

## An Investigator's Journey in Cardiology

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SUMMING up 60 years in academic medicine, in hospital wards, and in research laboratories is a difficult task: memories and impressions converge and the resonance from past events continually changes. How is one to judge one's past? Many would rate it by honors received, societies elected to, or fortune amassed. I judge my life by the degree of happiness I have received from my work, from my music, and from my family. I have been fortunate in having all my life done what I love most: pursuing the science of medicine and creating music. These have formed the anchor that has given my life stability and a continuous sense of value.

### Student Years in Europe

From the beginning of medical school I was interested in science and felt that the purely clinical side was only half the coin, for without a strong emphasis on science, medicine would become stagnant. But as a medical student in Germany in the early 1930s, I had no opportunity to acquaint myself with the science of medicine. Despite having excellent teachers in physiology, such as Otto Frank, MD, who formulated the Frank-Starling law of the heart, medical students were expected to earn their MD degrees before branching into science.

Medicine was taught in big lecture halls and direct contact between a student and a patient was difficult to come by. Occasionally, we were given glimpses of advances in medical research. One such occasion was a lecture in which a professor reported work on the chemical structure of sex hormones that had just been discovered in Germany and in the United States. I do not recall any specific lectures on cardiology, the subject of my later research. One professor was well known for his course in heart percussion, which students from all over the world attended, much as today's students are drawn to courses in echocardiography and magnetic resonance imaging.

Between examinations students were free to pursue their interests in the arts and humanities. I used this time for music composition lessons and continued to compose chamber music, which I had begun writing at an early age. These preparatory studies helped me compose more professionally and,

eventually, my music was performed in the United States and Europe.

### Research in Cell and Organ Cultures

To prepare my MD thesis on platelet function, I worked in the surgery department of a university hospital in Bern, Switzerland. Intrigued by new techniques of cell culture being developed at the Carlsberg Biological Institute in Copenhagen, Denmark, I spent the next year there. Cell culture at that time was mainly confined to fibroblasts that were grown in media containing embryonic extracts, which we now know contain a multitude of growth factors. In the 1930s this was an esoteric pursuit with little practical importance. The discovery of cytokines and growth substances derived from cell cultures lay in the future, as did the use of cell cultures to grow viruses.

While I was in Copenhagen trying to culture cells infected with the Shope virus (an animal tumor virus), the institute was visited by Charles A. Lindbergh, the famous flyer, and Alexis Carrel, MD, a surgeon, both affiliated with the Rockefeller Institute (now Rockefeller University) in New York, NY. They had just published a method for perfusing isolated organs as a means of studying the interplay between perfusion fluid and perfused organs. Lindbergh had designed a device in which circulating fluid, primarily a physiological salt solution fortified with glucose and vitamins, circulated from a reservoir through the artery of an organ.

The unusual feature of the Carrel-Lindbergh perfusion system was that the pulsation rate and pressures in the organ were adjustable and sterility could be observed. For this reason the isolated organ could be perfused for weeks. The Carrel-Lindbergh system was just one in a large series of perfusion systems, beginning with the preparation first described in 1895 by Langendorff in Germany and by Martin from Johns Hopkins in 1890. Perfusion of the isolated heart has contributed greatly to our understanding of cardiac physiology. For example, in the perfused frog heart, Otto Löwi, MD, in Graz, Austria, discovered the chemical transmission of nervous impulses, and Sidney Ringer, MD, in London, England, the importance of calcium in cardiac activity; and in the perfused dog heart, Starling and Evans, also in London, discovered how foodstuffs are metabolized. Their findings induced me, in 1945, to study the nutrition of the human heart

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in situ through the collection of coronary sinus blood by means of catheterization.

Lindbergh was interested in keeping organs alive because he wanted to help a relative who suffered from valvular heart disease. He had an inquiring mind and proposed methods for operating on a patient's bloodless heart. He even thought of cardiopulmonary bypass, years before Charles Gibbons, MD, performed, in 1946, the first successful cardiopulmonary bypass.

The main disadvantage of the perfusion system was a lack of oxygen-carrying capacity in the perfusion fluid, which limited the method to very small organs. It was a shortcoming I later tried to overcome by using hemoglobin, only to find that it rapidly converted to methemoglobin. I even tried hemocyanine, the beautiful copper-containing, blue respiratory pigment that I obtained from the horseshoe crab, whose history goes back millions of years. But the horseshoe crab is a slow-moving creature that lives in cold ocean waters, its activity limited by the low oxygen dissociation curve of its hemocyanine.

### Rockefeller Institute, New York

Carrel had obtained for me a Rockefeller stipend to study the culture of whole organs. After a brief visit to the Lindbergh's home in Sevenoaks, England, I arrived in New York in 1936 to begin my apprenticeship at the Rockefeller Institute. I had read Sinclair Lewis' *Arrowsmith*, in which much of the action takes place at the McGurk Institute, a pseudonym for the Rockefeller Institute. Youth needs heroes and there were plenty of them at the Rockefeller Institute.

The constellation of institute stars included Carl Landsteiner, MD, Philip Levine, PhD, Peyton Rous, MD, and Oswald Avery, MD. Landsteiner discovered the blood groups and belonged to the now rare breed of scientists who believed in working at the bench. Levine was not only a distinguished chemist, but also had studied with the Russian musician/physician/chemist Alexander Borodin. Rous had discovered the Rous virus (chicken virus) and, at the age of 80 years, received the Nobel Prize. Avery, who also should have received a Nobel Prize, discovered the importance of nucleic acid in cellular transformations. These stars and their satellites sat at their individual luncheon tables at the institute, beneath a large painting of Lavoisier and his wife in their laboratory.

