptible to placebo effects. Furthermore, even if CABG did relieve angina, it might have done so by damaging the coronary nerves or by inducing an intraoperative heart attack rather than by improving the underlying coronary artery disease. Some surgeons celebrated their patients’ ability to return to work. But since many patients had avoided work because of doctor-induced fear that work would cause angina, they could be “cured” by suggestion: “A patient who is not working because of iatrogenic prophylaxis and who later returns to work because of surgical charisma may be falsely designated as improved due to a bypass graft whose main effect was to evoke enthusiastic iatrotrophy.” Finally, demonstration of graft patency with angiography was also inconclusive: patency did not prove that significant blood flowed under ordinary conditions.²⁸

Instead, critics wanted definitive answers about the impact of CABG on mortality. Braunwald stated this firmly in 1971: “Many questions must be answered. First and foremost: How do the survival rates and symptoms compare in operated and nonoperated patients?” Ross, Spodick, and Schatz all agreed. Since medical treatments could provide three-year survival in 80 to 90 percent of patients, surgical treatments had only a small window in which to show improvement. This had to be balanced against the risk of the operation. These skeptics all believed that only an RCT had the necessary statistical rigor to manage these statistical subtleties. Admittedly, it would not be an ideal trial: since a sham operation for the medical control group was not considered ethical, the trial could not be blinded. However, by randomly assigning patients to medical or surgical treatment groups, the trial would minimize bias, provide a meaningful control group, and determine whether CABG could improve survival, “the most unequivocal and definitive” of all outcomes.²⁹

Spodick—who had trained under Thomas Chalmers, one of the chief advocates of

²⁷ Spodick, “Letter: Coronary Bypass Operations” (cit. n. 24), p. 56 (“time-dishonored approach”); Spodick, “Editorial: Revascularization of the Heart” (cit. n. 24), p. 149 (“peep-show report”); Spodick, “Aortocoronary Bypass” (cit. n. 25), p. 81 (audiences “beguiled”); Timothy Takaro, “The Controversy over Coronary Arterial Surgery: Inappropriate Controls, Inappropriate Publicity,” *J. Thorac. Cardiovasc. Surg.*, 1976, 72:944; and David H. Spodick, “The Randomized Controlled Clinical Trial: Scientific and Ethical Bases,” *Amer. J. Med.*, 1982, 73:420–425, on p. 425 (“battle of wits”).

²⁸ Alvan R. Feinstein, “The Scientific and Clinical Tribulations of Randomized Clinical Trials,” *Clinical Research*, 1978, 26:241–244, on p. 244. For less benign explanations of how CABG could relieve angina see Louis A. Soloff, “Letter: Effects of Coronary Bypass Procedures,” *New Engl. J. Med.*, 1973, 288:1302–1303, on p. 1303; and M. H. Frick, “An Appraisal of Symptom Relief after Coronary Bypass Grafting,” *Postgrad. Med. J.*, 1976, 52:765–769, on p. 765. On the inconclusiveness of patency see Masasyoshi Yokoyama, “A Critical Examination of the Validity of the Use of Vein Grafts in Treating Ischemic Heart Disease,” *Amer. Heart J.*, 1972, 84:61–65, on p. 64.

²⁹ Braunwald, “Direct Coronary Revascularization” (cit. n. 1), p. 9; Ross, “Surgery for Coronary Artery Disease Placed in Perspective” (cit. n. 19), p. 1172; Spodick, “Letter: Surgery in Coronary Artery Disease—I” (cit. n. 13), p. 582; Irwin J. Schatz, “The Need to Know,” *Chest*, 1973, 63:82–83, esp. p. 83; and Marvin L. Murphy, Herbert N. Hultgren, Katherine Detre, James Thomsen, Timothy Takaro, and Participants of the Veterans Administration Cooperative Study, “Treatment of Chronic Stable Angina: A Preliminary Report of Survival Data of the Randomized Veterans Administration Cooperative Study,” *New Engl. J. Med.*, 1977, 297:621–627, on p. 627. Mortality had long been the measure of choice for therapeutic reformers and RCT advocates. It was convenient, reliable, and objective: Marks, *Progress of Experiment* (cit. n. 4), p. 246.

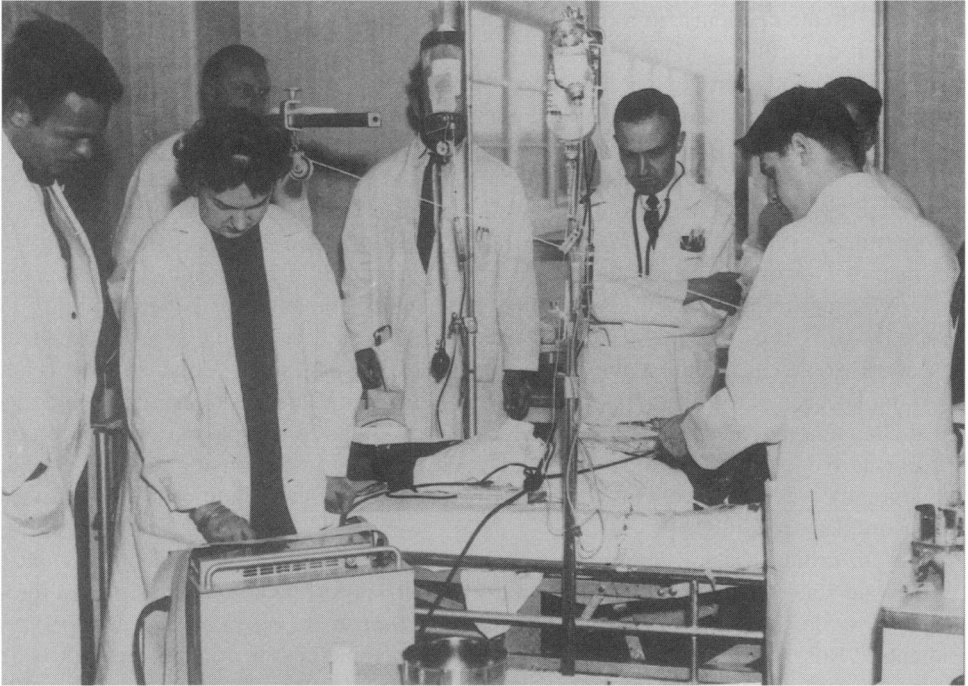


Figure 8. David Spodick at the bedside, Lemuel Shattuck Hospital, 1960s. From left to right: Ed Moore (hepatologist), Constance Dorr (technician), Thomas Chalmers (chief of medicine), [man blocked by I.V.], David Spodick (chief of cardiology), Joseph Cohen (resident), [man blocked]. Reprinted with permission of David Spodick.

RCTs—led the way (see Figure 8). Beginning in 1970, he waged a campaign of letters, editorials, and articles stressing that RCTs were valuable because they “tackle head-on the immediate problem of whether it works and, through stratification, for whom.” Since researchers and regulators, particularly the Food and Drug Administration, demanded RCTs of medical therapy, they should also require them of surgical therapy: “We abandon our patients along with our intellect if surgical treatment is immune to the high standards demanded of other kinds of treatment.” Accepting CABG on the basis of case series would establish an irrational double standard: “Somehow, the mystique of surgery—the presumed efficacy of a mechanical rearrangement of tissue”—made researchers and regulators “suspend disbelief in a way that no pill could.” Calling surgery a “Sacred Cow, faith in which continues to ensure immunity from disbelief,” Spodick argued that “we should demand quality control of the Sacred Cowboys who milk them and market the products.”³⁰

Other cardiologists, such as David Schatz and Eugene Braunwald, shared Spodick’s demand that RCTs be used to replace “common consent” with “rational analysis of data.” Chalmers asserted that RCTs were an ethical imperative, “in the best interest of the patient

³⁰ David H. Spodick, “Letter: Surgery for Coronary Artery Disease,” *Amer. J. Cardiol.*, 1972, 30:449 (on whether surgery works); Spodick, “Letter: Surgery in Coronary Artery Disease—I,” p. 582 (standards); Spodick, “Letter: Coronary Revascularization,” *Circulation*, 1971, 44:302 (“mystique of surgery”); and Spodick, “Editorial: The Surgical Mystique and the Double Standard,” *Amer. Heart J.*, 1974, 85:579–583, on p. 582 (Sacred Cows and Cowboys).

entering the trial as well as of all mankind.” Finally, RCTs provided the best means of defending surgeons against the specter of financial conflict of interest that loomed behind their case series.³¹

Some surgeons accepted these calls for trials. In 1968 Timothy Takaro and other Veterans Administration surgeons and cardiologists had begun an RCT of Vineberg implants. They ended this trial prematurely in 1970, with fewer than one hundred patients enrolled, when “attention and interest shifted almost completely” to CABG. Responding to this shift, they modified their trial protocol and began an RCT of CABG.³² At the 1970 meeting of the American Association of Thoracic Surgery Takaro admitted that this trial might seem “a little heretical” to surgeons, but he defended its importance: “Why don’t we require of ourselves the same degree of objectivity in assessing new operative procedures as we require of drugs?” He acknowledged that trials might be difficult to conduct but suggested that if surgeons demonstrated the “same high degree of boldness and ingenuity” that they brought to designing new operations, they would quickly produce results “that the agnostics among us, as well as among our medical colleagues, could accept.” Trials presented no threat: if CABG really was superior, it would be validated.³³

Results of randomized trials of CABG soon began to appear. One small trial was published in 1975 but provoked little interest.³⁴ Most observers awaited the results of the larger V.A. Cooperative Study, led by Takaro and his colleagues and published in 1977. The researchers sought to answer a basic question: Does CABG improve survival in patients with chronic stable angina? The results—reported for 310 patients treated medically and 286 treated surgically—showed that in most cases CABG did not provide a significant benefit: 87 percent of the medically treated patients were alive after three years, compared to 88 percent among the surgical group. However, early results had shown that 113 patients with obstruction of the left main coronary artery clearly benefited from surgery. This

³¹ Schatz, “Commentary on 1971 Reflection of 1970 Statistics” (cit. n. 11), p. 478; Braunwald, “Direct Coronary Revascularization” (cit. n. 1), p. 9; Thomas C. Chalmers, “Randomization and Coronary Artery Surgery,” *Ann. Thorac. Surg.*, 1972, 14:323–327; and Richard D. Sautter, “Reply to Effler,” *J. Thorac. Cardiovasc. Surg.*, 1974, 6:977–978, esp. p. 978. Braunwald recalls that cardiologists believed that cardiac surgeons “were making a fortune” inappropriately: Eugene Braunwald, personal communication, 17 June 1998.

³² On the RCT of Vineberg implants see Timothy Takaro, comment following Charles H. Dart, Yutaka Kano, Stewart M. Scott, Robert G. Fish, William M. Nelson, and Takaro, “Internal Thoracic (Mammary) Arteriography: A Questionable Index of Myocardial Revascularization,” *J. Thorac. Cardiovasc. Surg.*, 1970, 59:117–127, on p. 127; on its premature termination see Takaro, “The Enigma of the Vineberg-Sewell Implant Operation,” *Chest*, 1973, 64:150–151. On the RCT of CABG see Herbert N. Hultgren, Takaro, and Elizabeth C. Wright, “Veterans Administration Study of Coronary Bypasses,” *New Engl. J. Med.*, 1973, 289:105; and Hultgren, Takaro, Katherine Detre, and Participants in the Veterans Administration Cooperative Study, “Medical and Surgical Treatment of Stable Angina Pectoris: Progress Report of a Large Scale Study,” *Postgrad. Med. J.*, 1976, 62:757–764, esp. p. 759. The V.A. system had long been a favorite site for RCTs, starting with studies of streptomycin following World War II and continuing with studies on psychopharmacology and hypertension in the 1950s. At first glimpse, the V.A. system seems an ideal site—large, centralized, and organized: William G. Henderson, “Some Operational Aspects of the Veterans Administration Cooperative Studies Program,” *Controlled Clinical Trials*, 1980, 1:209–226. However, it is also a site of many conflicting interests: Marks, *Progress of Experiment* (cit. n. 4), pp. 12, 116–120, 132.

