Fifty Years of Cardiovascular Science Together

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Circulation Research began 50 years ago, as I entered medical school in St Louis, and we have grown up together. I have luckily worked during a golden age for cardiovascular medicine, when biological and engineering sciences have prospered and greatly benefited our patients. This remarkable half-century testifies to the power of science to promote health. It is a vindication of the commitment my colleagues and I made to medical science so long ago and a tribute to the mission of Circulation Research. I will trace some of the scientific milestones, reflected by my Cardiology career.

Having majored in history, I entered medical school in St Louis seriously deficient in science. I fortunately soon fell into the hands of Earl Sutherland, a physician who studied with Carl Cori and by 1952 was part of the Biochemistry faculty. He was trying to understand epinephrine action on glycogen metabolism, which subsequently led him to discover adenylyl cyclase and cAMP as the prototype “second messenger system,” winning the Nobel Prize in 1971. I worked half-time in his laboratory, purifying phosphorylase and absorbing his enthusiasm for science. During my second-year Pharmacology course, I was taught by Robert Furchgott, who received the Nobel Prize in 1998 for his work on nitric oxide. Medical school was exciting.

During internship interviews with the prestigious Chairmen of Medicine, I was surprised that they grilled me on my research, not my clinical skills. So I returned to school and with two other students embarked on my first independent research effort to develop an antibody to lupus protein for immunolocalization. I collected plasma from a patient with severe systemic lupus erythematosus by withdrawing whole blood and returning packed red cells. Surprisingly, the patient immediately went into remission, possibly the first therapeutic plasmapheresis. Several supportive faculty provided the resources I needed to purify the lupus γ-globulin, prepare antibodies in rabbits, and tag them with fluorescein to show nuclear staining.

My wife and I left in 1956 for Yale, and that was the year Forssmann, Cournand, and Richards received the Nobel Prize for the development of diagnostic cardiac catherization. During residency, I used Zoll’s external pacemaker for a series of patients with acute heart block, treated cardiac arrest unsuccessfully with the AC defibrillator, and saw the Gibbs extracorporeal circulation machine used for cardiogenic shock. This was the period when physiology studies of the 1930s developed into human diagnostics, with Circulation Research and the American Heart Association (AHA) leading the way.

In 1961, the year Starr and Edwards published their ball valve results, I began a cardiology fellowship in St Louis. I recall performing the first DC conversion for atrial fibrillation in Barnes Hospital in 1962, and not surprisingly the patient had no intrinsic sinus rhythm. My first five research publications were on cardiac hemodynamics, presented at Physiology meetings where Louis Katz, Editor of Circulation Research, sat in the front row asking critical questions. Then I committed myself to the new research field of cardiac electrophysiology, in spite of strong advice from my Chairman that the field was a dead end. To repair my poor scientific background, I traveled to the main University campus to take courses on differential equations, electricity and magnetism, and quantum mechanics. After learning to make micropipettes in Bill Searer’s laboratory and completing my first Circulation Research article on Na,K ATPase of 18 in the journal during my career, I tried to determine the electrical effects of glucose-insulin-potassium treatment of ischemic injury. It was immediately apparent that our basic understanding of cardiac electrophysiology was insufficient to ask the relevant clinical questions. Consequently, in 1963 I went to Bern, Switzerland, to work in the laboratory of Silvio Weidmann, considered the father of cellular cardiac electrophysiology. I have traced the history of basic cardiac electrophysiology in a recent article, but notable for my career was presenting my Bernese work to the Cambridge Physiological Society meeting dominated by Hodgkin and Huxley, who received the Nobel Prize in 1963, and other great physiologists such as A.V. Hill. Given the extraordinary pace of high-profile science related to the cardiovascular system, it is no wonder that we believed it would revolutionize cardiac care, although what role I could play was obscure.

