Adventures in Cardiovascular Research
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Abstract—This article, derived from an invited Distinguished Scientist lecture presented at the American Heart Association Scientific Sessions in 2007, reviews 4 themes (adventures) in clinical cardiovascular research carried out over a period of 58 years. It begins with the author’s introduction to cardiovascular hemodynamics during a medical school elective in 1951. The 4 adventures include valvular heart disease, hypertrophic cardiomyopathy, heart failure (HF), and myocardial ischemia. In each of these adventures, the author describes briefly what was known when he entered each field, followed by the author’s contribution to the field (the adventure), and ends with comments about the current status of the field. Of particular interest are the changes in the technologies used in clinical cardiovascular research over the past half century, commencing with pressure tracings in left heart chambers with the use of needle puncture in the operating room to genetic technologies designed to understand differences between drugs that inhibit platelet activation. The article ends with some general comments on conducting research and the rewards that can come with this activity. (Circulation. 2009;120:170-180.)

Key Words: cardiomyopathy | heart diseases | heart failure | infarction | ischemia

It was my good fortune to begin my training in cardiology in the 1950s, a most propitious time in the history of the specialty. Most important diagnostic measures and therapeutic strategies that we now take for granted had yet to be developed. For example, there was no effective treatment of hypertension. Only quinidine and digitalis were available for the treatment of arrhythmias; these drugs were also frequently used in patients with acute myocardial infarction (AMI) despite no evidence of any benefit. The coronary care unit, cardiac pacemaker, closed-chest defibrillation, thiazide diuretics, and concepts of coronary risk factors, double-blind randomized clinical trials, and evidence-based medicine were all off in the future. Nuclear cardiology, echocardiography, selective cardiac angiography, and coronary arteriography were not yet available. Yet there was considerable excitement in the small cardiology community of the time because of 2 areas in which progress was visible and future development appeared to be promising: (1) cardiac catheterization for the elucidation of cardiac pathophysiology and diagnosis and (2) the early stirrings of cardiovascular surgery.

My introduction to cardiovascular research began in 1951 when, as a senior medical student at New York University, I had the good fortune to have been accepted by Dr Ludwig Eichna to take a prolonged research elective in the cardiac catheterization laboratory that he headed at Bellevue Hospital (Figure I, left, in the online-only Data Supplement). At the time, Eichna’s laboratory was one of perhaps 2 dozen cardiac catheterization laboratories in the United States. We studied the hemodynamics in patients with chronic rheumatic valvular disease, hypertensive heart disease, and chronic HF. Cardiac output was measured by the Fick principle. We also used a primitive version of the indicator dilution technique to determine cardiac output at the bedside in patients with cardiogenic shock secondary to AMI. The calculation of systemic and pulmonary vascular resistances was considered to be “cutting-edge” clinical research and the subject of articles in prestigious journals. For instance, the finding that systemic vascular resistance was elevated in most normotensive patients with HF as well as in many hypotensive patients with cardiogenic shock attracted considerable attention. My introduction as a student to research in these 3 areas—valvular heart disease, AMI, and congestive HF—ignited my interest in these conditions, which have remained at the center of much of my subsequent research.

Valvular Heart Disease

Valvular heart disease, which was rampant in North America, especially in the northeastern United States, in the mid-20th century, was the “hottest” subject in cardiology at the time because of the recent development of closed mitral valvotomy. This was the most common operation in adults with heart disease and was being performed with increasing frequency as the number of cardiovascular surgeons multiplied. Because operation was risky and often led to adverse outcomes in patients with mitral stenosis who had more than slight mitral regurgitation, there were endless discussions.
both at the bedside and in the conference room about how to
detect the presence and severity of concomitant mitral
regurgitation.

Recording of the left atrial pressure pulse was identified as
an important goal to aid in the assessment of mitral valve
function. During my first postdoctoral fellowship, at the
Mount Sinai Hospital in New York, we measured left atrial,
left ventricular, and aortic pressures simultaneously, with the
collaboration of our surgical colleagues, who punctured all 3
sites simultaneously in open-chest patients at the time of
operation. We were able, for the first time, to measure
directly the actual transmitral pressure gradient both before
and after valvotomy in patients with mitral valve disease
(Figure 1). The hemodynamic consequences of closed finger
fracture valvotomy were usually far less impressive than
those shown in Figure 2.

