James B. Herrick Lecture

The Structure of Cardiological Revolutions

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Four revolutions are transforming the cardiology of our day. The first is a social revolution. It has resulted in plummeting esteem for the medical profession reflecting disenchantment coupled with the rapid emergence of the recognition that health care is a right rather than a privilege. The second revolution, interventional cardiology, has provided powerful therapeutic tools demanding technical as well as cognitive expertise. The third, the revolution in molecular and cellular biology, is transforming our understanding of mechanisms underlying disease. Because of the seminal importance of progress in basic science to advances in clinical cardiology, features of these three revolutions are being synthesized in a fourth, a revolution transforming cardiology itself. Novel approaches are needed for optimal training of clinicians with diverse areas of interest, investigators in fundamental and clinical research, house staff, and students; for optimal use of clinical and research resources; and for optimal responsiveness to the needs of patients. They must be developed with cognizance of and fidelity to our clinical and scientific heritage. (Circulation 1993;87:2047–2054)

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The significance of the James B. Herrick Award stems from Dr. Herrick himself, who was a paragon of medicine, science, and society, and from the eminence of the American Heart Association’s Council on Clinical Cardiology, which presents the award annually. As signified in this quotation from antiquity, it is those who bestow such an honor who endow it with its significance:

“The honor paid ... is a great good for those who honor.”

—Epicurus

Vatican Sayings

The award’s past recipients epitomize excellence in patient care, teaching, and research (Table 1). Lessons learned from Dr. Herrick’s life, chronicled in his memoirs,1 are remarkably relevant to several revolutions transforming the cardiology of our day. Herrick, by his own words, was not born to be a doctor. He was enamored with literature, which he taught for a time, and particularly with Chaucer. What, then, led him to choose an arduous path in medicine? What led to his profound accomplishments?

One determinant was Dr. Herrick’s personal interaction with intellectual leaders of his day. He was impressed by speakers heard personally, not on television and not in sound bites. As he says, “The stage presence of every one of these is clearly before me as I write,” and he was writing when he was 87 years old.

He was impressed also by the men of his medical school, Rush Medical College, even more than he was by its laboratories, by the number of its beds, or by its facilities. For physicians, scientists, and teachers, it is personal interactions with patients, colleagues, and students that make the difference.

Herrick’s abiding appreciation of science is reflected by his capacity to recognize the power for good of “epoch-making events,” including the discovery of x-rays, biological chemistry, physiology, and—perhaps of particular relevance today—a scientific view of public health.

The discovery for which Herrick is so respected came relatively late in his life. Although already a specialist in cardiology, at the admonition of Mrs. Herrick, he took a workaholic’s rest cure in 1899 by traveling to Europe for a brief sabbatical in Dr. Chiari’s pathology laboratory. There, he learned to appreciate the dangers of the “tendency to worship unquestioningly, much as did the medieval physicians, at the shrine of authority.”

His appreciation of the then-emerging field of biological chemistry led to his matriculation in chemistry at the University of Chicago in the fall of 1904, when he was already 43 years old. How many can claim today to be immersed in continuing education of such high quality and of such demanding nature? In Fischer’s chemistry laboratory where Herrick was studying the structure of complex carbohydrates, his intrepid pursuit of new knowledge met a formidable foe in the form of a mini-explosion encountered while he was learning how to perform Kjeldahl determinations. Despite feeling “small,” Herrick was undaunted.
His intellectual curiosity was intense. He paid homage in his autobiography to the “scholar who investigates and does excellent work in a limited field” in preference to “one whose knowledge may be extensive but who has accomplished nothing remarkable in any particular line.”

Herrick’s profound discovery of the relation between coronary thrombosis and acute myocardial infarction was made when he was 51 years old. As he notes, “The paper when read in 1912 aroused no interest. It fell like a dud.” This should serve as solace to all whose clinical or scientific insights are met with initial skepticism or pejorative reviews. Only after what Herrick called 6 years of “missionary work” did “physicians in America and later in Europe (wake) up, and (did) coronary thrombosis (come) into its own to become later a household word translated by the laymen into ‘heart attack.’” Ironically, even his missionary zeal failed to settle the issue. It was only 68 years later, in the early 1980s, that our paradigm for heart attack fully embraced coronary thrombosis as a proximate cause.