³³ Timothy Takaro, comment following René G. Favaloro, Donald B. Effler, Laurence K. Groves, William C. Sheldon, Earl K. Shirey, and F. Mason Sones, “Severe Segmental Obstruction of the Left Main Coronary Artery and Its Divisions: Surgical Treatment by the Saphenous Vein Graft Technique,” *J. Thorac. Cardiovasc. Surg.*, 1970, 60:469–482, on pp. 479–480.

³⁴ Virendra S. Mathus, Gene A. Guinn, Lakis C. Anastassiades, Robert A. Chahine, Ferenc L. Korompai, Alfredo C. Montero, and Robert J. Luchi, “Surgical Treatment for Stable Angina Pectoris: Prospective Randomized Study,” *New Engl. J. Med.*, 1975, 292:709–713. Two other large trials were also under way at this time. Organized by the National Heart, Lung, and Blood Institute, they studied patients with exertional angina and with unstable angina: Kolata, “Coronary Bypass Surgery” (cit. n. 20), p. 1265.

subgroup was partitioned from the remainder of the study and the results published separately.³⁵

The V.A. study, published in the *New England Journal of Medicine* with tremendous publicity, was celebrated by those who had been skeptical of CABG all along. In a strongly supportive editorial, Braunwald celebrated the trial's results and refuted anticipated criticisms. In a special correspondence section published by the *Journal*, Spodick praised the V.A. study as a "meticulously controlled trial" and Braunwald argued that the results merited "the most careful consideration."³⁶

OPPOSITION TO TRIALS

How did CABG enthusiasts respond to the damaging results of the V.A. study? Many surgeons, especially those at the Cleveland Clinic and the Texas Heart Institute, had opposed the trials before the study was published, criticized it afterward, and continued to publish traditional case series. Members of the Cleveland Clinic team had been particularly outspoken in their opposition to the need for trials. In 1969 Effler expressed his belief that the obvious mechanical evidence justified his faith in CABG: "Arteriographic proof that the pathological ligature has been removed effectively and myocardial perfusion has been restored is prima facie evidence that the needs of that particular individual have been met. The cardiologist who would loudly deny the existence and validity of such factual evidence by refusal to examine it is, in my opinion, allowing emotion to prevail over scientific evaluation." In 1974 he dismissed the "constant harping" of those who demanded RCTs. In 1976 he espoused a different ethic than that of Chalmers, arguing that performing an RCT for CABG would be unethical: no patient who had been adequately informed would consent to go without surgery.³⁷ Even after the V.A. study was published, many surgeons continued to be categorical in their dismissals of RCTs, mocking "the almost religious fervor of those who would sanctify randomized studies as the only means of learning the truth." DeBakey agreed: to insist that an RCT "is the only scientific basis for assessment is, itself, unscientific."³⁸

Surgeons acknowledged that RCTs had value in principle but held that they were inappropriate for surgery. In 1975 Jack Love argued that Spodick's call for routine surgical

³⁵ For the general results see Murphy *et al.*, "Treatment of Chronic Stable Angina" (cit. n. 29), p. 621; for the subgroup results see Timothy Takaro, Herbert N. Hultgren, Martin J. Lipton, Katherine M. Detre, and Participants in the Veterans Administration Study Group, "The VA Cooperative Randomized Study of Surgery for Coronary Arterial Occlusive Disease, II: Subgroup with Significant Left Main Lesions," *Cardiovascular Surgery*, 1976, 54:III-107-III-116, esp. p. III-107.

³⁶ Braunwald, "Editorial: Coronary-Artery Surgery at the Crossroads" (cit. n. 19); and "Special Correspondence: A Debate on Coronary Bypass," *New Engl. J. Med.*, 1977, 297:1464-1470, on pp. 1465-1466 (Spodick), 1469-1470 (Braunwald).

³⁷ Donald B. Effler, "The Role of Surgery in the Treatment of Coronary Artery Disease," *Ann. Thorac. Surg.*, 1969, 8:376-379, on p. 377; Effler, "Revascularization Surgery—Letter," *J. Thorac. Cardiovasc. Surg.*, 1974, 6:977; and Kolata, "Coronary Bypass Surgery" (cit. n. 20), p. 1264 (RCT for CABG unethical). By the mid 1970s, the original Cleveland Clinic team had split up. In 1971 Favalaro returned to Buenos Aires to establish a cardiovascular surgery center; by 1976 Effler had moved to St. Joseph's Hospital in Syracuse, New York, where he established a CABG center in a community hospital.

³⁸ Lawrence I. Bonchek, "Are Randomized Trials Appropriate for Evaluating New Operations?" *New Engl. J. Med.*, 1979, 301:44-45, on p. 45; and De Bakey and Lawrie, "Aortocoronary-Artery Bypass" (cit. n. 1), p. 839. See also Ralph Berg, "Reply to Spodick," *J. Thorac. Cardiovasc. Surg.*, 1982, 83:150-151. Hywel Davies, a V.A. surgical chief, mocked Chalmers as "the high priest among the randomizer theologians" and was skeptical of the "cult nature" of RCT advocates: Davies, "Letter: More on Coronary Bypass Surgery—I," *Amer. J. Cardiol.*, 1979, 43:1060-1061.

RCTs was “unrealistic and naive. It fails completely to take into account some important differences between drugs and operations.” After all, every patient presented a unique challenge, every surgeon had different skills, and each operation could utilize a bewildering range of procedures. Since sham operations were not considered ethical, the study could not be blinded: patients and physicians would know which treatment each patient received, reintroducing a bias RCTs were designed to eliminate. And, as many surgeons noted, since the studies required many years of follow-up, they faced the problem of evolving techniques: “Just when we have accumulated enough data over a sufficient time period, we find that surgical technique has improved or medical therapy changes, or both, and conclusions no longer apply.” Surgeons used these excuses to avoid RCTs. Since the results of RCTs would not be “completely *objective*,” David Sabiston argued in 1971, the studies should not be done. In 1979 Hywel Davies described how he had feared that the V.A. study would be “an expensive and time-consuming effort without valid conclusions”; as a result, the V.A. hospital at which he was chief of surgery did not participate.³⁹

As soon as the main report of the V.A. study was published, CABG enthusiasts responded with a firestorm of critique. The *New England Journal of Medicine* received so many letters that it published a special correspondence section in a subsequent issue. Cardiac surgeons highlighted weaknesses in the design and conduct of the study (complaining that it was “marred by very serious flaws”), suggested that the study’s surgeons had performed CABG poorly, and provided their own superior (and retrospective) results to demonstrate the real value of CABG. Many surgeons were so eager to contest the findings of the V.A. study that they arrived at academic conferences armed with slides illustrating their own mortality data.⁴⁰

Debate about the V.A. study continued for years. The *American Journal of Cardiology* published a typical exchange. The Cleveland Clinic team critiqued the V.A. trial, described their own superior results (95 percent survival after CABG, better than both the medical and surgical groups in the V.A. trial), and protested, “Why should we judge a mode of therapy on the basis of mediocre performance?” The V.A. group responded that their results were consistent with those from other centers and that the study’s weaknesses were insignificant. Braunwald praised the study as “at least a step in the direction of rationally attempting to compare the results of two methods of management of chronic stable angina pectoris.” In a similar symposium in *Clinical Research*, Chalmers defended the rigor of the V.A. trial, while the Cleveland Clinic cardiologist William Proudfit argued that RCTs are “not the only route to wisdom.” Leading surgical groups fueled the controversy by publishing ever larger retrospective case series. For example, the Texas Heart Institute team insisted that their experience, with more than 10,000 operations, demonstrated the superiority of CABG.⁴¹

³⁹ Jack W. Love, “Drugs and Operations: Some Important Differences,” *J. Amer. Med. Assoc.*, 1975, 232:37–38; Daniel J. Ulyot, Judith Wisneski, Robert W. Sullivan, and Edward W. Gertz, “Reply to Takaro,” *J. Thorac. Cardiovasc. Surg.*, 1976, 72:945; David C. Sabiston, “Reply to Spodick,” *Circulation*, 1971, 44:302; and Davies, “Letter: More on Coronary Bypass Surgery—I,” pp. 1060–1061.

⁴⁰ See, e.g., Floyd D. Loop, comment following Raymond C. Read, Marvin L. Murphy, Herbert N. Hultgren, and Timothy Takaro, “Survival of Men Treated for Chronic Stable Angina Pectoris: A Cooperative Randomized Study,” *J. Thorac. Cardiovasc. Surg.*, 1978, 75:1–16, on pp. 13–14. For the special section see “Special Correspondence: A Debate on Coronary Bypass” (cit. n. 36).

⁴¹ Floyd D. Loop, William L. Proudfit, and William C. Sheldon, “Coronary Bypass Surgery Weighed in the Balance,” *Amer. J. Cardiol.*, 1978, 42:154–156, on p. 155 (Cleveland Clinic team); Herbert N. Hultgren, Timothy Takaro, Katherine M. Detre, and Marvin L. Murphy, “Evaluation of the Efficacy of Coronary Bypass Surgery—I,” *ibid.*, pp. 157–160; Eugene Braunwald, “Evaluation of the Efficacy of Coronary Bypass Surgery—II,” *ibid.*,

Amidst this controversy, one aspect of the V.A. study went unquestioned. Critics neither noted that all 596 patients in the V.A. study were men nor criticized the authors for not indicating the racial composition of the patient groups. When CABG appeared, coronary artery disease was defined as a problem of affluent men, though, ironically, Favaloro's first CABG patient seems to have been a woman.⁴² What was going on here? On the surface, race and gender were not relevant categories for the surgeons. In choosing patients for CABG surgeons focused on angiographic details of their coronary arteries. Favaloro chose his first patient because she had an obstructed right coronary artery with good collateral flow: if the experiment failed, she would have been no worse off than before. Three years and 228 patients later, Favaloro still chose patients according to the angiographic state of their vessels.⁴³ After all, once the patient was draped for surgery only the heart and its obstructed arteries remained visible.

Indifference to race and gender does not explain the selection of patients for CABG, however. When gender was specified, the patients were overwhelmingly male. When race was specified, the patients were overwhelmingly white. White men were over-represented among patients chosen for CABG given the distribution of heart disease in the population. Did the surgeons at elite centers, such as the Cleveland Clinic and the Texas Heart Institute, see only "professional people" with the resources to reach those centers?⁴⁴ Did racial and gender biases skew both the diagnosis of coronary artery disease and the choice of surgical treatment? Careful analysis of patient selection in the surgical series and randomized trials might unearth the forces at work in the 1970s. When these questions began to receive adequate scrutiny in the 1990s, researchers confirmed the importance of gender and racial

pp. 161–162, on p. 162; Thomas C. Chalmers, Harry Smith, Alexander Ambroz, Dinah Ritman, and Biruta J. Schroeder, "In Defense of the VA Randomized Control Trial of Coronary Artery Surgery," *Clin. Res.*, 1978, 26:230–235; Proudfit, "Criticisms of the VA Randomized Study of Coronary Bypass Surgery," *ibid.*, pp. 236–240, on p. 236; and Frank M. Sandiford, Denton A. Cooley, and Don C. Wukasch, "The Aortocoronary Bypass Operation: Myth and Reality: An Overview Based on 10,000 Operations at the Texas Heart Institute," *International Surgery*, 1978, 63:83–89.

