From Pump to Molecules

John Ross, Jr

In response to Eduardo Marbán’s invitation to prepare a brief reminiscence on the occasion of the 50th anniversary of Circulation Research, I recount here a few of the ideas and events that have marked my 47 years in research.

My research career began when, fresh from a surgical internship at the Johns Hopkins Hospital, I arrived at the then National Heart Institute in 1956. There, having watched Andrew Morrow perform transbronchial left heart catheterization, I thought there must be a better way. I soon became immersed in developing a method for transseptal left heart catheterization, first in dogs, then in human cadavers, and finally in patients; thus, my first research experience proved to be “translational.” It was satisfying to later see this approach used for balloon mitral valvuloplasty and in cardiac electrophysiology.

Some Reflections on Cardiac Physiology

In the early 1960s, there was considerable ferment in the Cardiology Branch of the National Heart Institute in Bethesda within a group of investigators brought together by Eugene Braunwald, one important aspect of which concerned cardiac function. We discussed the current state of cardiac physiology, comparing the approach of Robert Rushmer in intact animals with that of Stanley Sarnoff in the tightly regulated isolated supported heart. Playfully, we formulated two laws of the heart: Rushmer’s Law “When nothing is held constant everything changes” and Sarnoff’s Law “When everything is held constant nothing changes.”

Stimulated primarily by the work of Ed Sonnenblick (then at the NIH), I pondered how we might begin to apply the principles of isolated muscle mechanics to the intact heart using an approach in which only one component of an otherwise intact system is perturbed. Assisted by Jim Covell, a method was devised for assessing cardiac function that involved sudden changes in aortic pressure during a single diastolic interval so that the subsequent heartbeat operated at unchanged preload, myocardial contractility, and heart rate, the other major determinant of cardiac performance. Under these conditions, upon ejection the left ventricle faced a higher or lower afterload. This approach demonstrated the inverse relation between afterload and in myocardial contractility, which years afterward evolved into ideas about afterload mismatch in the setting of absent or limited preload reserve in the failing heart.

Much later, in my laboratory at the University of California San Diego, we again applied this principle to another physiological problem, the role of heart rate alone in regulating enhanced myocardial contractility during exercise. Use of a compound that specifically blocks the I_{1} current in the sinoatrial node permitted us to markedly slow the nodal frequency and control the heart rate at the natural exercise level by atrial pacing during strenuous, sustained treadmill exercise in dogs. Then, with a maintained neurohormonal background, we could abruptly, briefly change the heart rate alone over a range. We discovered that remarkable decreases in myocardial contractility accompanied substantial reductions in heart rate alone, demonstrating a dominant role of the force-frequency effect in the contractility increase accompanying β-adrenergic stimulation during exercise, which led to subsequent observations on β-adrenergic regulation of the force-frequency relation in the normal and failing heart.

Thus, I learned that playfulness of the intellect sometimes can stimulate novel approaches to problem solving.

An Era of Research on Myocardial Infarction and Ischemia

When the late Robert Grant surveyed research opportunities in the late 1960s, he observed that very little research was being done on acute myocardial infarction. Consequently, an NIH initiative was launched in 1967 resulting in the funding of several Myocardial Infarction Research Units (MIRUs). The MIRU that I headed beginning in 1968, like the other MIRUs, encompassed clinical research on myocardial infarction, as well as laboratory investigations. Among the latter at the University of California San Diego were studies initiated by Gene Braunwald on the pharmacological reduction of myocardial infarct size. In the meantime, I became entranced with the possibility of salvaging ischemic myocardium by coronary artery reperfusion, and in 1972 we were able to demonstrate reduction of transmural damage at 1 week in dogs by reperfusion after 3 hours of coronary occlusion and subsequently to show delayed recovery of regional myocardial function after reperfusion following 2 hours of coronary occlusion. I wrote an editorial at the time, expressing enthusiasm for potential clinical application of reperfusion, prematurely, for it was not until 12 years later that the groundbreaking large scale GISSI clinical trial of thrombolysis in Italy showed significantly increased survival with intravenous streptokinase administration within 6 hours of symptom onset. In my view, it was Bob Grant and his initiative that stimulated the efflorescence of laboratory and clinical research on myocardial infarction and ischemia, which persists to this day.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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The Molecular/Genetic Revolution