My next postdoctoral fellowship was in the laboratory of
Dr André Cournand at Columbia University and Bellevue
Hospital (Figure I, right, in the online-only Data Supple-
ment). Cournand was awarded the Nobel Prize for his
contributions as the “father” of cardiac catheterization, his
studies of the pulmonary circulation in normal and diseased
humans, and the elucidation of hemodynamics in patients
with congenital and acquired heart disease, including valvular
heart disease. Up to the mid-1950s, clinical cardiovascular
research had been largely observational. However, Cournand
introduced me to what was then a new paradigm, hypothesis-
driven research, an approach that subsequently became of
immense importance to me.

In 1955, I moved to the intramural program of the National
Heart Institute, the forerunner of the National Heart, Lung,
and Blood Institute, where I had the opportunity to work
closely for the next 13 years with a talented, physiologically
oriented, cardiac surgeon, Dr Andrew Glenn Morrow (Figure
II, left, in the online-only Data Supplement), who, only 7
years my senior, taught me an enormous amount of clinical
cardiology and physiology (from a surgeon’s practical
perspective). We began our collaboration by measuring left heart
pressures directly in several hundred closed-chest subjects.

As a postdoctoral fellow in Thoracic Surgery at the Univer-
sity of Oxford, Morrow had developed transbronchial left
heart catheterization, a technique that involved puncturing
the left atrium with a needle passed through a rigid bronchoscope
(the flexible bronchoscope had yet to be developed) (Figure
III in the online-only Data Supplement). After the needle had
entered the left atrium, a thin polyethylene catheter was
passed through it into the left ventricle. “Pull-back” pressure
tracings across the mitral valve were recorded routinely for
the first time. My assignment was to record and analyze the
pressure tracings.

It is difficult to describe the excitement that we felt when
we obtained these measurements on patients with valvular
heart disease, those with left ventricular failure of varied
etiology, and adults with various forms of congenital heart
disease. Rarely did a week pass when we did not observe or
measure something that was new; occasionally, we found
something important. We experienced the exhilaration that
we imagined Lewis and Clark must have felt when they
explored the great American wilderness early in the 19th
century.

We hypothesized that if significant mitral regurgitation
were present, the left atrial pressure pulse could be modified
by pharmacologically altering systemic vascular resistance.
After studies in dogs with experimental mitral regurgitation,
we developed a new “test” for significant mitral regurgita-
tion: the extent of augmentation of the left atrial V wave,
determined by transbronchial left heart catheterization, during

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**Figure 1.** “The Hemodynamics of the Left Side of the Heart as Studied by Simultaneous Left Atrial, Left Ventricular, and Aortic Pressures: Particular Reference to Mitral Stenosis” (Reprinted from Braunwald et al1 with permission of the publisher. Copyright © 1955, the American Heart Association).

the infusion of norepinephrine. However, patient discomfort despite sedation and local anesthesia, the inability to make measurements with the patient in a steady, basal state, and the short period during which measurements could be made were obvious limitations to the transbronchial approach. Therefore, we were anxious to be able to measure left heart pressure in the cardiac catheterization laboratory. This was made possible by John Ross, Jr, who led our group in the development of transseptal left heart catheterization (Figure IV in the online-only Data Supplement). The development of cardiopulmonary bypass and open heart surgery in the late 1950s led to an even greater need for precise preoperative diagnosis because simply placing a patient on cardiopulmonary bypass entailed substantial risk.

In the early 1960s, when prosthetic mitral valve replacement became possible, patients with mitral valve disease with markedly elevated pulmonary vascular resistance were generally not submitted to operation because of the fear that the changes in the pulmonary vascular bed were irreversible and that these patients would not be benefited by this then difficult operation, especially risky in these patients. My awareness of the lability of the pulmonary circulation, which I had learned about a decade earlier in the Courand laboratory, now served me well. We tested the hypothesis that mitral valve replacement would reduce the elevated pulmonary vascular resistance by studying the effects of this procedure in patients with markedly elevated pulmonary vascular resistance. Measurements performed 6 months postoperatively showed an almost uniform reduction in this resistance (Figure V in the online-only Data Supplement). We concluded that even marked elevations of pulmonary vascular resistance in patients with mitral valve disease were reversible and should no longer be considered a contraindication to mitral valve surgery as long as the elevated left atrial pressure was lowered substantially by the procedure. As a consequence, the number of such patients eligible for these operations, especially mitral valve replacement, rose strikingly.