⁴² For the study see Murphy *et al.*, "Treatment of Chronic Stable Angina" (cit. n. 29), p. 621. On Favaloro's first CABG patient see Favaloro, "Present Era of Myocardial Revascularization" (cit. n. 17), p. 334; and Favaloro, "Critical Analysis of Coronary Artery Bypass Graft Surgery" (cit. n. 1), p. 2B. Elsewhere, however, Favaloro writes that his first CABG patient was a man: Favaloro, *Challenging Dream of Heart Surgery*, p. 95. Braunwald's discussion of risk factors for coronary artery disease compared men with a history of high cholesterol, high blood pressure, and smoking to men free of those diseases: Lesch *et al.*, "Ischemic Heart Disease" (cit. n. 9), pp. 1262–1263. As mentioned earlier, Effler emphasized the impact of coronary artery disease on "professional people, executives and men in public office": Effler, "Surgery for Coronary Disease" (cit. n. 7), p. 43.

⁴³ Favaloro, "Present Era of Myocardial Revascularization," p. 334; and Favaloro *et al.*, "Severe Segmental Obstruction of the Left Main Coronary Artery and Its Divisions" (cit. n. 33), p. 475. Explicit discussions of race or gender rarely appeared in the cardiac surgery literature before the 1990s. A keyword search on Medline for "race" or "gender" in the *Annals of Thoracic Surgery* and the *Journal of Thoracic and Cardiovascular Surgery* revealed no matches from 1966 to 1974; "race" had four matches and "gender" three matches between 1975 and 1986.

⁴⁴ Effler provided one clue: "The Cleveland Clinic experience is based upon private patients who are referred from all parts of the world." Effler, "Myocardial Revascularization" (cit. n. 25), p. 79. Of the Cleveland Clinic's first 1,000 patients, 87.4 percent were men: W. C. Sheldon, G. Rincon, D. B. Effler, W. T. Proudfit, and F. M. Sones, "Vein Graft Surgery for Coronary Artery Disease: Survival and Angiographic Results in 1,000 Patients," *Circulation*, 1973, 47–48 (Suppl. 3): III-184–III-189, on p. III-185. Of 4,522 patients at the Texas Heart Institute, 86 percent were men: Reul *et al.*, "Long-Term Survival Following Coronary Artery Bypass" (cit. n. 26), p. 1419. Neither the early Cleveland Clinic trials nor the V.A. study mentions race. The first mention of race in a study of CABG that I found was the CASS trial, published in 1983. Of the 780 patients, 90.3 percent were male and 98.3 percent were white; CASS Principal Investigators and Their Associates, "Coronary Artery Surgery Study (CASS): A Randomized Trial of Coronary Artery Bypass Surgery: Survival Data," *Circulation*, 1983, 68:939–950, on p. 942. Death rates per 100,000 from "diseases of heart" in 1968: white male, 362.9; white female, 180.5; other male, 391.4; other female, 271.4. See U.S. Department of Health and Human Services, *Vital Statistics of the United States, 1968*, Vol. 2: *Mortality* (cit. n. 3), Table 1-6.

analysis in cardiac trials; the role of bias in referral for cardiac procedures remains contested.⁴⁵

The V.A. trial was not the last word on the problem of CABG. RCTs, case series, and consensus reports continued to appear for decades. But the debate over the V.A. study was the defining moment in the history of RCTs for CABG. Many physicians wished the whole affair had never happened. Cardiologists at Emory feared that the controversy over the RCTs had “blunted the enthusiasm for such an approach.” As Braunwald wrote in 1981, everyone would have been better off without the “major controversy, even acrimony. The conflicts among cardiologists and cardiovascular surgeons spilled into the lay press, confusing patients and physicians alike.”⁴⁶ What had produced such a contentious and intractable debate?

WAS IT ALL IN THE DETAILS?

As Harry Marks, Steven Epstein, and Evelleen Richards have shown, RCTs are never simple to conduct. Problems with patient selection, adherence to assigned treatments, and interpretation of results all fuel fierce debate. There is much evidence that this happened with RCTs of CABG. Critics immediately attacked perceived weaknesses of the V.A. study: selection of a low-risk group of patients (resulting in remarkably high survival in the medical group), poor surgical results (high operative mortality, low graft patency), and poor compliance with the treatment specified (many patients initially assigned to the medical group subsequently had surgery).⁴⁷

Consider operative mortality. Supporters of the study defended its 5.6 percent operative mortality rate as consistent with rates for most surgery performed between 1972 and 1974. But opponents argued that the results were unacceptably poor. Both groups were right, depending on what standards (elite, national average, community hospital) were seen as most relevant. As the controversy continued, some contestants resorted to rhetorical chicanery. Critics from the Cleveland Clinic and the Texas Heart Institute argued that the V.A. data—399 patients operated on in thirteen hospitals over three years—proved that the participating surgeons had inadequate experience with CABG, performing less than one operation per hospital per month. The V.A. group was quick to defend their experience:

⁴⁵ Women had different cardiac outcomes than men: E. S. Tan, J. van der Meer, P. Jan de Kam, P. H. Dunselman, B. J. Mulder, C. A. Ascoop, M. Pfisterer, and K. I. Lie, “Worse Clinical Outcome but Similar Graft Patency in Women versus Men One Year after Coronary Artery Bypass Graft Surgery Owing to an Excess of Exposed Risk Factors in Women,” *J. Amer. Coll. Cardiol.*, 1999, 34:1760–1768. Minorities were less likely to receive invasive cardiac procedures than whites: M. B. Wenneker and A. M. Epstein, “Racial Inequalities in the Use of Procedures for Patients with Ischemic Heart Disease in Massachusetts,” *J. Amer. Med. Assoc.*, 1989, 261:253–257; and J. Whittle, J. Conigliaro, C. B. Good, and R. P. Lofgren, “Racial Differences in the Use of Invasive Cardiovascular Procedures in the Department of Veterans Affairs Medical System,” *New Engl. J. Med.*, 1993, 329:621–627. On questions of gender and racial bias see H. J. Geiger, “Race and Health Care—An American Dilemma?” *ibid.*, 1996, 335:815–816; and L. M. Schwartz, S. Woloshin, H. G. Welch, and the V.A. Outcomes Group, “Misunderstandings about the Effects of Race and Sex on Physicians’ Referrals for Cardiac Catheterization,” *ibid.*, 1999, 341:279–283.

⁴⁶ J. Willis Hurst, Spencer B. King, R. Bruce Logue, Charles R. Hatcher, Ellis L. Jones, Joe M. Craver, John S. Douglas, Robert H. Franch, Edward R. Dorney, B. Woodfin Cobbs, Paul H. Robinson, Stephen D. Clements, Joel A. Kaplan, and James M. Bradford, “Value of Coronary Bypass Surgery: Controversies in Cardiology: Part I,” *Amer. J. Cardiol.*, 1978, 42:308–329, on p. 310; and Eugene Braunwald, “Let’s Not Let the Genie Escape from the Bottle—Again,” *New Engl. J. Med.*, 1981, 304:1294–1296, on p. 1295.

⁴⁷ See, e.g., “Special Correspondence: A Debate on Coronary Bypass” (cit. n. 36).

during the study period they operated on over 1,300 patients who were not enrolled in the study.⁴⁸

But were such methodological criticisms really at the core of critics' evaluation of the V.A. study? Their own actions indicate that this cannot be the case. First, Favaloro and many other CABG enthusiasts, though they attacked the main V.A. study, accepted the data subset showing the benefit of CABG in treating left main coronary artery obstruction. The V.A. group was quick to mock the illogic of such a position: "this subset was part of the Cooperative Study and was treated by the same surgeons, in the same institutions, under the same conditions, and in the same time frame as the remaining 88% of the patients in the study." Second, enthusiasts continued to publish and rely on their own case series, which they admitted were even more methodologically flawed than the V.A. study.⁴⁹

Alvan Feinstein, professor of medicine and epidemiology at Yale, had a valuable insight. He had observed the competing claims about the quality of the V.A. study and concluded that both sides were right: V.A. surgery was worse than that at the Cleveland Clinic but comparable to surgery in most institutions and better than that in some. The V.A. study was flawed, but so were retrospective case series. Reasonable arguments could support either position; reasonable criticisms could undermine them. For Feinstein, this was the "essence of tragedy": "the destructive collision of two protagonists holding opposing positions, each of which is right."⁵⁰

Such a conclusion suggests that responses to the trial were underdetermined by the available information. In fact, the responses depended on contestants' prior commitments—a fact that is made particularly clear by how observers reported the results of the V.A. study. While skeptics emphasized the negative results (no benefit in most patients), enthusiasts emphasized the positive results (benefit for patients with left main disease). Many observers noted the crucial role played by preconceptions. Spodick complained that too many people had "their minds made up in advance as to the outcome." Braunwald and McIntosh agreed. One review concluded that responses to the trials seemed "related to how such results compare with preconceived views." Chalmers decried the "reluctance of physicians to accept the results of clinical trials when the conclusions are contrary to conventional wisdom."⁵¹

⁴⁸ On the issue of standards see Braunwald, "Evaluation of the Efficacy of Coronary Bypass Surgery—II" (cit. n. 41), p. 161; and Feinstein, "Scientific and Clinical Tribulations of Randomized Clinical Trials" (cit. n. 28), p. 243. For the charges of inadequate experience see Don C. Wukasz, Denton A. Cooley, Robert J. Hall, George J. Reul, Frank M. Sandiford, and Sherri L. Zillgitt, "Surgical versus Medical Treatment of Coronary Artery Disease: Nine Year Follow-up of 9,061 Patients," *Amer. J. Surg.*, 1979, 137:201–207; and Loop, comment following Read *et al.*, "Survival of Men Treated for Chronic Stable Angina Pectoris" (cit. n. 40), p. 13. For the V.A. group's defense see Timothy Takaro and the Participants in the V.A. Cooperative Study of Surgery for Coronary Arterial Occlusive Disease, "Results of a Randomized Study of Medical and Surgical Management of Angina Pectoris," *World Journal of Surgery*, 1978, 2:797–807, on p. 803.

⁴⁹ For an essay that accepted the results regarding left main coronary artery obstruction see Favaloro, "Critical Analysis of Coronary Artery Bypass Graft Surgery" (cit. n. 1), p. 9B. The V.A. authors mocked this logic in Takaro and Participants in V.A. Cooperative Study, "Results of a Randomized Study of Medical and Surgical Management of Angina Pectoris," pp. 800–801; on reliance on methodologically flawed case series see Thomas A. Preston's comment following this essay: p. 809. See also the contributions of Spodick and Braunwald to "Special Correspondence: A Debate on Coronary Bypass" (cit. n. 36), pp. 1465–1466, 1469–1470.

⁵⁰ Feinstein, "Scientific and Clinical Tribulations of Randomized Clinical Trials" (cit. n. 28), p. 241.

⁵¹ David H. Spodick, "Coronary Bypass: How Good and for Whom?" *Modern Medicine*, 2 Apr. 1973, 41: 80–81; Braunwald, "Editorial: Coronary-Artery Surgery at the Crossroads" (cit. n. 19), p. 662; Henry D. McIntosh and Robert A. Buccino, "Value of Coronary Bypass Surgery: Controversies in Cardiology (Continued)," *Amer. J. Cardiol.*, 1979, 44:387–389, on p. 388; Robert L. Frye, Lloyd Fisher, Hartzell V. Schaff, Bernard J. Gersh, Ronald E. Vliestra, and Michael B. Mock, "Randomized Trials in Coronary Artery Bypass Surgery," *Progress in Cardiovascular Diseases*, 1967, 30:1–22, on p. 15; and Thomas C. Chalmers, "The Clinical Trial,"

The debates over the V.A. study and about RCTs for CABG in general, therefore, did not grow out of technical concerns with the studies. Those who attacked RCTs most fiercely were those who had previously denied the need for them, and vice versa. Participants' positions were not the products of rational analysis of study data. Instead, the debates grew out of faith, or lack of it, in CABG itself. Preconception and rationalization drove the technical debates. But what was the source of participants' faith? What generated their allegiances, the preconceptions through which they perceived the trial?