Armed with insights from Herrick, we can better consider phenomena impacting on the practice of cardiology and cardiovascular research presently. Thomas Kuhn’s Structure of Scientific Revolutions provides a useful format for reflection. The first revolution affecting cardiology is social.

The Social Revolution

Paul Starr’s book, The Social Transformation of American Medicine, emphasizes the enormous impact of the Abraham Flexner report, disseminated in 1910. It established standards for scientific medicine. It led to the conversion of trade schools to medical schools steeped in biomedical science, but something happened: As Starr notes, modern medicine is experiencing a collapse of the cohesive center, an “end of a mandate,” and the need for “radical change.” The way it was put by Dr. Robert A. O’Rourke in a previous Herrick lecture was that “The love affair between the American public and American medicine, extant since World War II, has come to an inevitable end.”

Disenchantment is deep, and explanations are legion. Eli Ginzberg, the Hepburn Professor Emeritus of Economics at Columbia University, discussed both in his book, From Physician Shortage to Patient Shortage. He notes that World War II was a watershed. For the first time in our history, many Americans (members of the military and their families) experienced a form of prepaid health insurance and apparently free care. The concept that health care was a right rather than a privilege emerged rapidly, accompanied by what Ginzberg called “tacit political recognition of the need for universal access.” Concurrently, federal largesse for research expanded. In 1940, the federal outlay was $3,000,000. By 1987, it had increased more than 2000-fold, to $7.6 billion.

Unfortunately, however, many advocates of biomedical research began to couple federal support to the immediate cure of disease. Many urged Congress to expand the research base by implying that additional support would promptly conquer the “disease of the month.” One example was the war on cancer. The hollow nature of the promises was, of course, soon exposed by the refractoriness to prevention and cure of this and other plagues of modern society, including heart disease and acquired immune deficiency syndrome (AIDS).

Both the end of the mandate and society’s disenchantment have been fueled by the media. Sensationalism, jealousy, and disillusionment, coupled with harsh recognition of failures in our profession, contributed. Persistence of illness, not only biological but also sociological, such as tuberculosis in prisons and in the homeless as well as endemic chemical abuse and homicide, have been contrasted with allegedly unfulfilled promises of medical research. A survey of indicting headlines culled from the press even during the past few months is indicative of the relentless criticism. The indictment focuses not only on scientists but also on practitioners. It is evident day after day, week after week, on front page after front page. Its denigration is difficult to deny.

Its impact has not been lost on potential medical students. On its front page in August 1988, the New York Times called attention to the recent decline in the number of medical school applicants despite expansion of the number of positions available for them. The indictment has not been lost on potential house staff, either. In my medical school class, the class of 1962, 56% of the categorical internship matches were in medicine. In the class of 1992, the corresponding figure was 23%, a 10-year record low.

The social revolution has influenced clinical practice, induced a rush to defensive medicine, and altered clinical research. Less than a decade ago, pooling of data was viewed with skepticism because of what Furberg and Morgan called “inherent problems in any systematic pooled analysis,” including publication and overview bias, investigator bias, and lack of consideration of mechanistic determinants. Why, then, does the press now uncritically rush to embrace results of meta-analyses and megatrails with such enthusiasm? The embrace is not a result of appreciation of the elegant mathematical basis of the analytic procedures involved or the central limit theorem of statistics. More likely, it is attributable to the appeal of simplicity and a reluctance to grapple with complex mechanistic determinants.

Herrick was not oblivious to the tenuous nature of the interface between medicine and society. He asked, “Does medicine as a profession get a black eye from charges that are plainly exorbitant?” He was sensitive to the risks of undue dependence on the bureaucracy and
knew that "the valued personal relation between the patient and the doctor of his choice will be lost" if ultrapolitical methods are used by the government.