John Ross and I also had the opportunity to help to define the natural history of severe calcific aortic stenosis because aortic valve replacement was not yet widely practiced. We observed that most medically managed patients with aortic stenosis had a prolonged asymptomatic period, but once they became symptomatic, their prognosis was grave (Figure VI in the online-only Data Supplement). These observations led to earlier operation in symptomatic patients with severe aortic stenosis, not only in our institution but elsewhere as well.

Now we leave the 1960s and “fast forward” about 4 and a half decades. Of course, many changes have occurred in the demographics, diagnosis, and treatment of valvular heart disease. An increasing fraction of serious valvular heart disease is degenerative rather than rheumatic in etiology. The changes in the role of the cardiac catheterization laboratory have also been striking. Insofar as diagnosis and assessment are concerned, modern imaging techniques have virtually replaced the need for diagnostic cardiac catheterization, except for coronary arteriography performed to ascertain, preoperatively, the presence of coronary artery disease. The latter, too, will soon be unnecessary with advances in computed tomographic coronary angiography. On the other hand, treatment of valve disease is performed increasingly in the catheterization laboratory. Valvotomy for mitral stenosis now usually involves transseptal left heart catheterization and the inflation of a balloon that traverses the mitral orifice. The repair of mitral regurgitation, mitral annuloplasty, and aortic valve replacement are all being performed with increasing frequency in the catheterization laboratory.

Transseptal left heart catheterization was practiced widely during the 1960s and the early 1970s. It then fell into disuse as the measurement of left ventricular pressure by retrograde arterial catheterization and of pulmonary capillary wedge pressure by right heart catheterization became relatively simple. However, there is now a resurgence of transseptal left heart catheterization because it allows the treatment of mitral valve disease, as described above. This technique is now also used widely to gain access to the left atrium for electrophysiological studies and ablation procedures, especially pulmonary venous ablation for atrial fibrillation, as well as to provide access for left heart assisted circulation.

**Hypertrophic Cardiomyopathy**

I consider my adventure with hypertrophic cardiomyopathy to have been the most exciting of my professional life. In 1959, Morrow and I described 2 patients with large subaortic pressure gradients, whom we found to be particularly puzzling (Figure 3). Because the obstruction was shown to be subaortic (Figure 4), I assumed that they had membranous subaortic stenosis, a relatively uncommon congenital malformation, and that they were candidates for excision of the membrane. At operation, Morrow was shocked not to find any left intraventricular obstruction with the patients on cardiopulmonary bypass and with potassium arrest of the
heart. However, he noted in both patients that the left ventricular walls were thickened with prominent trabeculae. Although we realized that we were onto something new, we just didn’t know what it was. This ignorance was reflected in the clumsy title of our first report, entitled “Functional Aortic Stenosis: A Malformation Characterized by Resistance to Left Ventricular Outflow Without Anatomic Obstruction.”

We saw an increasing number of patients with this condition, which we soon renamed idiopathic hypertrophic subaortic stenosis, but which is now more properly termed hypertrophic cardiomyopathy. We found that it had many unusual and interesting features. With Brockenbrough, a surgical resident rotating through the cardiac catheterization laboratory, we described a sign that has proved to be a useful diagnostic aid. Shown in Figure VII in the online-only Data Supplement are left ventricular and brachial artery pressure tracings; on the left are tracings obtained from a patient with valvular aortic stenosis and regurgitation. In the beat following a premature contraction, both the left ventricular-arterial pressure gradient and the arterial pulse pressure rose, a normal response that reflected an increase in stroke volume for that beat. The right panel shows the tracings from a patient with idiopathic hypertrophic subaortic stenosis; the post-premature contraction beat again showed an increase in the systolic pressure gradient, but the arterial pulse pressure was reduced, reflecting a reduction in the stroke volume secondary to enhanced contractility of the muscular subaortic stenosis.

We hypothesized that because the subaortic obstruction was not fixed but was dependent on the muscular contraction of the left ventricular outflow tract and hence the size of the subaortic orifice, it would be quite dynamic. We examined 4 different interventions that reduced ventricular volume: infusion of the \( \beta \)-adrenergic agonist isoproterenol, the strain of the Valsalva maneuver, the administration of sublingual nitroglycerin (Figure VIII in the online-only Data Supplement), and assumption of erect posture. All 4 of these interventions increased the severity of obstruction, presumably as a result of a reduction of the diameter of the muscular area in the left ventricular outflow tract. We then described patients who had clinical features similar to those of patients with obstructive idiopathic hypertrophic subaortic stenosis but without obstruction in the resting state, in whom a systolic pressure gradient could be provoked by an infusion of isoproterenol. On the other hand, the infusion of a vasoconstrictor or the assumption of the horizontal posture, both of which increased cardiac dimensions, reduced or abolished the obstruction. It was of considerable interest that there was a positive family history consistent with autosomal dominant inheritance in almost one half of our patients (Figure IX in the online-only Data Supplement).