SPODICK AS PSYCHOLOGIST

One explanation for the faith of CABG enthusiasts appeared very early in the debates. In 1971 Spodick wrote an editorial in which he described factors that influenced the psychological disposition of cardiologists and cardiac surgeons toward CABG.⁵² He sought to explain why so many people in both groups (for nearly every cardiac surgeon performing CABG, there was a diagnosing cardiologist who recommended the procedure) did not see a need for trials. He traced this "credulity" to human, statistical, and professional factors.

At the human level, Spodick believed that the Cleveland Clinic team and other surgical pioneers were blinded by hopes that their innovation would succeed: "Few treatments succeed as well as they do in the hands of their originators. Here, Invention too often becomes the mother of Necessity." At the statistical level, Spodick argued that enthusiasts succumbed to classic statistical delusions, demonstrating both a remarkable willingness to be convinced by anecdotal reports and an uncritical awe of massive case series. At the professional level, Spodick characterized cardiac specialists as "prima donnas." Their professional stature had given them a sense of "olympianism." "The loftily self-sufficient doctor is convinced that he is a uniquely qualified judge of his own decisions, which therefore require little or no outside assistance." Finally, surgeons were motivated by ideals of activism. Like climbers facing a new mountain, surgeons performed CABG "simply 'because it's there.'" ⁵³

Spodick's analysis, however, begs the question. These psychological factors might have operated. But where did they come from? Why were some people outside of this psychological atmosphere calling for RCTs? Enthusiasm and olympianism must be contextualized.

DISCIPLINARY WARFARE?

An effort to explain the origins of controversy and enthusiasm must be grounded in an understanding of the disciplinary perspectives of cardiology and cardiac surgery. Before exploring this background, however, I must stress that a simple framework of interdisciplinary hostility does not explain the actions of the participants in the debates. To begin with, cardiologists themselves were fundamentally involved in the CABG industry, often performing the diagnostic angiography and providing pre- and postoperative care. Fur-

Millbank Mem. Fund Quart., 1981, 59:324–339, on p. 328. For skeptics' views of the V.A. study see Braunwald, "Editorial: Coronary-Artery Surgery at the Crossroads," p. 661; and McIntosh, "Commentaries on the Consensus Conference of Coronary Artery Bypass Surgery" (cit. n. 20), p. 835. For enthusiasts' views see Hurst *et al.*, "Value of Coronary Bypass Surgery" (cit. n. 46), p. 327; and James Jude, "Comment," *J. Florida Med. Assoc.*, 1981, 68:835.

⁵² Spodick, "Editorial: Revascularization of the Heart" (cit. n. 24).

⁵³ *Ibid.*, pp. 152, 154, 155.

thermore, the controversy did not split cleanly along disciplinary lines. Spodick blamed not surgeons, but journal editors who did not demand RCTs from surgical researchers. Braunwald collaborated with cardiac surgeons, including Nina Braunwald, his wife. Favaloro had nothing but praise for Mason Sones, his cardiologist collaborator. Effler, who rarely restrained his attacks against cardiologists, admitted that the problem was not with the whole specialty, just its older and more conservative members.⁵⁴ And some surgeons, like Takaro and his V.A. collaborators, were willing to perform trials.

Letters and editorials provide ample evidence that the debate was perceived by some as a disciplinary battle, however. Military metaphors abounded, with Effler and Edward Diethrick, who had trained with DeBakey, writing about “battle lines,” “gladiators,” and the “resistance movement.” Participants had a clear sense of right and wrong. Henry McIntosh contrasted rational skeptics and surgical zealots. Spodick earned the accolade “the conscience of cardiology” for his advocacy of RCTs. Each side accused the other of being old-fashioned. Diethrick decried the “atmosphere of notorious conservatism” that pervaded cardiology; Effler accused cardiologists of “wallowing in the glory that came with the development of the electrocardiogram (which happened in my childhood).” Cardiologists, in turn, criticized surgeons for their reliance on case series, the method “used to support previous (now discredited) operations that produced a similar relief of angina”; it was “no more scientific today than it was 40 years ago.”⁵⁵

Such rhetoric is not surprising. CABG involved the health of millions of patients and billions of dollars in physician fees. At some hospitals there was considerable tension between the two groups. Further controversy appeared in debates about whether CABG should be confined to elite academic medical centers or allowed into local community hospitals.⁵⁶

This competitiveness was exacerbated by the different histories of the cardiologists and cardiac surgeons over the previous three decades. As described by Bruce Fye, traditional taboos against cardiac surgery dissolved between 1940 and 1970, transforming the field from helplessness to hopefulness. New technologies, especially the development of cardiopulmonary bypass in the 1950s, greatly expanded surgeons’ therapeutic abilities, as demonstrated by DeBakey’s successful repairs of previously fatal aortic aneurysms. This work reached its climax with the first successful heart transplant, by Christiaan Barnard, in December 1967. The media celebrated surgeons’ heroics and chronicled the feuds between their “quite enormous egos.”⁵⁷ Such dramatic progress created a specialty of people

⁵⁴ For criticism of journal editors see David H. Spodick, “More on Coronary Bypass Surgery—II,” *Amer. J. Cardiol.*, 1979, 43:1061–1062, on p. 1061. On Eugene Braunwald’s collaboration with his wife see Harvard University Press Release, 7 Jan. 1972, Countway Library Archives, Harvard Medical School, Boston, Archives GC File: Eugene Braunwald, M.D. New York U., 1952. Sones is praised in Favaloro, *Challenging Dream of Heart Surgery*, p. 115. Effler criticizes conservative cardiologists in Effler, “Myocardial Revascularization—Direct or Indirect?” (cit. n. 17), p. 499.

⁵⁵ Donald B. Effler, “Myocardial Revascularization at the Community Hospital Level,” *Amer. J. Cardiol.*, 1973, 32:240–242; Effler, “Myocardial Revascularization—Direct or Indirect?” pp. 498–499; Edward B. Diethrick, “. . . And the War Goes On,” *Chest*, 1973, 63:83–85; McIntosh, comment following Read *et al.*, “Survival of Men Treated for Chronic Stable Angina Pectoris” (cit. n. 40); introduction given to Spodick’s Ewart Angus Lecture at the Wellesley Hospital, Univ. Toronto, 14 May 1981; Spodick, personal communication, 3 June 1998; Diethrick, “. . . And the War Goes On,” p. 83; Effler, comment following Effler *et al.*, “Coronary Endarterectomy with Patch-Graft Reconstruction” (cit. n. 13), p. 601; and Preston, “Hazards of Poorly Controlled Studies in the Evaluation of Coronary Artery Surgery” (cit. n. 23), p. 441.

⁵⁶ Braunwald remembers tensions at Boston’s Brigham and Women’s Hospital in the 1970s: Eugene Braunwald, personal communication, 17 June 1998. On the debate regarding the spread of CABG see Effler, “Myocardial Revascularization at the Community Hospital Level.”

⁵⁷ On the transformation of cardiac surgery see Fye, *American Cardiology* (cit. n. 13), pp. 164–175. DeBakey’s

with tremendous confidence in themselves, as manifested in the olympianism described by Spodick. Cardiac surgeons had learned that direct repair of damaged hearts cured patients. Why should CABG be different?

As noted earlier, cardiologists had been feeling substantially less triumphant in 1968, especially about coronary artery disease. This might have made them particularly sensitive to surgeons' enthusiastic claims about the powers of CABG. But while cardiologists might have been overshadowed in the media, they did make dramatic progress in many areas during the first decade of CABG. New understanding of risk factors, such as diet, lack of exercise, and smoking, enabled them to suggest better preventive care for their patients. New drugs enabled them to treat anemia, hypertension, and other conditions that exacerbated coronary artery disease. New technologies, including echocardiography and radio-nucleotide imaging, improved diagnostic accuracy. Better methods of resuscitation and intensive care enabled them to save the lives of patients whose coronary artery disease culminated in a heart attack. While cardiologists might have lacked the boundless confidence of their surgical colleagues, they had faith that continued work would eventually lead to definitive medical treatments of coronary artery disease. By 1978 Braunwald could declare that the "golden age" was at hand.⁵⁸ With success seemingly within their reach, cardiologists found the heroics of surgery unnecessary.

DISCIPLINARY STANDARDS OF KNOWLEDGE

Disciplinary allegiances were not simply a medium through which disagreement was voiced. The different disciplinary histories left other traces as well. By 1970 RCTs had become enshrined—in principle—as the standard for evaluating the efficacy of drug-based therapeutics. But as the debates about CABG show, the expansion of this standard into cardiac surgery met substantial resistance.

Traditionally, surgeons had relied on three types of research: animal experiments, case reports, and case series. Many groups (though not the Cleveland Clinic team) had experimented with CABG in animal models before attempting it in humans. Similarly, Favalaro's first two reports about CABG involved only small groups of patients. His evaluation focused on operative technique and technical feasibility: the patients survived and revascularization was achieved; clinical concern was secondary. Many surgeons believed that

work is treated in Michael E. DeBakey, "Developments in Cardiovascular Surgery," *Cardiovascular Research Center Bulletin*, 1980, 19:12–20; DeBakey, "Development of Vascular Surgery" (cit. n. 18); and Francis D. Moore, "Perspectives, Surgery," *Perspectives in Biology and Medicine*, 1982, 25:698–721. Barnard's transplant is discussed in Fye, *American Cardiology*, p. 297; R. Dewall and R. J. Bing, "Cardiopulmonary Bypass, Perfusion of the Heart, and Cardiac Metabolism," in *Cardiology*, ed. Bing (cit. n. 6), pp. 54–83; and J. C. Baldwin, S. A. Lemaire, and Bing, "Transplantation of the Heart," *ibid.*, pp. 104–117. For cover stories on these heroics see "The Ultimate Operation," *Time*, 15 Dec. 1967, 90:64–72; and Matt Clark, "New Hearts for Old," *Newsweek*, 18 Dec. 1967, 70:86–90. Reporting on the media circus see "Surgery and Show Biz," *Time*, 15 Jan. 1968, 71:49. For references to "quite enormous egos" see Thomas Thompson, "The Texas Tornado vs. Dr. Wonderful: Houston's Two Master Heart Surgeons Are Locked in a Feud," *Life*, 10 Apr. 1970, 68:62B–74; and "Transplants: An Act of Desperation," *Time*, 18 Apr. 1969, 93:58.

⁵⁸ Eugene Braunwald, "The First Twenty Years of the *American Journal of Cardiology*: A Chronicle of the Golden Age of Cardiology," *Amer. J. Cardiol.*, 1978, 42:5–7. See also Fye, *American Cardiology*, p. 249. On progress in cardiology during the first decade of CABG see David H. Spodick, "Current Treatment of Angina: What Do We Know?" *Louisiana State Medical Journal*, 1972, 124:99–104; McIntosh and Garcia, "First Decade of Aortocoronary Bypass Grafting" (cit. n. 20), p. 415; Aronowitz, "From the Patient's Angina to the Cardiologist's Coronary Heart Disease" (cit. n. 8); Robert A. Aronowitz, "The Social Construction of Coronary Heart Disease Risk Factors," in *Making Sense of Illness* (cit. n. 8), pp. 111–144; Fye, *American Cardiology*, p. 176; and Ryan, "Revascularization" (cit. n. 21), p. 92B.

such simple methods were sufficient to confirm the efficacy of CABG, just as they had proven the value of penicillin and appendectomies.⁵⁹

Critics had a simple response. Howard Hiatt, an oncologist at the Harvard School of Public Health, agreed that therapeutic efficacy could be self-evident in some cases, when the disease was “uniformly fatal in outcome and often devastating in manifestations.” This had been the case with appendicitis and aortic aneurysms. But coronary artery disease was not such a case: CABG “does not lead to speedy and uniform improvement,” and the symptoms of coronary artery disease “are subject to inexplicable remissions and exacerbations.”⁶⁰ Even when surgeons operated following the acute drama of a heart attack, they focused on preventing a second heart attack, a probabilistic phenomenon that could be demonstrated only with well-controlled trials. Surgeons thus faced a chronic condition that did not allow dramatic, definitive demonstrations of therapeutic efficacy. Furthermore, by moving into an area traditionally managed medically, they had to confront medical standards of knowledge—the RCT. In this model, the ensuing controversy reflected the growing pains of a new standard of knowledge introduced into surgery.