The origin of this revolution is often credited to Watson and Crick’s publication of a molecular model for the structure of deoxyribonucleic acid (DNA). However, the critical preceding work of Oswald Avery, who reported that DNA, not a protein, was the “transforming factor” that determined bacterial inheritance generally goes uncited. As editor (Circulation, 1988 to 1993), I tried not to limit bibliographies to recent references only, but scientific reporting has become increasingly ahistorical, enhanced by the policy of many journals requiring short discussions and abbreviated bibliographies. Is not something lost when the evolution of ideas and the process of scientific discovery are not presented together with the recent research advance?

Cardiovascular research and cardiology came late to the molecular/genetic revolution, which was well established in a number of laboratories and clinical disciplines by the early 1980s. My interest was aroused when a presentation was made to the National Heart, Lung, and Blood Institute (NHLBI) Advisory Council in the mid-1980s on the potential of molecular biology for cardiovascular research. There were then very few, if any, organized research and training programs in cardiovascular molecular biology. I began a serious search for a scientist who could lead such a program; Kenneth Chien arrived in La Jolla in 1988 to undertake this task. In the ensuing years, my laboratory became involved in many collaborations with Ken Chien’s steadily expanding program, initially in physiological phenotyping, as in characterizing perhaps the first genetically engineered mouse model of dilated cardiomyopathy, and more recently in developing molecular therapy for heart failure.

The Romance of Gene Therapy

My interest in gene transfer began with the realization that genetic forms of dilated cardiomyopathy in humans account for 25% to 30% of idiopathic cases. Subsequently, while we were working with the hereditary cardiomyopathy of the hamster, a mutation in 30% of idiopathic cases. Subsequently, while we were working with the hereditary cardiomyopathy of the hamster, a mutation in 30% of idiopathic cases. Subsequently, while we were working with the hereditary cardiomyopathy of the hamster, a mutation in the 3-α-sarcoglycan gene was reported to be responsible for this disorder, and restoration of the normal protein seemed an inviting target. As a senior scientist, I was old enough to recall the use of total body hypothermia to markedly slow and protect the heart (along with other organs) during open-heart operations in adults. (I had gone from the NIH to Denver in the late 1950s to watch the cardiac surgeon Henry Swan successfully repair an atrial septal defect under hypothermia.) It occurred to me that this approach might allow us to control some of the variables that influence transvascular gene transfer by viral vectors, such as dwell time and vascular permeability. The potential negative effect of hypothermia on gene transfer proved to be more than overcome by favorable actions on other variables. Beginning in 1989, working primarily with Yasuhiro Ikeda and Yusu Gu, both then postdoctoral researchers, we found that immersion hypothermia allowed safe occlusion of both great vessels, with intra-aortic (transcoronary) delivery of cardioplegic and vascular permeability agents, followed by adenoviral vectors during a brief period of cardiac arrest. A marker gene was expressed in a high percentage of left ventricular myocytes (70% to 75%), and high transduction of 3-α-sarcoglycan protein persisted for 3 weeks. Later, working with Masa Hoshijima and Ken Chien, we successfully delivered a therapeutic gene using an adenosassociated virus in the cardiomyopathic hamster, showing long-term expression of a mutant phospholamban protein and improved cardiac function at 7 months.

The opportunity to continue with laboratory research and to contribute to new directions has been enthralling for me, and I encourage other senior scientists to stay the course.

An Era of Globalization

During nearly 50 years in research, I have witnessed the evolution of cardiovascular investigation from a focus on physiology and rheology using specialized research tools and circumscribed internal logic to an entirely new research dynamic. Globalization is generally thought of in political, economic, and cultural terms, but we have also entered a period of globalization of the scientific imagination, in which research links are occurring among many disciplines, fueling constant innovation. Biological and medical research in all fields has become multilateral, often multinational, and includes exchanges not only of ideas but also of new technologies, DNA and proteins, genes, and a variety of databases, which are greatly enhanced by the Internet. Within the 50 years encompassed by Circulation Research, we find an astonishing expansion of basic and translational research, changes aptly reflected in the current content of this journal, which should lead to solutions for many currently intractable disease mechanisms, as well as to highly specific molecular therapies.

References

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