A 2-pronged approach to therapy was developed. In 1962, I met Dr. now Sir, James Black, who had just discovered pronethalol, the first specific intravenous \( \beta \)-receptor blocker. (This discovery, together with that of histamine-2 receptor blockers, was later rewarded with the Nobel Prize.) We observed that intravenous injection of pronethalol reduced the outflow tract pressure gradient, suggesting that adrenergic activation contributed to the obstruction. Subsequently, when oral propranolol became available, we were excited to find that this well-tolerated drug reduced symptoms and improved exercise tolerance (Figure X in the online-only Data Supplement). The other therapeutic approach was surgical. Morrow developed septal myotomy-myectomy for patients with severe obstruction whose symptoms persisted despite \( \beta \)-blocker therapy (Figure XI in the online-only Data Supplement), a procedure that has been appropriately referred to as the “Morrow” procedure. It has proved to be successful in relieving left ventricular outflow tract obstruction and reducing symptoms. In some patients, these beneficial findings have been sustained for decades. It remains the “gold standard” against which all other interventions must be assessed.

Interestingly, both of these therapies (\( \beta \)-blockade and myotomy-myectomy) that were developed almost a half century ago have stood the test of time, with \( \beta \)-blockers the first pharmacological agents that are currently recommended, while the Morrow procedure still serves as an important backup for failure of pharmacological therapy in patients with severe obstruction who have failed on medical therapy. This is unusual for therapies, which usually change quite rapidly. Of course, other drugs such as disopyramide and verapamil have also been found to be useful, and catheter-based alcohol septal ablation has, in some instances, been used in place of myotomy-myectomy.

Hypertrophic cardiomyopathy was a “poster child” of the hemodynamic era of the 1960s, largely because of the unique dynamic nature of the obstruction and its clinical sequelae. It has now become a poster child of the application of genetics to cardiology. Hypertrophic cardiomyopathy is the most common cardiac disease that is inherited in a simple mendelian fashion, occurring once in \( \approx 500 \) live births. It has been thrilling for me to observe the Seidman team at Harvard Medical School and Brigham and Women’s Hospital describe the >900 different mutations in 13 myofilament-related genes and to observe their “creation” of hypertrophic cardiomyopathy in rabbits with gene insertion.

Heart Failure

I had begun to appreciate the complexity of HF during my aforementioned research elective as a medical student. I have divided my adventure with this condition into 2 sections: (1) the study of normal and abnormal cardiac contraction and (2) the broadening of the concept of HF beyond failure of the cardiac muscle and pump.

Starling’s law of the heart was established from experiments in the dog heart-lung preparation at the beginning of the 20th century by the great British physiologist, Ernest Starling. It stated simply, “Within physiological limits, the larger the volume of the heart, the greater the energy of its contraction and the amount of chemical change at its contraction.” In the early 1960s, it was widely debated whether or not Starling’s law applied to the human heart. As was the case in valvular heart disease, the cooperation of our surgical colleagues was of critical importance to our research in this area. In the eighth of a series of investigations on Starling’s law in humans, they sewed strain gauge arches to the right ventricle, and we measured myocardial tension development.
as the arch was extended. The large increases in tension development that occurred with increasing muscle length showed that Starling’s law was clearly operative in humans. In another investigation, performed in the catheterization laboratory, large volumes of fluid were infused. As left ventricular end-diastolic pressure rose, so did stroke volume, stroke work, and stroke power; again, left ventricular performance appeared to be dependent on left ventricular end-diastolic pressure.

The late Edmund H. Sonnenblick, already recognized as a brilliant cardiovascular scientist at the age of 30 years, performed some of his most important and groundbreaking work on myocardial mechanics of normal isolated mammalian cardiac muscle at the National Heart Institute in the early 1960s. He, Morrow, and I teamed up to study the contraction of isolated human papillary muscles, which were routinely excised at the time of mitral valve replacement. Figure XII in the online-only Data Supplement shows the inverse relation between developed isometric force and the velocity of shortening at a constant resting length. This was the first demonstration of the force-velocity relation in human myocardium.