When I returned to the cardiology faculty of Washington University, my patients with myocardial infarction were dying of ventricular arrhythmias. The AHA meetings were full of reports of 30% to 35% in-hospital mortality and of the new experiment with coronary care units (CCUs). After some political effort, I was allowed to open a CCU, but I found myself director and on call 24/7. It started a very rewarding collaboration with Jerry Cox of the Biomedical Computer Laboratories, developing AZTEC, a real-time arrhythmia analysis program for the CCU using a dedicated LINC computer, and setting the stage for a subsequent huge industry. Engineering was becoming a basic medical science, and it continues to make huge contributions to cardiac medicine.
In 1966, I joined Murray Rabinowitz, Ernest Page, and George Eisenman in Chicago as part of Hans Hecht’s ambitious cardiovascular research program. We helped establish the Myocardial Infarct Research Unit program of the National Heart, Lung, and Blood Institute (NHLBI), and locally I was obliged to run our computer core, computerizing the cath lab and inpatient and outpatient records. A very exciting experiment in 1978 was our use of parallel processing for 60× ECG arrhythmia analysis. In the CCU, we realized the interdependence of hemodynamic and rhythm support, using the new tools of lidocaine and the Swan-Ganz catheter. We learned that we could accelerate progress by interinstitutional cooperation, a relatively new idea in cardiology. I am particularly proud that my proposal to the NHLBI Council led to the successful Beta-Blocker Heart Attack Trial (BHAT), after several discouraging intervention trials where placebo was superior. About this time, Julius Comroe visited Chicago and interviewed me for membership on the Circulation Research editorial board. My Program Project required the first recombinant DNA approval by NHLBI for Murray Rabinowitz’ cloning work. Sharing leadership of Cardiology with the remarkable Leon Resnekov was a pleasure, but this meant that I was on-service 5 to 6 months each year. My life was frankly schizophrenic, because rarely did my basic research activity intersect directly with cardiac care. However, as Vice President for Research for the AHA and subsequently as Editor of Circulation Research, I began to see the fruits of basic cellular and molecular science translated into cardiac medicine.

Especially during the early years, my laboratory attracted outstanding PhD students and postdoctoral candidates, supported by our incredibly important NHLBI training grant (now in its 40th year at Chicago). Only later did cardiology fellows also commit themselves to this basic research. Our experiments in voltage-tension relationships, intracellular ion activities, and single perfused-cell voltage clamp were all clinically motivated, but also with much recognition from the basic science community. By 1990, I found myself chairman of Chicago’s Pharmacological and Physiological Sciences Department, overseeing three graduate programs, while continuing clinical work and venturing into molecular studies. This has given me a rare opportunity to see biomedical research from the perspectives of both the basic PhD scientist and the clinical investigator, leading to the following viewpoint.

When I started, most of the biomedical scientists were physicians; now most are PhD scientists with many years of specialist training in their field. Medicine has long recognized that specialization is beneficial, and research is no exception. PhD scientists, who can spend almost full-time in research, have now created an avalanche of basic knowledge applicable to cardiovascular disease, as published regularly in Circulation Research. Rather than our needing physicians to focus part-time on basic science, we now need physicians to translate this huge basic knowledge into clinical care. Medical schools prepare students well to practice medicine, necessary but not sufficient training for clinical investigators. Few medical graduates express interest in research, and the fraction of physicians who are engaged in research has decreased dramatically from 5% in 1984 to 2% in 1996, just when we have more and better science to transfer to medical care. The major challenge in the next decades is how to recruit, train, and support clinical investigators. Furthermore, we can no longer recruit representative study populations from only academic medical centers. Unfortunately, less than 1% of Medicare recipients participate in clinical trials.

The valiant few who undertake the long and challenging paths to both MD and PhD degrees are crucial to the leadership of cardiovascular science. By sharing both cultures, they can hold these two burgeoning cultures together. Although the PhD investigator is as eager for medical application as the clinician, those with a combined degree are a needed bridge. The stress on these people to live and excel in both worlds has become overwhelming, but we would not choose to turn the clock back to slower times. The MD in basic research is becoming a rare species now, because our system actively discourages such a career. There are still some outstanding young people following this course, driven by some internal fire, and they deserve our maximal support. We need to find ways for inclusion of community physicians in the massive translational research effort we now need. It is a testimony to the effectiveness of Circulation Research and of cardiovascular scientists of the last half-century that the future of scientific cardiovascular medicine is bright.

References

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