However, as already noted, the antagonists in the controversy over CABG did not split cleanly along disciplinary lines. To begin with, the status of RCTs within cardiology was complicated: RCTs did not have a monopoly on knowledge production. Instead, different standards of knowledge coexisted. Some, like Spodick, who had trained with RCT guru Thomas Chalmers, remained thoroughly committed to trials as the surest route to knowledge. Others, like Braunwald, experienced in the instrumental traditions of cardiac physiology, moved freely between advocacy of RCTs for CABG and the use of less rigorous protocols for other research questions.⁶¹

There were many reasons for cardiologists’ continuing affinity for the traditional methods of cardiac physiology. Spodick claims that cardiologists were the last of the medical subspecialists to join the RCT bandwagon because of their unique ability to measure and modify the heart’s function and dysfunction: “we can make the heart perform tricks, with everything from simple bedside maneuvers to sophisticated pharmacologic and physiologic interventions. It reacts promptly, with responses we can measure in milliseconds, and even our treatments often produce rapid and quantifiable responses.”⁶²

This ability to make the heart perform tricks had long shaped the traditions of cardiac research. Into the late 1960s cardiologists, like cardiac surgeons, maintained active research programs in cardiac physiology. Braunwald’s 1966 review of progress in cardiology reveals a veritable menagerie of animal models and organ preparations: cows, rabbits, dogs, cats, frogs, and humans; normal hearts, isolated hearts, trypsin-digested embryonic hearts,

⁵⁹ On use—or not—of animal models see Favaloro, *Challenging Dream of Heart Surgery*, p. 98; and Connolly, “History of Coronary Artery Surgery” (cit. n. 15), pp. 734–741. Favaloro’s focus is clear in Favaloro, “Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion” (cit. n. 16). For another surgeon’s view see Sir John Loewenthal, “Comment,” *Australian and New Zealand Journal of Medicine*, 1979, 9:118–120. Ellen Koch has described the empirical focus of surgical research in the 1950s: Koch, “In the Image of Science? Negotiating the Development of Diagnostic Ultrasound in the Cultures of Surgery and Radiology,” *Technology and Culture*, 1993, 34:858–893, on p. 875.

⁶⁰ Howard H. Hiatt, “Lessons of the Coronary-Bypass Debate,” *New Engl. J. Med.*, 1977, 297:1462–1464, on p. 1462.

⁶¹ See, e.g., Peter R. Maroko, Peter Libby, and Eugene Braunwald, “Effect of Pharmacologic Agents on the Function of the Ischemic Heart,” *Amer. J. Cardiol.*, 1973, 32:930–936. As Braunwald describes it, he was not an RCT “crusader” like Spodick. He believed that they were crucial for some questions but that other research designs still had tremendous value: Braunwald, personal communication, 17 June 1998.

⁶² David H. Spodick, “Controlled Clinical Trials of Cardiac Surgery—What Happens Next Time?” *Cardiovascular Medicine*, 1978, 3:871–876, on p. 871.

transplanted hearts, and acutely failing dog hearts. This physiological tradition shaped cardiologists' clinical research. In 1967 Nina and Eugene Braunwald developed a new method of treating angina, electrical stimulation of the carotid sinus. Two reports—case series based on only two, and then seventeen, patients—were published in the prestigious *New England Journal of Medicine*. A controlled trial of this new technique was only in the planning stage when Favaloro and Effler's "landmark report" on CABG made carotid sinus stimulation obsolete.⁶³

The central presence of physiological research in cardiology was strengthened, throughout the 1960s and 1970s, by a series of new technologies. As Fye has described, cardiac care units, catheterization, angiography, cardiac ultrasound, nuclear cardiology, and pacemakers all captured the attention of cardiologists. This affinity for physiological and instrumental approaches persisted as RCTs became the new standard for clinical research. Cardiologists were left suspended between ideals of research, between the rigorous power of RCTs and the simpler, more accessible appeal of case series, between statistical analyses of mortality and physiological assessments of cardiac blood flow and perfusion. While large studies and the abstracted experience of hundreds of patients provided the surest evidence of the impact of CABG on life expectancy, their generalized results could not be easily applied to the specific circumstances of individual patients.⁶⁴ More narrowly defined subgroups could improve the clinical applicability of RCTs, but they would require larger, more complicated trials. All the while cardiologists remained ambivalent about the relevance of clinical (angina, work capacity) and statistical (life expectancy) outcomes, about prioritizing the quality or the quantity of life.

IS SEEING BELIEVING?

Such ambivalence was exacerbated by disagreement about the persuasiveness of visualization. CABG, as its supporters celebrated, had direct, immediate, and visible mechanical effects. When Favaloro's team completed their first saphenous vein graft, they "could see the branches of the right coronary artery fill with blood." Subsequent publications always described the visual evidence of graft patency provided by angiography. Patient and surgeon could see that the pathological obstruction had been removed and that coronary circulation had been restored: the patient was cured. As one historian of CABG has noted, "the morphological aspect seemed so convincing and self-evident that functional proof seemed unnecessary."⁶⁵

⁶³ Eugene Braunwald, "Heart," *Annual Review of Physiology*, 1966, 28:227–266; Eugene Braunwald, Stephen E. Epstein, Gerald Glick, Andrew S. Wechsler, and Nina S. Braunwald, "Relief of Angina Pectoris by Electrical Stimulation of the Carotid-Sinus Nerves," *New Engl. J. Med.*, 1967, 277:1278–1283; Epstein, David Beiser, Robert E. Goldstein, David Redwood, Douglas R. Rosing, Glick, Wechsler, Morris Stampfer, Lawrence S. Cohen, Robert L. Reis, Nina S. Braunwald, and Eugene Braunwald, "Treatment of Angina Pectoris by Electrical Stimulation of the Carotid-Sinus Nerves," *ibid.*, 1969, 280:971–978; and Eugene Braunwald, "Myocardial Ischemia, Infarction, and Failure: An Odyssey," *Cardioscience*, 1994, 5(Suppl. 3):139–144, on p. 140 ("landmark report").

⁶⁴ Fye, *American Cardiology* (cit. n. 13), pp. 250–273; and Kolata, "Coronary Bypass Surgery" (cit. n. 20), p. 1265.

⁶⁵ Favaloro, *Challenging Dream of Heart Surgery*, p. 96 ("fill with blood"); Favaloro, "Saphenous Vein Autograft Replacement of Severe Segmental Coronary Artery Occlusion" (cit. n. 16), p. 337 (description of visual evidence); René G. Favaloro, "Saphenous Vein Graft in the Surgical Treatment of Coronary Artery Disease: Operative Technique," *J. Thorac. Cardiovasc. Surg.*, 1969, 58:178–185, on pp. 184–185 (description of visual evidence); Effler, "Role of Surgery in the Treatment of Coronary Artery Disease" (cit. n. 37), p. 377 (obstruction removed); and Schaefer, "Case against Coronary Artery Surgery" (cit. n. 6), p. 159 (functional proof unnecessary).

The appeal of visualization is easy to understand. Humans are visual creatures. Vision dominates our experience of the world, our study of nature, and our scientific epistemology. As Peter Galison has observed, “Vision and visibility have come to be culturally super-valued, not only but markedly in the history and philosophy of science.”⁶⁶ In cardiology, visualization has been a central element of research since William Harvey’s demonstrations of the circulation of the blood. Electrocardiograms became popular in the 1920s because of their ability to turn the electrical activity of the heart into a visible tracing that the cardiologist could read. In the 1940s and 1950s cardiologists learned to use contrast agents in ventricular and coronary angiography to make the soft tissues of the heart visible. The study of blood flow, especially in the coronary circulation, was a major area of research in cardiology in the 1960s; it depended on techniques of visualizing this flow, including electromagnetic flowmeters and radioisotopes.⁶⁷

Visualization of flow was crucial for treatments of coronary artery disease. Effler and his team believed that obstructed flow caused both angina and heart attacks: “Atherosclerotic obstructions that produce major myocardial perfusion deficits constitute a threat to the myocardium and, thereby, to the life of the patient.” Therefore: “Any surgical procedure that could remove, or circumvent, a significant arterial occlusion and relieve a myocardial perfusion deficit would have theoretic value.”⁶⁸ To put it simply:

flow = health
no flow = disease
restored flow = cure.

CABG cured this disease, as demonstrated by postoperative angiography.

The Cleveland Clinic team tried to document these assertions in a series of studies. In 1969 they reported that graft patency predicted relief of angina: “There was a direct correlation between the angiographic findings and the clinical evaluation.” In 1971 they used flowmeters to show that CABG increased myocardial perfusion, which increased oxygen consumption and improved cardiac output.⁶⁹ These studies confirmed the link between visualization of flow and restoration of function. If the flow could be visualized, the obstruction had been repaired and the patient had been cured. For the Cleveland Clinic team, seeing was believing.

However, while the Cleveland Clinic team found visual evidence compelling, others were less convinced. There has long been anxiety among scientists about the extent to which visualization technologies, such as angiography, accurately represent living tissue. Ellen Koch, Nicolas Rasmussen, and Peter Galison have shown that scientists often struggle to determine whether images accurately portray the objects they study. Cardiologists had debated the extent to which angiography accurately reflected the state of the coronary arteries. In a 1973 review McIntosh and his colleagues found that, in certain circumstances,

⁶⁶ Peter Galison, *Image and Logic: A Material Culture of Microphysics* (Chicago: Univ. Chicago Press, 1997), pp. 463–464. Similarly, only the visual power of electron microscopes could have resolved such crucial issues as the structure of cells and the nature of viruses: Nicolas Rasmussen, *Picture Control: The Electron Microscope and the Transformation of Biology in America, 1940–1960* (Stanford, Calif.: Stanford Univ. Press, 1997).

⁶⁷ Braunwald, “Heart” (cit. n. 63).

⁶⁸ Donald B. Effler, René G. Favaloro, and Laurence K. Groves, “Coronary Artery Surgery Utilizing Saphenous Vein Graft Techniques: Clinical Experience with 224 Operations,” *J. Thorac. Cardiovasc. Surg.*, 1970, 59:147–154, on p. 152.