We went on to apply the principles of muscle mechanics to closed-chest humans several weeks postoperatively. Ventricular dimensions, their change, and the rate of change during the cardiac cycle were obtained by measuring the distance between clips sewn to the epicardium at corrective operations. We observed that (as in the isolated papillary muscle) when force (afterload) was increased with the infusion of methoxamine or was reduced by impeding venous return, there was a reciprocal relation between force and both the extent and velocity of myocardial shortening. These observations paved the way for subsequent studies of the effect of muscular exercise on the position of the human ventricular force-velocity relation and the effects of β-blockade on this relationship.

We also examined myocardial mechanics in experimental heart failure, which was produced in cats by surgically constricting the pulmonary artery. Three months later, the animals were euthanized, and their right ventricular papillary muscles were excised and studied in a myograph. Compared with the muscles from sham-operated cats, the force-velocity curves obtained from muscles from cats with heart failure were depressed and shifted to the left (ie, at any given end-diastolic muscle length [preload] and afterload, both the extent and the velocity of shortening were reduced) (Figure XIII in the online-only Data Supplement). This supported the hypothesis, not widely accepted at the time, that chronic HF produced by excess afterload was associated with intrinsic depression of contractility of the cardiac muscle. The latter was defined as the position of the force-velocity curve of excised cardiac muscle uninfluenced by neural activity and biochemical and hormonal milieu.

In 1962, Roland Folse, a surgical resident rotating through the catheterization laboratory, and I developed a technique for the measurement of the left ventricular ejection fraction, which we clumsily termed the “fraction of the left ventricular end-diastolic volume ejected per beat.” After extensive experimentation in an in vitro model as well as in open-chest dogs, we extended our work to closed-chest patients in the catheterization laboratory. We injected I131-labeled diodrast (a radiocontrast medium) into the left ventricular cavity through a transseptal catheter and recorded radioactivity continuously with a precordial gamma detector. Figure XIV in the online-only Data Supplement is a time-activity curve of the gamma emitter in a subject after aortic valvotomy in whom the left ventricular ejection fraction was depressed at 38%. From these studies, we concluded that: “The estimations of the fraction of the left ventricular end-diastolic volume that is ejected into the aorta during each cardiac cycle . . . provides information that is fundamental to a hemodynamic analysis of left ventricular function.” It has been gratifying to observe the continuing clinical value of the ejection fraction in assessing ventricular function. Of course, the limitations of this measurement, especially its dependence on the loading conditions of the heart, are now well recognized.

The second portion of my HF adventure involved broadening of the concept from failure of the myocardium and cardiac pump summarized above to the study of an inflammatory biomarker and the neurohormonal system in this condition. In the 1950s, a relatively crude method for detecting the presence of elevated concentrations of C-reactive protein (CRP) in serum became available. At the time, this marker of inflammation was employed clinically in the detection of rheumatic activity. The presence of any detectable CRP by this relatively insensitive method was considered abnormal. In 1956, my colleagues and I found that CRP was commonly present in the serum of patients with HF caused by chronic hypertension or coronary artery disease in the absence of rheumatic activity. This study suggested that inflammation may play a role in HF, and it was the first to show the elevation of a biomarker in this condition. If we “fast forward” by a half century to the large Valsartan Heart Failure Trial (Val-HeFT), which showed the benefit of the angiotensin receptor valsartan in HF, Anand and associates reported that CRP is indeed elevated in patients with HF and is a strong independent predictor of mortality in such patients.

In the 1890s, William Osler noted that patients with severe HF often exhibit vasoconstriction in the extremities, tachycardia, sweating, and suppression of urine formation. On the basis of these important clinical observations, we set out in the early 1960s to test the hypothesis that they were manifestations of a hyperactive sympathetic nervous system. We were fortunate that our laboratory at the National Institutes of Health was adjacent to that of Julius Axelrod, who was soon to win the Nobel Prize for his seminal work on autonomic pharmacology. In 1961, Axelrod’s technician kindly taught ours to measure norepinephrine in plasma, urine, and tissue by their newly developed fluorometric technique.