The social revolution has led to plummeting esteem for our profession, denigration of contributions of basic science to public health, and disparagement of physicians as responsible advocates for their patients.

**Interventional Cardiology**

The second revolution affects us daily, as does the first. Spawned by the brilliant contributions of Dr. Andreas Gruentzig and his colleagues, interventional cardiology emerged rapidly from the laboratory into the clinic. The vitality of training programs in interventional cardiology is evidenced by their continued exponential growth despite Dr. Gruentzig’s death in 1985.

Like so many other advances in clinical medicine, interventional cardiology was predicated on fundamental advances in basic science (Figure 1). Without Bernard’s measurements of intracardiac pressures in hearts of animals in 1847; without Roentgen’s serendipitous discovery of x-rays while he was working on Crooke’s tubes in 1895; without the courageous self–cardiac catheterization by Forssman in 1929; without the diagnostic applications of catheterization for which Courand and Richards won the Nobel Prize; without coronary angiography, pioneered by Sones in 1962; and without the invention of peripheral arterial angioplasty by Dotter, coronary angioplasty would not have been possible. Thus, we must consider a third revolution that is shaping cardiology, the revolution in basic biomedical science.

**Advances in Basic Science**

Consumed by clinical demands, we cardiologists may contemplate advances in basic science only rarely. However, their implications, even for common cardiac problems, cannot be overemphasized. As you know, hospital mortality associated with acute myocardial infarction was approximately 30% before the development of coronary care units. The advent of prompt defibrillation in coronary care units reduced hospital mortality by 50%. Elucidation of the dynamic nature of infarction, pioneered by Dr. Eugene Braunwald (see Maroko et al19), and its assessment with plasma enzyme time–activity curves in our collaborative studies with him and Drs. John Kjekshus, Peter Maroko, Robert Roberts, and William Shell,19,20 followed soon by the evolution of vigorous coronary thrombolysis to salvage jeopardized myocardium, contributed to a further reduction in hospital mortality associated with myocardial infarction and to a striking decline in overall mortality attributable to ischemic heart disease (Figure 2). In each case, progress in clinical cardiology depended on progress in basic science.

Emerging developments offer the promise of rendering very fundamental processes such as atherosclerosis amenable to prevention or amelioration. Figure 3 illustrates how the genetic expression of the physiological inhibitor of fibrinolysis, plasminogen activator inhibi-
tor–1 (PAI-1), not only in the blood but also within the vessel wall, may potentiate atherosclerosis by shifting the balance between thrombosis and thrombolysis toward thrombosis and by modifying the rate of turnover of matrix protein within the vasculature. It shows also how the vasculopathy of type II diabetes may be mediated in part by vascular PAI-1. Patients with type II diabetes have fasting hyperinsulinemia. Recently, we found that the synthesis of PAI-1 is markedly augmented in cultured hepatic and endothelial cells by pathophysiological concentrations of insulin. Precursors of insulin such as proinsulin, concentrations of which are known to be increased in plasma in patients with type II diabetes, increased the synthesis of PAI-1 as well. Thus, toxic effects of intraluminal insulin and its precursors on the vessel wall may contribute to the evolution of diabetic vascular disease.

In fact, the modern cardiologist is becoming increasingly acquainted with specific components of cells that control and modulate the genetic expression of their constituents and account for their distinctive properties. A partial list of cytokines and mediators that endow the luminal surfaces of vessels with either anticoagulant or procoagulant properties is shown in Figure 4. Undoubtedly, pharmacological modification of vessel walls to attenuate thrombosis will improve the treatment of patients with coronary, cerebral, peripheral vascular, and valvular heart disease even further in the years to come.

The Role of the Clinician

The full potential of the revolutions in interventional cardiology and in basic biomedical science will be realized by clinicians. Catheters with so-called leaky balloons and double-balloon devices have been developed already to facilitate introduction of modulators of gene expression directly into the cellular components of vessel walls.