⁶⁹ Favaloro *et al.*, “Direct Myocardial Revascularization with Saphenous Vein Autograft” (cit. n. 17), p. 283 (quotation); and René G. Favaloro, “Surgical Treatment of Coronary Arteriosclerosis by the Saphenous Vein Graft Technique: Critical Analysis,” *Amer. J. Cardiol.*, 1971, 28:493–495, esp. p. 494.

angiography could be “accurate”: “High quality, selective coronary arteriography can define the presence or absence of significant occlusive disease of the coronary arteries with greater than 90 percent accuracy in the hands of an experienced angiographer.” However, “the degree of correlation between what is seen on the film and what is actually present in the vessel” depended on the quality of the film and the experience of its interpreter. An analysis of the angiography in the V.A. study revealed enough problems with intra- and interobserver reliability that the researchers instituted second evaluations of all films in the study.⁷⁰

Most of the debate about coronary angiography centered on a different question of visual representation, however. Most people accepted that angiography accurately represented the state of the arteries. But they debated whether the state of the arteries represented the disease. As I have described, coronary artery disease had many facets: blocked flow both injured cells (angina) and killed cells (heart attack). Each facet could be evaluated: flow, symptoms, and mortality. Did relief of obstruction, as evidenced by the visual method of angiography, provide the most meaningful indicator of disease treatment? Or was relief of symptoms and improvement in survival, as evidenced by RCTs, more significant? Could revascularization be a meaningful “surrogate marker” for mortality?⁷¹

In an ideal world, the methods of angiography and RCT should have produced compatible data. Galison has demonstrated such a productive tension between visual and statistical traditions in physics. However, those who were skeptical about angiography saw a discontinuity in the chain of representation between restoration of flow and decreased mortality. In the 1960s Takaro and other members of the V.A. study group had learned to doubt the “functional significance of the morphological findings of angiography.” They performed a series of animal studies and concluded that angiographic findings did not reliably reflect blood flow under physiological conditions. Subsequent clinical research showed that angiographic findings did not reliably predict relief of symptoms or mortality rates. Instead, angiographic results depended on the exact position of the angiographic catheter and the pressure used when injecting the contrast media.⁷² The researchers’ critical disillusionment with angiography motivated their decision to begin the RCT of the Vineberg implants that would become the RCT of CABG.⁷³

Spodick had become similarly disillusioned with the visual evidence offered by angiography. His own experience taught him that angiographic measures of coronary artery dimensions and blood flow often did not correlate with relief of angina. The immediate

⁷⁰ Koch, “In the Image of Science?” (cit. n. 59), pp. 873, 876; Rasmussen, *Picture Control* (cit. n. 66), pp. 245, 253; Peter Galison, “Judgment against Objectivity,” in *Picturing Science, Producing Art*, ed. Caroline A. Jones and Galison (New York: Routledge, 1998), pp. 327–359; James S. Cole, Rudolf F. Trost, Kinsman E. Wright, and Henry D. McIntosh, “Who Should Have Coronary Arteriography,” *Geriatrics*, May 1973, pp. 125–129, on pp. 125, 125–126; and Katherine M. Detre, Elizabeth Wright, Marvin L. Murphy, and Timothy Takaro, “Observer Agreement in Evaluating Coronary Angiograms,” *Circulation*, 1975, 52:979–986.

⁷¹ Steven Epstein has reviewed the debates over “surrogate markers” in HIV trials: Epstein, “Activism, Drug Regulation, and the Politics of Therapeutic Evaluation in the AIDS Era” (cit. n. 5), pp. 693, 699–700.

⁷² Galison, *Image and Logic* (cit. n. 66); and T. Takaro, C. H. Dart, S. M. Scott, R. G. Fish, and W. M. Nelson, “Coronary Arteriography: Indications, Techniques, Complications,” *Ann. Thorac. Surg.*, 1968, 5:213–221, on p. 219. See also Dart *et al.*, “Internal Thoracic (Mammary) Arteriography” (cit. n. 32), p. 127; and Takaro, “Enigma of the Vineberg-Sewell Implant Operation” (cit. n. 32), p. 150.

⁷³ Takaro and his colleagues did not demand, and perform, RCTs of CABG as a knee-jerk response. RCTs were needed in this case because the two short-term indicators, angina (clinical) and angiography (physiological), were unreliable. Like Braunwald, they believed that other, less rigorous research protocols could have value in specific circumstances, as in their own small case series of carotid sinus nerve stimulation: C. H. Dart, S. M. Scott, W. M. Nelson, R. G. Fish, and T. Takaro, “Carotid Sinus Nerve Stimulation Treatment of Angina Refractory to Other Surgical Procedures,” *Ann. Thorac. Surg.*, 1971, 11:348–359.

and visible mechanistic success of CABG was reassuring but unimportant. Only evidence of long-term benefit, provided by RCTs, could demonstrate a successful treatment.⁷⁴

Takaro and Spodick did not doubt that angiography produced accurate images of coronary arteries. Rather, they doubted that angiography, as a proxy for flow, provided a meaningful representation of the disease. Since restoration of flow did not necessarily yield relief of symptoms, it could not reliably indicate that the patient's problem had been fixed. Visual evidence of revascularization did not necessarily prove that life expectancy would be increased. Since angina, in its unpredictability, was suspect as well, mortality was left as the only meaningful measure of success. And demonstration of subtle changes in mortality rates required an RCT.

But why were Effler and his colleagues so enthusiastic about the visual power of angiography, while Spodick, Takaro, and others remained unconvinced? Effler himself had noted significant limitations of angiography. In his work with endarterectomy and patch-graft repairs, he encountered a number of cases in which "the localized obstruction proved to be far more extensive than anticipated": the team had been "misled by the preoperative angiograms." Other evidence, however, suggests that the Cleveland Clinic team had access to higher quality angiography than other centers; perhaps this strengthened their faith in the technique's results.⁷⁵ Surgeons' individual clinical experiences with angiography must have contributed to their assessments of the value of its visual evidence.

VISUALIZATION AND THE GHOSTS OF TREATMENTS PAST

I have described how participants in the debates over CABG had contrasting assessments as to whether angiography could represent coronary artery disease. These views in turn determined whether they held angiography to be a reliable measure of therapeutic efficacy. Assessments of angiography had one further crucial impact: in evaluating the relevance of the legacies of the history of cardiac therapeutics, specifically the checkered history of surgical treatments of coronary artery disease.

For many skeptics, the strongest argument against CABG was the history of cardiac therapeutics. Braunwald saw a clear lesson: "even the most casual student of medical history will acknowledge the frequency of noncritical, overenthusiastic acceptance of newly developed modes of therapy, whether medical or surgical." The cycle of enthusiasm and disillusionment was painfully familiar for those concerned with the treatment of coronary artery disease. Surgeons had produced a long series of failures, "a long, chequered and, until recently, undistinguished history." Spodick and McIntosh had both learned that few therapies are "obviously efficacious." Everyone in the field was aware of the classic work of Leonard A. Cobb, E. Grey Dimond, and others on sham trials of internal mammary artery ligation. These experiments demonstrated the necessity of controlled trials.⁷⁶ Recent experience with Vineberg implants had reinforced many observers' caution.

⁷⁴ Spodick, "Current Treatment of Angina" (cit. n. 58), p. 99; Spodick, "Editorial: Revascularization of the Heart" (cit. n. 24), p. 156; and Spodick, "Letter: Surgery for Coronary Artery Disease" (cit. n. 30), p. 449.

⁷⁵ Donald B. Effler, "Myocardial Revascularization Surgery since 1945 A.D.: Its Evolution and Its Impact," *J. Thorac. Cardiovasc. Surg.*, 1976, 72:823–828, on p. 826; and Effler, "Surgical Treatment of Myocardial Ischemia" (cit. n. 15), p. 8. By the time of Favaloro's first CABG, Sones had the world's most extensive experience with angiography. In contrast, during an earlier visit to the Texas Heart Institute (1964), Favaloro had been struck by the "poor quality of their angiography": Favaloro, *Challenging Dream of Heart Surgery*, p. 60.

⁷⁶ Braunwald, "Evaluation of the Efficacy of Coronary Bypass Surgery—II" (cit. n. 41), p. 161; Braunwald, "Coronary Artery Bypass Surgery—An Assessment" (cit. n. 20), p. 733; David H. Spodick, "Letter: Surgical

Skeptics saw CABG as just the most recent entrant in this series. As Spodick noted—and Ross and Takaro agreed—“Well founded optimism for the effectiveness of coronary bypass surgery cannot be divorced from the knowledge that previous attempts at revascularization were proclaimed and hotly pursued with equal optimism.” Charles Bailey, who had experienced his own cycle of enthusiasm and disillusionment after developing endarterectomy in 1957, felt obliged “to pour cold water” on the enthusiasm for CABG generated by a Cleveland Clinic presentation at the 1970 meeting of the Society for Thoracic Surgery. He reminded the audience that in 1967 Effler had described patch-graft repairs “as the next best thing to sexual intercourse. Today he will tell you it wasn’t so good.”⁷⁷ Skeptics saw little reason to expect the fate of CABG to be different.

How did CABG enthusiasts respond? They did not deny the notorious history of coronary revascularization. After the failures of sympathectomy, omentopexy, and Vineberg implants, Effler could understand the “widespread disillusionment” of cardiologists, who saw persistent surgeons “as dubious characters, if not true charlatans.” He regretted that these early efforts had ever been made, “as the rewards were meager and the heritage of medical resentment and suspicion remains today.” Instead of denying the lessons of history, Effler and his colleagues denied their relevance: the clear moral of past failures did not apply to CABG. Why? Not because of surgical superiority, but because of the new diagnostic power of angiography. Effler argued that all previous operations had violated “the basic principle of therapy”: “treatment was undertaken before adequate diagnosis.” Traditional diagnostic methods—looking at symptoms, age, weight, occupation, ethnicity, and EKG—had yielded notoriously unreliable diagnoses. Healthy patients were given diagnoses of serious disease, while others suffered heart attacks “shortly after they have been given a clean bill of health.” Because of inaccurate diagnosis, surgeons had in the past operated on many patients who did not actually have coronary artery disease: “it is little wonder that the early era of coronary artery surgery was destined to end in disrepute.”⁷⁸

For Effler and his colleagues, this historical pattern was shattered by the advent of selective coronary angiography. As the technique spread rapidly in the 1960s, physicians—at least those who had faith in angiography—could for the first time directly visualize the coronary arteries of their patients. Sones’s “monumental work” transformed the world for surgeons at the Cleveland Clinic. It provided “visual diagnosis,” a “leap forward in our ability to read coronary disease that can be fairly likened to the impact of the invention of the printing press on the written word.” It gave surgeons “a literal ‘road map’ of the heart’s

Treatment of Aortic Stenosis,” *New Engl. J. Med.*, 1970, 282:340; and Henry D. McIntosh, “Benefits from Aortocoronary Bypass Graft,” *J. Amer. Med. Assoc.*, 1978, 239:1197–1199, on p. 1198. On the demonstrated need for controlled trials see, e.g., Hultgren *et al.*, “Evaluation of the Efficacy of Coronary Bypass Surgery—I” (cit. n. 41), pp. 159–160; and Barsamian, “Rise and Fall of Internal Mammary Artery Ligation in the Treatment of Angina Pectoris and the Lessons Learned” (cit. n. 12), pp. 213, 217–218.

⁷⁷ Spodick, “Letter: Coronary Bypass Operations” (cit. n. 24), pp. 55–56; Ross, “Surgery for Coronary Artery Disease Placed in Perspective” (cit. n. 19), pp. 1167, 1163; Herbert N. Hultgren, Timothy Takaro, Katherine M. Detre, and Marvin L. Murphy, “Aortocoronary-Artery-Bypass Assessment after Thirteen Years,” *J. Amer. Med. Assoc.*, 1978, 240:1353–1354; and Charles Bailey, comment following René G. Favaloro, Donald B. Effler, Laurence K. Groves, William C. Sheldon, and F. Mason Sones, “Direct Myocardial Revascularization by Saphenous Vein Graft: Present Operative Technique and Indications,” *Ann. Thorac. Surg.*, 1970, 10:97–111, on p. 111.

⁷⁸ Donald B. Effler, “A New Era of Coronary Artery Surgery,” *Surgery, Gynecology, and Obstetrics*, 1966, 123:1310–1311, on pp. 1311, 1310; Effler, “Myocardial Revascularization Surgery since 1945 A.D.” (cit. n. 75), p. 824; Effler, “Current Era of Revascularization Surgery,” *Surg. Clin. North Amer.*, 1971, 51:1009–1013, on p. 1009; Effler, “Surgery for Coronary Disease” (cit. n. 7), pp. 36, 38; and Effler, “New Era of Coronary Artery Surgery,” p. 1311.

blood supply, with the obstructions clearly visible.”⁷⁹ It provided preoperative diagnoses and postoperative evidence of successful revascularization.