We measured plasma norepinephrine at rest and during exercise in normal subjects and in patients with HF and found that it was abnormally elevated at rest in one half of the patients. However, during exercise, the concentration exceeded the upper limit of normal in all (Figure 5). We followed this up with an analysis of 24-hour urinary excretion of norepinephrine, which we considered to be a marker of...
integrated sympathetic activity. The values in patients in New York Heart Association classes I and II HF were similar to those found in normal subjects but then rose progressively in patients in classes III and IV (Figure XV in the online-only Data Supplement). These findings indicated that the sympathetic nervous system is indeed activated in severe HF, and they suggested to us that neurohormonal disturbances could play an important role in this condition. In addition, we found that synthesis of norepinephrine occurred in the heart, and we suggested that under circumstances when the heart produced substantial quantities of norepinephrine, it might be considered an endocrine organ. We also observed that cardiac norepinephrine stores were markedly reduced in patients with HF. Unfortunately, we did not “close the loop” by studying the effects of neurohormonal disturbances on heart function. Thus, we tried to understand the role of the renin-angiotensin system in the development of HF in these patients.

The importance of neurohormonal abnormalities in the development and progression of HF is now supported strongly by the finding that both β-adrenergic blockers and angiotensin-converting enzyme inhibitors have become cornerstones in the treatment of HF. I would not be surprised if, in the not too distant future, anti-inflammatory agents will also have a role in the management of some patients with HF and the measurement of CRP not only will play a role in the identification of these patients but also will be used to assess their response to therapy.

**Myocardial Ischemia and Infarction**

My fourth adventure, myocardial ischemia and infarction, has been my longest adventure and has been ongoing since 1955. At that time, almost all we knew about the pathophysiology of myocardial ischemia was that it was caused by an imbalance between myocardial oxygen supply and demand and that angina pectoris and myocardial infarction were caused by reversible and irreversible forms of ischemia, respectively. Although it had not yet been definitively established by clinical-pathological observation, many believed that infarctions accompanied by HF and/or cardiogenic shock were usually quite large. Certainly, that was the concept to which I had been exposed in Eichna’s laboratory in the aforementioned studies on cardiogenic shock.

When I arrived at the National Institutes of Health in 1955, my clinical research was with Glenn Morrow, as described above, and my laboratory work was in the Laboratory of Cardiovascular Physiology, headed by a brilliant, scintillating scientist, Stanley J. Sarnoff (Figure II, right, in the online-only Data Supplement), the founder of the Sarnoff Foundation, who taught me a great deal about experimental design. During my first week in the laboratory, we began preparations for experiments to elucidate the determinants of myocardial oxygen consumption. We used an isolated cardiac preparation whose circulation was in series with and supported by another dog. This preparation allowed continuous measurement of the heart’s oxygen consumption with independent control of preload, afterload, heart rate, contractility, temperature, and metabolic milieu. The Table is a summary of these patients.

**Table. Determinants of Myocardial O2 Consumption**

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Adapted from Braunwald. *Tension development, contractility, and heart rate account for 92%.

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**Figure 5.** Plasma norepinephrine concentrations at rest and during exercise in patients with heart failure. The normal range is represented by the shaded area. Modified from Chidsey et al. with permission of the publisher. Copyright © 1962, Massachusetts Medical Society. All rights reserved.
of what we learned from canine experiments over a 13-year period, first in Sarnoff’s laboratory41,42 and then in mine, performed with Ross, Covell, and Sonnenblick.43 Ninety-two percent of the heart’s oxygen consumption was determined by just 3 variables: tension development, myocardial contractility, and cardiac rate.44

While the experiments on myocardial oxygen consumption were being conducted in 1 section of our laboratory, in another we were studying cardiac and circulatory control by the carotid sinuses. Stimulation of the carotid sinus nerves causes reflex release of sympathetic tone, thereby lowering arterial pressure through arteriolar vasodilation and reduced myocardial contractility; also, it slows heart rate largely by vagal activation and sympathetic release. In other words, carotid sinus stimulation reduces all 3 of the major determinants of myocardial oxygen consumption. Our team, which included Steven Epstein, Nina S. Braunwald, and Andrew Wechsler, studied the effects of electric stimulation of the carotid sinus nerves in patients with intractable angina (ie, in patients with an imbalance between oxygen supply and demand). This was accomplished with a patient-activated external power generator the size of a pack of cigarettes that sent radiofrequency signals transcutaneously through an antenna placed on the chest wall. The receiver, whose electrodes were attached to the carotid sinus nerves, was implanted subcutaneously.45,46 This approach was helpful in the management of intractable angina but was never widely adopted because of the development of aortocoronary bypass surgery, a more direct and much more effective approach to the management of severe angina pectoris.