Such methods will ultimately permit clinical cardiologists to favorably modify vessels through somatic gene therapy. Thus, if inappropriately augmented synthesis of PAI-1 or a specific cytokine or growth factor within vessel walls is shown to be a determinant of accelerated atherogenesis or restenosis, the introduction of antisense oligonucleotides to downregulate the genetic expression of the offending moiety may arrest or retard the process.

Dr. Jeffrey Leiden and his colleagues (Lin et al23) have already shown that recombinant genes can be introduced into and expressed in myocardium in vivo. Their study, auguring well for the improved treatment of cardiomyopathies, appeared in Circulation in 1990.

The initial excitement accompanying the first cardiovascular therapeutic agent produced by recombinant DNA technology, tissue-type plasminogen activator, was but a forerunner of the excitement we can expect. As Watson and Tooze25 have written, "Recombinant DNA is no ordinary technical development."

Unfortunately, today’s social revolution often disparages the revolution in basic biomedical science. It pits practitioners against scientists. However, as Pasteur noted in the Revue Scientifique in 1871, “There does not exist a category of science to which one can give the name applied science. Science and applications of science (aré) bound together as the fruit to the tree which bears it.” Pasteurization of milk met a public health need throughout the world. It was a product of microbiology, not health care economics.

The Wellsprings of Clinical Progress

One of the most eloquent advocates for the practical importance of advances in basic science was Dr. Julius H. Comroe Jr., former director of the Cardiovascular Research Institute at the University of California in San Francisco, editor of Circulation Research, and a brilliant physiologist. In a scholarly and meticulous inquiry undertaken with Dr. Robert D. Dripps, Comroe examined the top 10 clinical advances in cardiopulmonary medicine that had been made over three decades.23

In each case, the clinical advance was found to have remote roots in fundamental science. For example, open heart surgery could not have developed without Einthoven and electrocardiography, cardiac catheterization, angiography, blood typing, antimicrobial agents, anticoagulants, membrane pump oxygenators, electrical defibrillation, and numerous other critical stepping stones.

In his book, Exploring the Heart, Dr. Comroe illustrated the principle with a cartoon. He suggested that the ascent to open heart surgery, pictured here as the pinnacle of an intimidating mountain that had to be climbed, appeared to be straightforward when viewed from the front (Figure 5, left panel). However, when viewed from the back of the mountain, the ascent was unmasked as a succession of steps, each an advance in basic science (Figure 5, right panel). The ascent would not have been possible at all without advances in
anatomy, physiology, physics, microbiology, biochemistry, pharmacology, immunology, roentgenology, and bioengineering, among many others.

Forty years ago, paralytic polio evoked panic annually. Iron lungs were common. Charlatans profited by disbursing useless remedies embraced by desperate families. Fudenberg estimated that the cost of the 154,000 cases of paralytic polio anticipated between 1955 and 1961, before specific immunization, would have been $6.389 billion. As shown in Figure 6, the incidence of paralytic polio declined precipitously after Enders' observation that viruses could be grown in monkey kidney cells in culture — for which he received the Nobel Prize. His work had, in fact, not focused initially on poliomyelitis at all. Instead, it had addressed the possible role of viruses in cancer. Nevertheless, it led ultimately to the introduction of both the Salk and Sabin polio vaccines, accounting in 1955 for a precipitous decline in the number of cases of paralytic polio. The total cost of the vaccine itself was $611,000. The cost of the research and field trials was $41,000,000 — a modest sum in comparison with the $6.389 billion (in 1965 dollars) saved in only 6 years. In human terms, the savings are incalculable. The advent of specific immunization reduced the case rate of this devastating disease from 10 per 100,000 to less than one per 20,000,000 annually. As Fudenberg noted, it is unfortunate that "scientists have neglected to document the vast economic savings resulting from past expenditures in biomedical research."