Acknowledging the transformative power of visualization, Cleveland Clinic surgeons divided their knowledge of coronary artery disease into two eras: “that before and that after coronary angiography.” Other CABG advocates agreed about the pivotal contribution of Sones’s technique, “the seminal event that prepared the way for the development of coronary revascularization.” This new diagnostic power made angiography “the *sine qua non* of revascularization surgery.” Postoperative demonstration of graft patency, again provided by angiography, validated the era of CABG. Effler hoped that it was “an era that may never end.”⁸⁰

So while critics argued that the legacy of past failures required that the burden of proof for CABG be set very high, enthusiasts disagreed. Revascularization surgery in the era of angiography bore no relation to what had come before. For Effler, this meant that CABG should not be constrained by the failures of the past: “Whatever surgical efforts were expended before are of historical interest only, and it does little good to dwell on past failures; besides, the statute of limitations for an earlier era should have expired by now.”⁸¹

HISTORY REPEATS ITSELF?

The debates over CABG showed that faith in angiography, or lack thereof, shaped not only protagonists’ evaluations of physiological and clinical data but also their evaluations of the legacy of the history of cardiac therapeutics. In subsequent controversies over treatments of coronary artery disease, visualization remained crucial as cardiologists and cardiac surgeons struggled to apply the lessons of CABG.

By the end of the 1970s, the controversy over CABG began to diminish. Continuing study and consensus panels essentially confirmed the findings of the V.A. study.⁸² Spodick and Braunwald conceded that while survival was similar in most patients treated medically or surgically, surgery produced longer survival in some groups and better quality of life in most. Consensus panels from the American Medical Association and the National Institutes of Health agreed. For many physicians, the fact that trials had been conducted was as important as the findings themselves. As Spodick was pleased to note in 1977, “whole-sale application of the procedure finally is being channeled by appropriate studies of what it accomplishes and for whom.”⁸³

⁷⁹ Effler, “Surgery for Coronary Disease,” p. 38; and Richards, *Heart to Heart* (cit. n. 10), p. 99. On the changes wrought by angiography see Fye, *American Cardiology* (cit. n. 13), pp. 112, 175; and F. M. Sones, E. K. Shirey, W. T. Proudfit, and R. N. Wescott, “Cinecoronary Arteriography,” *Circulation*, 1959, 20:773–774.

⁸⁰ Favaloro, *Challenging Dream of Heart Surgery*, p. xv (see also Favaloro, “Critical Analysis of Coronary Artery Bypass Graft Surgery” [cit. n. 1], p. 1B); Ryan, “Revascularization” (cit. n. 21), p. 90B (“seminal event”); and Effler, “Myocardial Revascularization Surgery since 1945 A.D.” (cit. n. 75), p. 828.

⁸¹ Effler, “Myocardial Revascularization at the Community Hospital Level” (cit. n. 55), p. 240.

⁸² The V.A. researchers refined their analysis for many years: Katherine Detre, Peter Peduzzi, Marvin Murphy, Herbert Hultgren, James Thomsen, Albert Oberman, Timothy Takaro, and the Veterans Administration Cooperative Study for Surgery for Coronary Arterial Occlusive Disease, “Effect of Bypass Surgery on Survival in Patients in Low- and High-Risk Subgroups Delineated by the Use of Simple Clinical Variables,” *Circulation*, 1981, 63:1329–1338, esp. p. 1336. Other large trials were conducted: Kolata, “Coronary Bypass Surgery” (cit. n. 20), p. 1265; CASS Principal Investigators and Their Associates, “Coronary Artery Surgery Study” (cit. n. 44); and Baldwin *et al.*, “Coronary Artery Surgery” (cit. n. 6), p. 160. The basic finding of the V.A. study, as described by one cardiologist, remains true today: “the sicker the patient clinically and angiographically and the poorer the heart function, the greater my enthusiasm for surgical therapy.” Ryan, “Revascularization” (cit. n. 21), p. 94B.

⁸³ David H. Spodick, “Aortocoronary Bypass Surgery: Emerging Triumph of Controlled Clinical Trials,” *Chest*,

However, while the RCTs of CABG eventually came to be seen as a success, it had taken ten years for adequate evaluation of CABG to emerge. The experience of the RCTs of CABG became a story that no one wanted to repeat. Time, effort, money, and even patients' lives had been wasted while the controversy lingered. Participants in the CABG debates committed themselves to doing a better job the next time around. As early as 1973, Spodick argued that although "prejudice has now made it too late to do properly designed, controlled trials of bypass operations, we should at least be mindful of the need in the next procedure to come along." In 1978 Braunwald expressed the hope that after the experiences with CABG physicians would insist on "careful, objective assessment, by prospective randomized trials when necessary." These needed to be done as early as possible, "before the genie escapes from the bottle."⁸⁴

These dreams did not come true. Since the 1970s, new treatments for coronary artery disease have continued to appear and spread without trials, generating the same post hoc calls for trials. CABG was applied to the treatment of acute heart attacks as early as April 1968. Favaloro, Effler, and fellow enthusiasts quickly accepted its value: postoperative angiography showed that "the vast majority of heart muscle can be saved." Although they lacked long-term follow-up data, they believed that the operation prevented impending heart attacks and preserved heart muscle in patients experiencing heart attacks. Chalmers, McIntosh, and others demanded long-term data and called for trials: "Can we learn from our mistakes of the past?"⁸⁵

When cardiologists developed drugs, such as streptokinase and other fibrinolytic agents, that could dissolve the blood clots implicated in heart attacks, Braunwald immediately called for trials "to prevent a decade or more of confusion about the powers of this latest genie." Angiography did indeed show that streptokinase could restore blood flow through an acutely occluded vessel. But did streptokinase really prevent the progression of a heart attack? Braunwald warned that the old ideal of restoring blood flow might actually create a risk: experience from animals and patients had shown that reperfusion of myocardium during an infarction could lead to serious hemorrhage. Controversy lingered for years.⁸⁶

The desired lesson of CABG—that all subsequent treatments should be evaluated with RCTs immediately—had been inverted. CABG had demonstrated that certain kinds of techniques, particularly those supported by physiological common sense and visual dem-

1977, 71:318–319; Braunwald, "First Twenty Years of the *American Journal of Cardiology*" (cit. n. 58), p. 5; American Medical Association, "Report on Aortocoronary Bypass Graft Surgery," *J. Amer. Med. Assoc.*, 1979, 242:2701; Council on Scientific Affairs, American Medical Association, "Indications for Aortocoronary Bypass Graft Surgery," *ibid.*, 1979, 242:2709–2711; "National Institutes of Health Consensus Development Conference Statement on Coronary Artery Bypass Surgery: Scientific and Clinical Aspects," *Circulation*, 1982, 65(Suppl. 2):II-126–II-129; and Spodick, "Aortocoronary Bypass Surgery," p. 318.

⁸⁴ Spodick, "Coronary Bypass" (cit. n. 51), p. 81; and Braunwald, "Evaluation of the Efficacy of Coronary Bypass Surgery—II" (cit. n. 51), p. 162.

⁸⁵ Favaloro, "Direct Myocardial Revascularization" (cit. n. 17), p. 1041 (heart muscle saved); René G. Favaloro, Donald B. Effler, Chalit Cheanvechai, Robert A. Quint, and F. Mason Sones, "Acute Coronary Insufficiency (Impending Myocardial Infarction and Myocardial Infarction): Surgical Treatment by the Saphenous Vein Graft Technique," *Amer. J. Cardiol.*, 1971, 28:598–607; Chalmers, "Randomization and Coronary Artery Surgery" (cit. n. 31), p. 326 (learning from mistakes); and Henry D. McIntosh and Robert A. Buccino, "Editorial: Emergency Coronary Artery Revascularization of Patients with Acute Myocardial Infarction: You Can . . . But Should You?" *Circulation*, 1979, 60:247–250.

⁸⁶ Braunwald, "Let's Not Let the Genie Escape from the Bottle—Again" (cit. n. 46), pp. 1296 (quotation), 1294–1295. Trials sponsored by the National Heart, Lung, and Blood Institute and other groups did eventually appear. See Michael B. Mock, Guy S. Reeder, Hartzell V. Schaff, David R. Holmes, Ronald E. Vliestra, Hugh C. Smith, and Bernard J. Gersh, "Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass: Isn't It Time for a Randomized Trial?" *New Engl. J. Med.*, 1985, 312:916–919, esp. p. 918.

onstrations, could be incorporated into medical practice without trials. The history of angioplasty provides the most striking example. In 1977 cardiologists introduced percutaneous transluminal coronary angioplasty (PTCA) as a less invasive alternative to CABG for relieving obstructed coronary arteries. In this procedure a balloon-tipped catheter is threaded into the coronary arteries and inflated within the narrowed atherosclerotic region. By cracking the plaque and stretching the vessel walls, PTCA increases the functional lumen of the vessel, allowing new pathways for blood flow.⁸⁷

PTCA shared the aesthetic and mechanistic appeals of CABG. It modified the plaques perceived to be the cause of coronary artery disease. Its effects were direct and immediate, visualizable with angiography and real-time fluoroscopy. Furthermore, PTCA required a shorter hospital stay than CABG and was much cheaper to perform. As a result, PTCA experienced an even more spectacular spread in the 1980s than CABG had in the 1970s. The first PTCA was performed in 1977; 2,000 were performed in 1979 (compared to 144,000 CABGs). More than 80,000 PTCAs were performed annually in the mid 1980s (compared to roughly 205,000 CABGs). By the late 1980s, the number of PTCAs done by cardiologists surpassed the number of CABGs done by cardiac surgeons (see Figure 7). This growth continued into the 1990s, with more than 300,000 PTCAs performed each year.⁸⁸

As with CABG, the early spread of PTCA occurred in the absence of rigorous statistical data about its efficacy. Calls for trials came early. Spodick again led the way. In 1979 he expressed his frustration that the Food and Drug Administration did not hold new procedures to the same standards as drugs. He called on cardiologists not to repeat the mistakes surgeons had made with the Vineberg procedure and CABG: “we must not prematurely let this new genie out of its bottle.” Although PTCA seemed promising, cardiologists had not demonstrated that it provided long-term benefits. Since medical therapy already offered excellent survival rates for most patients, the main question was whether PTCA gave better relief of symptoms. Spodick hoped that hospital committees and journal editors would be “professional guardians of scientific integrity” and demand RCTs.⁸⁹ But no trials appeared.

Consensus was quickly reached that PTCA worked best for single vessel disease and CABG for left main disease. However, indications for patients with intermediate disease—“the vast majority of patients requiring revascularization”—remained ambiguous. But still no trials appeared. Calls for trials continued throughout the 1980s and early 1990s, citing RCTs as the most reliable way of comparing the symptomatic relief, the survival benefit, and the cost of PTCA and CABG. Trials comparing PTCA to CABG did not begin to be

⁸⁷ Andreas Grüntzig, “Transluminal Dilatation of Coronary-Artery Stenosis,” *Lancet*, 1978, 1:263; Donald S. Baim, “New Devices for Coronary Revascularization,” *Hospit. Pract.*, 15 Oct. 1993, pp. 41–52, esp. p. 41; Howell, “Concepts of Heart-Related Diseases” (cit. n. 8), pp. 92–93; and Charles Landau, Richard A. Lange, and L. David Hillis, “Percutaneous Transluminal Coronary Angioplasty,” *New Engl. J. Med.*, 1994, 330:981–993, on p. 981.

⁸⁸ On the visibility of PTCA’s effects see Landau *et al.*, “Percutaneous Transluminal Coronary Angioplasty,” p. 982. For the statistics see *ibid.*, p. 981; and Jay L. Hollman, “Myocardial Revascularization: Coronary Angioplasty and Bypass Surgery Indications,” *Medical Clinics of North America*, 1992, 76:1083–1097, on pp. 1084–1085. On the spectacular spread of PTCA see Fye, *American Cardiology* (cit. n. 13), pp. 301–304.