However, our work with the carotid sinus stimulator was not wasted. In 1967, I became intrigued by the chance observation, in a patient ≈4 hours into the course of an ST-segment elevation AMI, that electric stimulation of his carotid sinus nerves reduced the height of his ST-segment elevations. When carotid sinus nerve stimulation was interrupted, his ST segments returned to their previously elevated levels; this sequence was repeated several times. This observation, an “aha” moment, led to a new hypothesis, namely, that AMI is a dynamic process taking place over hours rather than virtually instantaneously after coronary artery occlusion. When our group moved from the National Institutes of Health to the University of California, San Diego in 1968, we returned to the dog laboratory to study this further.

We reported that the quantity of myocardium that was rendered ischemic by a coronary occlusion could be altered profoundly by a number of physiological and pharmacological interventions.47,48 In considering the clinical implications of these findings, we concluded the following: “In patients with myocardial ischemic injury resulting from coronary occlusion, measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion, when effected promptly after a patient has been brought to a hospital, might reduce the ultimate size of the infarct” (emphasis added) (Figure 6). We also observed that coronary artery reperfusion performed as late as 3 hours after occlusion resulted in less pathological evidence of myocardial necrosis, less myocardial creatine kinase–MB depletion, and improved cardiac function than when the occlusion was sustained.49

Several years later, Professor E.I. Chazov and his team in Moscow reported on a patient experiencing an inferior wall myocardial infarction in whom coronary arteriography showed that the right coronary artery was totally occluded. He startled the cardiological world when patency of the occluded artery was restored by the intracoronary infusion of streptokinase.50 This observation ushered in the era of early coronary reperfusion therapy for AMI. Although restoration of the patency of the coronary arteries occluded by thrombus was clearly possible,51 it was not clear whether reperfusion actually prevented the development of ischemic necrosis. We used the then just developed technique of myocardial scintigraphy after intracoronary thallium-201 and showed that in patients after streptokinase-induced reperfusion, myocardial salvage did indeed occur.52 Because care systems needed for intracoronary injection of lytic agents immediately after arrival in the hospital were not available in the early 1980s, the intravenous route for the administration of fibrinolytic agents was substituted for the intracoronary approach.

The formation of the Thrombolysis in Myocardial Infarction (TIMI) research group, a confederation of experienced investigators sponsored by the National Heart, Lung, and Blood Institute, followed soon thereafter. In the first TIMI trial, we compared intravenous tissue plasminogen activator, a fibrin-specific lytic that had just become available, with intravenous streptokinase, the gold standard at the time. The results with tissue plasminogen activator were encouraging; at 90 minutes after the onset of administration of the lytic, both reperfusion of initially totally occluded arteries and coronary arterial patency were clearly superior with tissue plasminogen activator than with streptokinase, even though the dose and schedule of administration of tissue plasminogen activator employed, we know now, were far from optimal (Figure XVII in the online-only Data Supplement). Furthermore, achievement of coronary artery patency was associated with a 40% lower mortality than when the vessel remained occluded.54 These observations gave rise to the “early open artery theory,” which posited that if a coronary artery is
opened promptly after the occlusion and remains open, not only will cardiac necrosis be reduced, but both left ventricular function and patient survival will be improved.

Since its inception in 1984, the principal goal of the TIMI Study Group has been to conduct high-quality clinical trials that enhance the care of patients with coronary artery disease. TIMI has been involved in 52 major studies, which include a wide array of phase 1 to phase 4 trials, performed in >45 countries. These trials and database have ranged in size from <30 to >150,000 subjects. The interventions studied include fibrinolytic, anticoagulant, antiplatelet, anti-ischemic, and lipid-lowering agents as well as percutaneous coronary intervention. In addition, the TIMI Study Group has used its growing database of clinical findings, biomarkers, and genetic tests to enhance the understanding of coronary artery disease. An equally important goal has been to train the next generation of clinical investigators in this field.

Three TIMI trials are of particular interest. Given the enormous and growing prevalence of unstable angina and non–ST-segment elevation myocardial infarction, the TIMI Study Group has also focused on this syndrome. The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18 (TACTICS–TIMI 18) trial, led by Christopher Cannon, was performed in patients with acute coronary syndromes to compare an invasive strategy consisting of coronary arteriography and, if anatomically appropriate, coronary revascularization with a more conservative strategy in which catheterization was performed only if the patient experienced recurrent ischemia or exhibited a positive stress test. At 42 days, there was a significant reduction of the primary end point, consisting of death, myocardial infarction, or rehospitalization, in patients randomized to the invasive strategy compared with the primary end point, consisting of death, myocardial infarction, or rehospitalization, in patients randomized to the invasive strategy (Figure XVIII in the online-only Data Supplement).