In our field, clinical advances predicated on progress in basic science have reduced the incidence of death from heart disease consistently over more than two decades (Figure 2). Nevertheless, the toll continues to exceed that from other prominent disease processes (Figure 7). Its cost exceeds $110 billion annually.

Why, then, does our society commit only $1,000 per heart disease death per year to cardiovascular research? Why can we not see that a commitment to fundamental research is pivotal? These questions lead us to consider the fourth revolution, one in which we must all participate — the restructuring of cardiology itself.

**The Revolution in Cardiology**

Herrick was remarkably prescient. He recognized, a century ago, the inevitability and virtues of specialization and the necessity of avoiding a clash between the laboratory research worker and the practitioner. His admonition that "there should be friendly cooperation between these two groups" could not be more pertinent at a time when our field is under intense scrutiny; when we face increasing constraints; when many policy makers, spurred by pressures for cost containment, seek to regulate us; and when traditional support for funda-

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**Figure 4. Schematic drawings and partial list of cytokines and mediators that endow luminal surfaces of vessels with procoagulant or anticoagulant properties.** PMA, phorbol myristate acetate; vWF, von Willebrand factor; t-PA, tissue-type plasminogen activator; u-PA, urokinase-type plasminogen activator; scu-PA, single-chain u-PA; EDRF, endothelium-derived relaxation factor; PGJ_2, prostaglandin I_2; TNF, tumor necrosis factor; II-1, interleukin-1; TGF-β, transforming growth factor-β; INF, interferon; LPS, lipopolysaccharide; LDL, low density lipoprotein; TF, tissue factor; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late activation antigen-4; MHC II, major histocompatibility complex II; PAF, platelet activating factor.
mental research is being eroded. Diverse and demanding challenges confront us. We must nourish rapidly emerging sub-subspecialties such as nuclear cardiology, electrophysiology, and interventional cardiology without erecting barriers potentially detrimental to patient care. We must nourish both clinical cardiology and research at a time when the demands of each are growing exponentially. We must redefine the nature and duration of training required. We must remain dedicated to the education of students, house staff, and fellows despite ever-increasing clinical pressures.

Herrick's personal accomplishments were amplified by his vigorous participation in constructive organizations, only some of which are listed in Table 2. He might well have applauded the efforts of the Association of Professors of Cardiology, founded several years ago by Drs. Leonard Geddes, Arnold Katz, Robert O'Rourke, and Barry Zaret in response to the revolutions they sensed were transforming cardiology. Many outstanding cardiologists are lending their expertise to task forces commissioned by the association and dedicated to acquiring the data needed to define optimal courses for training of clinical cardiovascular specialists in diverse areas of expertise, training of basic and clinical cardiovascular researchers, training of house staff and students, and effective utilization of clinical and research resources (Table 3). Their work is essential.

The origin of the word "doctor" underscores the legitimacy of our involvement. Its middle English root means "teacher."27 We must be teachers not only as purveyors of facts to students, house staff, and fellows but also by empowering our fellow citizens to appreciate the wellsprings and nature of genuine advances in clinical cardiology. Through our work on the Councils of the American Heart Association, in our scientific societies, and in our medical centers and hospitals, we must make certain that the restructuring of cardiology is consistent with our scientific and clinical heritage and with our scientific and clinical responsibilities.

The "politically correct" of our day claim that biomedical science has grown to excess at the expense of patient care. Compassionate concern for the welfare of the public; recognition of the need for improved education, housing, and hygiene; reduction of crime; and the
The archetypical physician described in the prologue of the Canterbury Tales, written by Dr. Herrick’s literary icon, Chaucer, was admired (albeit with qualifications) for his knowledge of determinants of disease. If we participate responsibly in the restructuring of cardiology being shaped by both the social and scientific revolutions, if we enhance its scientific foundations, and if we ensure universal access for our patients to the remarkable clinical advances made possible by basic research, future Herrick lecturers will be able to point with pride to cardiology’s continuing contribution to the care of the sick. We will be—as Herrick might want to think of us in the words of his beloved Chaucer—"very perfect practitioners."

References

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