⁸⁹ David H. Spodick, “Letter: Percutaneous Transluminal Coronary Angioplasty,” *Annals of Internal Medicine*, 1979, 90:850–851 (“new genie”); Spodick, “Letter: Percutaneous Transluminal Coronary Angioplasty,” *Mayo Clinic Proceedings*, 1981, 56:526 (question of symptom relief); Spodick, “Editorial: Percutaneous Transluminal Coronary Angioplasty: Opportunity Fleeting,” *J. Amer. Med. Assoc.*, 1979, 242:1658–1659, on p. 1659 (“guardians of scientific integrity”); and Spodick, “PTCA: Need for Prospective Randomized Controlled Trials,” *Amer. J. Cardiol.*, 1983, 51:1467–1468.

published until 1992.⁹⁰ Cardiologists, who had aggressively criticized the epistemological standards of cardiac surgeons in the 1970s, thus accepted and performed coronary angioplasty for fifteen years without data from RCTs.

Like CABG enthusiasts before them, PTCA enthusiasts offered many reasons why RCTs were too difficult to conduct and too limited in their results. They cited many methodological complications: inadequate criteria for characterizing each patient's degree of atherosclerosis; variations in how the procedure is performed and in how success and complications are evaluated; statistical problems in analyzing small patient populations and rare adverse outcomes. They also complained that the trials were both too time consuming and too expensive to conduct. As Andreas Grüntzig, the developer of PTCA, stated: "the call for randomization is easily made but difficult to follow."⁹¹ Meanwhile, supporters found solace in the compelling evidence provided by angiography: as they deflated the balloon and removed the catheter, they could see blood flowing where none, or not enough, had flowed before.

Eventually, some RCTs of PTCA were completed. The parallels with CABG are striking. The results of two long-awaited trials were published, with an accompanying editorial, in the *New England Journal of Medicine* in 1994. Both trials found that, in most cases, PTCA and CABG produced equivalent long-term outcomes. In the absence of definitive answers about therapeutic efficacy, the choice was left to individual patients and doctors.⁹²

The pattern did not end with angioplasty. Starting in 1995, new techniques of minimally invasive CABG became increasingly popular in the United States. Instead of requiring a 30-cm incision through the patient's sternum, these procedures used an 8-cm "keyhole" incision and a series of small ports, like those used in laparoscopic abdominal surgery, to gain access to the heart. In some versions cardiopulmonary bypass was not used: the surgeon operated on a slowed but beating heart. Early results—from case series—showed that minimally invasive CABG caused less pain, required shorter hospital stays, and cost less than traditional CABG. Formal evaluation of its efficacy, however, did not appear.⁹³

⁹⁰ Hollman, "Myocardial Revascularization" (cit. n. 88), p. 1088. For a call for trials see Mock *et al.*, "Percutaneous Transluminal Coronary Angioplasty" (cit. n. 86), p. 917; and Tom Treasure, "Angioplasty: Where's the Proof?" *British Journal of Hospital Medicine*, 1990, 43:95, 99. For a discussion of these trials see L. David Hillis and John D. Rutherford, "Coronary Angioplasty Compared with Bypass Grafting," *New Engl. J. Med.*, 1994, 331:1086–1087, on p. 1086.

⁹¹ Andreas R. Grüntzig and Jay Hollman, "Reply to Spodick," *Amer. J. Cardiol.*, 1983, 51:1468. For examples of PTCA enthusiasts' complaints see Ronald E. Vliestra, David R. Holmes, Hugh C. Smith, Geoffrey O. Hartzler, and Thomas A. Orszulak, "Reply to Spodick," *Mayo Clin. Proc.* 1981, 56:526–527; Baim, "New Devices for Coronary Revascularization" (cit. n. 87), pp. 51–52; and Joseph Lindsay, Ellen E. Pinnow, Jeffrey J. Popma, and Augusto D. Pichard, "Obstacles to Outcomes Analysis in Percutaneous Transluminal Coronary Revascularization," *Amer. J. Cardiol.*, 1995, 76:168–172.

⁹² C. W. Hamm, J. Reimers, T. Ischinger, H.-J. Rupprecht, J. Berger, and W. Bleifeld, "A Randomized Study of Coronary Angioplasty Compared with Bypass Surgery in Patients with Symptomatic Multivessel Coronary Disease," *New Engl. J. Med.*, 1994, 331:1037–1043; S. B. King, N. J. Lembo, W. S. Weintraub, A. S. Kosinski, H. X. Barnhard, M. H. Kutner, N. P. Alazraki, R. A. Guyton, and X.-Q. Zhao, "A Randomized Trial Comparing Coronary Angioplasty with Coronary Bypass Surgery," *ibid.*, 1994, 331:1044–1050; and Hillis and Rutherford, "Coronary Angioplasty Compared with Bypass Grafting" (cit. n. 90), pp. 1086–1087.

⁹³ For descriptions of "keyhole" procedures see Tea E. Acuff, Rodney J. Landreneau, Bartley P. Griffith, and Michael J. Mack, "Minimally Invasive Coronary Artery Bypass Grafting," *Ann. Thorac. Surg.*, 1996, 61:135–137; Landreneau, Mack, James A. Magovern, Acuff, Daniel H. Benckart, Tamara A. Sakert, Lynda S. Fetterman, and Griffith, "Keyhole Coronary Artery Bypass Surgery," *Ann. Surg.*, 1996, 224:453–462; and James A. Magovern, Benckart, Landreneau, Sakert, and George J. Magovern, "Morbidity, Cost, and Six-Month Outcome of Minimally Invasive Direct Coronary Artery Bypass Grafting," *Ann. Thorac. Surg.*, 1998, 66:1224–1229. Preliminary reports have focused on initial safety, cost, and morbidity and cannot yet answer questions of long-term efficacy. See Aubrey C. Galloway, Richard J. Shemin, Donald D. Glower, Joseph H. Boyer, Mark A. Groh, Richard E. Kuntz, Thomas A. Burdon, Greg H. Ribakove, Bruce A. Reitz, and Stephen B. Colvin, "First Report of the Port Access International Registry," *ibid.*, 1999, 67:51–58.

Surgeons assumed that if the immediate revascularization was comparable to that with traditional CABG, then the long-term results should be as good. But even this had not been well studied: intra- or postoperative angiography was not consistently performed.⁹⁴ How did the technique prosper despite such lack of validation? Like traditional CABG, minimally invasive CABG provided a direct, mechanical fix for the perceived cause of coronary artery disease. When the clamps are released, the surgeon can see the blood flow. This sight was so convincing that angiography seemed unnecessary.

As cardiac surgeons continued to refine their techniques, cardiologists introduced a fundamentally new approach: gene therapy. In November 1998 Jeffrey Isner—who was first exposed to cardiology as a medical student working with Mason Sones in 1967—reported the successful use of vascular endothelial growth factor to induce the formation of new blood vessels in ischemic myocardium. Within thirty days the gene therapy had relieved angina in all five patients, each of whom had had crippling, intractable angina despite multiple previous revascularization procedures. All had evidence of improved perfusion, as visualized with single photon emission computed tomography. Isner acknowledged the ideal of an RCT and hoped that one would be done soon. But since his technique required an operation for administering the genes, a proper RCT would require a sham operation for the control group, which he, the National Institutes of Health, and the Food and Drug Administration were unwilling to allow.⁹⁵ It seems likely that Isner's treatment will be held to the high standard of an RCT once less invasive methods of gene administration are developed, both because of widespread cultural anxieties over gene therapy and because gene therapy lacks the direct, immediately visualizable appeal of both CABG and PTCA.

Meanwhile, the evaluation of these new techniques is no longer simply a matter of physicians debating their efficacy. Instead, in the financially constrained contexts of managed care, physicians must not only convince themselves, but also their insurers, not only of efficacy, but also of cost efficiency. To complicate matters further, these new technologies have become major growth areas for commercial enterprise. Physicians have formed alliances with private companies. Millions of dollars have poured in from venture capital firms. This raises serious concerns about financial conflicts of interest as physicians claim to generate objective knowledge of therapeutic efficacy.⁹⁶

As historians such as Harry Marks, Steven Epstein, and Norman Richards have shown, the ability of RCTs to resolve questions of therapeutic efficacy will always be contested. The specific case of CABG demonstrates not only the decisive role played by precon-

⁹⁴ See, e.g., Acuff *et al.*, "Minimally Invasive Coronary Artery Bypass Grafting," p. 136; Landreneau *et al.*, " 'Keyhole' Coronary Artery Bypass Surgery," p. 461; Robert R. Lazzara and Francis E. Kidwell, "Minimally Invasive Direct Coronary Bypass versus Cardiopulmonary Technique: Angiographic Comparison," *Ann. Thorac. Surg.*, 1999, 67:500–503; and Mohammad Bachar Izzat, Kim S. Khaw, Wassim Atassi, Anthony P. C. Yim, Song Wan, and H. Hazem El-Zufari, "Routine Intraoperative Angiography Improves the Early Patency of Coronary Grafts Performed on the Beating Heart," *Chest*, 1999, 115:987–990. The assumption that long-term results should be similar if early revascularization is comparable appears in Robert H. Jones, commentary following Landreneau *et al.*, " 'Keyhole' Coronary Artery Bypass Surgery," p. 460.

⁹⁵ Douglas W. Losordo, Peter R. Vale, James F. Symes, Cheryl H. Dunnington, Darryl D. Esakof, Michael Maysky, Alan B. Ashare, Kishor Lathi, and Jeffrey M. Isner, "Gene Therapy for Myocardial Angiogenesis: Initial Clinical Results with Direct Myocardial Injection of phVEGF₁₆₅ as Sole Therapy for Myocardial Ischemia," *Circulation*, 1998, 98:2800–2804 (on unwillingness to allow sham operations see p. 2804); N.S., "Gene Therapy Advances Go to the Heart," *Science News*, 1998, 154:346; and William Clifford Roberts, "Jeffrey Michael Isner, M.D.: A Conversation with the Editor," *Amer. J. Cardiol.*, 1999, 82:78, 83, 86.

⁹⁶ On money from venture capital firms see Joan O'C. Hamilton, "Bypassing the Trauma," *Business Week*, 4 Sept. 1995, pp. 32–34; on financial conflicts of interest see Stephen Klaidman, "Should Smart Operators Mix Business and Surgery?" *Ann. Thorac. Surg.*, 1998, 66:1119–1120.

ceived opinions but also the origins of such preconceptions. Personal experiences—from Spodick’s training under Chalmers to Takaro’s disillusionment with angiography—played a role. Interdisciplinary hostility, though present, was overshadowed by intradisciplinary differences in standards of knowledge, specifically the relevance of physiological and clinical measures of coronary artery disease. Assessments of the persuasiveness of visual evidence were crucial. Did angiographic demonstration of restoration of blood flow represent a successful treatment? Did angiographic diagnosis and postoperative assessment make CABG different from all the treatments that had come before? Individuals’ answers to these questions guided their evaluation of CABG and its RCTs.

Fundamentally, these cases demonstrate the consequences of the coexistence of multiple representations of a single disease. Each representation, whether physiological or clinical, visual or statistical, allows different modes of assessing therapeutic efficacy. In the case of cardiac therapeutics, the traditions of visual demonstration will always stand as an alternative to the statistical ideals of RCTs. But as Galison and others have shown, such disunity in science need not be feared.⁹⁷ The cost of pluralism might be therapeutic confusion at best and the infliction of untested treatments on patients at worst. Nonetheless, it continues to spark imaginative efforts against the “greatest scourge of Western man.”

⁹⁷ Galison concludes: “Science is disunified, and—against our first intuitions—it is precisely the disunification of science that brings strength and stability.” Galison, *Image and Logic* (cit. n. 66), p. 781. See also Koch, “In the Image of Science?” (cit. n. 59), p. 892.