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, again led by Cannon, demonstrated that in patients after an acute coronary syndrome, intensive lowering of low-density lipoprotein cholesterol (LDL–C) to an average of 62 mg/dL improved clinical outcome compared with guideline-approved lipid lowering (to an average of 95 mg/dL) (Figure XIX in the online-only Data Supplement). This observation is changing practice guidelines to reduce the target level of LDL–C to <70 mg/dL in patients at high risk of coronary events. Although many physicians were concerned about reducing the LDL–C to <50 mg/dL, our data showed no ill effects, even in patients whose LDL–C fell to <40 mg/dL.

The third trial was based on the observation that platelets are importantly involved in the pathogenesis of coronary thrombi, both in ST-segment elevation and non–ST-segment elevation acute coronary syndrome. Dual antiplatelet therapy with aspirin and the thienopyridine (P2Y_12 antagonist) clopidogrel has become a cornerstone in the management of these conditions. Although there is considerable interpatient variability in the response to clopidogrel, it is currently the most widely used thienopyridine. However, this variability is not observed with a new thienopyridine, prasugrel, which was shown in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation–Thrombolysis in Myocardial Infarction 44 (PRINCIPLE–TIMI 44) trial to be a much more potent, consistent, and more rapidly acting inhibitor of platelet aggregation. The TIMI Study Group, led by Steven Wiviott and Elliott Antman, recently completed the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38), a 13,608 patient trial that compared prasugrel with clopidogrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Prasugrel was significantly more effective than clopidogrel in reducing the composite end point of death, myocardial infarction, or stroke (Figure XX in the online-only Data Supplement) and reduced coronary stent thrombosis by half, although it was accompanied by more bleeding (Figure 7). The latter can probably be mitigated by lowering the dose in selected patients at high risk of experiencing these complications.

To understand this difference between the 2 thienopyridines, Mega, Sabatine, and others on the TRITON–TIMI 38 team studied common polymorphisms in the gene that encodes CYP2C19, a hepatic enzyme in the P450 class that is...
responsible for the production of the active metabolite of thienopyridine.\(^6^2\) A common polymorphism of this gene (termed *2), present in approximately one third of the population, significantly reduced the concentration of the active metabolite of clopidogrel, along with a reduction in the inhibition of platelets in response to clopidogrel. Not surprisingly, it was found that this variant is associated with more adverse clinical outcomes in clopidogrel-treated patients. Thus, these results provide evidence linking a common variant of the CYP gene to less protection from recurrent ischemic events with clopidogrel. This variant does not affect the development of the active metabolite of prasugrel, and therefore it does not interfere with the ability of this drug to block platelet aggregation.\(^6^3\)

In ongoing TIMI trials, we are investigating the potential benefits of lowering LDL-C to levels even lower than those achieved in PROVE IT–TIMI 22.\(^6^4\) We are also studying the effects of a novel protease-activated receptor antagonist in the secondary prevention of atherothrombotic events and 3 new anti–factor Xa agents, 1 intravenous and 2 orally active, in patients after an acute coronary syndrome as well as in patients with atrial fibrillation.

**Conclusions**

I would like to offer some “take-home messages” from my adventures in cardiovascular research, now conducted over a period of 58 years. The first is the immeasurable importance of early research experience with inspiring mentors. This was my very good fortune with my medical school mentor, Ludwig Eichna, as well as with my postdoctoral mentors: Andre Cournand, Glenn Morrow, and Stanley Sarnoff. I learned very different lessons from each, and I profited enormously from their generous mentorship. From these personal experiences, I became aware of our enormous opportunities and awesome responsibilities as mentors.

Second, it is important for investigators at all stages of development to identify truly important problems.\(^6^5\) Ultimately, it is the hypotheses that are tested that are of overriding importance; precious time should not be wasted asking trivial questions. In addition, investigators should not become mesmerized by a single technique but instead should adapt and become skilled in whatever techniques are required to test their hypotheses.

Third, research is no longer a “one-person show,” as it often was a half century ago, but it requires input from colleagues, some close by and others from around the world. Team building is of critical importance and requires considerable effort and sensitivity to the needs of all members of the team.

Finally, I believe that for a satisfying career in research, it should be regarded as an end in itself, rather than a means to an end, such as promotion, higher salary, increased power, or attractive job offers; all of these usually come naturally to a successful investigator. However, the principal rewards from a research career involve experiencing the thrill of the chase and the (very occasional) joy of discovering something new that turns out to be important.

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**References**