Carrel himself had performed ingenious experiments on organ transplantations and done pioneering work in vascular surgery. All of his surgical work was based on one technique, blood vessel sutures by triangulation. He had even performed the first experimental coronary bypass operation, in 1912! He was one of a handful of surgeons to receive the Nobel Prize. But his tendency to use his scientific observations as a springboard to philosophical, cultural, and even parapsychological speculations was not always appreciated by his institute colleagues.

As a young European I was unaware of the adulation and glamor surrounding Lindbergh. The man I encountered was a tall Midwesterner with a direct approach to technical problems, who was kind to younger people and had the ability to get along well with glassblowers and laboratory technicians. During the war our paths separated. When we later met again, he was involved with the preservation of endangered wildlife species and had acquired the ability to look at the past

with understanding and, therefore, at the future with equanimity.

After a short return to Denmark, I came back to New York to assume a 3-year appointment as a house officer in the Department of Surgery at the Columbia Presbyterian Medical Center. Allen O. Whipple, MD, was the department chairman and a great surgeon, beloved by his house officers, colleagues, and patients. I learned little surgery during the first year, because, Carrel's opinion to the contrary, I simply was not interested in surgery. I was still working on fundamental physiological projects such as the culture of organs, and Lindbergh often lent a helping hand with technical problems, such as adapting the perfusion system to larger organs. I recall some members of the Department of Surgery, among them Charles Drew, MD, a wonderful physician and surgeon, whom Whipple had recruited. Drew also did much to advance surgical training among black Americans.

### Homer Smith, Renal Physiology, and Johns Hopkins

When, in 1938, I was offered a position as instructor of physiology at the College of Physicians and Surgeons at Columbia University (New York, NY), I accepted. Here I finally learned physiology the hard way: by lecturing to freshman medical students and by teaching in the laboratory. I taught all fields of physiology, from circulation to neurophysiology, and began doing more structured research in circulation. I had found that an amino acid dopa (dihydroxyphenylalanine), when injected into the renal artery of an experimental animal, produced an acute rise in blood pressure. This aroused my interest in renal physiology and fortunately my publications came to the attention of Homer W. Smith, PhD, professor of physiology at New York University, with whom I spent the next 3 years. Smith was a fascinating man, who was not only a physiologist, but also a writer of novels and technical books that read like novels. His novel *Kamongo*, the story of the discovery of the lung fish, revealed Smith as a highly perceptive novelist.

Smith was then working on renal clearances, a term first used by Donald VanSlyke, PhD, of the Rockefeller Institute. Smith's concept of maximal excretory and reabsorptive capacity of the renal tubular cells was a novel approach to renal physiology.

This was the period just before Pearl Harbor, and I was eager to get back to doing clinical medicine, which I thought I could best accomplish by joining the army as a physician. Thus, when Warfield Longcope, MD, head of the Department of Medicine at Johns Hopkins Hospital, offered me a job as instructor, I accepted. At Hopkins I hoped to gain the clinical preparation I needed to pass the practical part of the National Board Examination and thus qualify for a commission in the medical corps. It was wartime and many staff physicians had gone overseas. I was given a Commonwealth Grant to study hypertension and I attended as an assistant resident. My interest was neurogenic hypertension, which ensues from cutting the buffer nerves; I published a paper on treating this type of hypertension with sympatholytic drugs.

Longcope was a wonderful chief and a superb clinician whose medical rounds provided the preparation I needed. Soon I was ready to join the US Army Medical Corps. In 1943, I was ordered to report to Edgewood Arsenal in Maryland to work on chemical warfare agents. My superior officer was Arthur Gilman, MD (a major), who, with Louis Good-

man, MD, had published a classic textbook of pharmacology. The Medical Corps Division at Edgewood Arsenal was replete with talent, including Oscar Bodansky, MD (a major), in biochemistry, and David Karnovsky, MD (a captain), who later became a leading oncologist.

### **Congenital Heart Disease and Heart Catheterization**

One day, while eating in the mess hall, I received a call from Alfred Blalock, MD, head of the Department of Surgery at Johns Hopkins Hospital, offering me a position in the Department of Surgery to set up a laboratory for the physiological study of congenital heart disease. Blalock had already operated on children with the tetralogy of Fallot. The surgical technique (subclavian pulmonary artery anastomosis) had been experimentally used in 1929, when Blalock, together with Sanford Leeds, MD, anastomosed the subclavian artery to the pulmonary artery. Blalock also wanted to investigate whether an increase in pulmonary flow could elevate pulmonary artery pressure. Technically he was ready for Dr Helen Taussig's suggestion that hypoxemia in the tetralogy of Fallot could be relieved by increasing pulmonary blood flow. Taussig's idea—that decreased pulmonary blood flow produces decreased oxygen tension in peripheral arterial blood—was incorrect. Rather, hypoxemia in the tetralogy of Fallot is the result of a shunt of unsaturated blood into the systemic circulation. But, as sometimes happens, the wrong idea produced the right solution.

Blalock was a superbly trained physiologist and surgeon, who already had made outstanding contributions to the understanding of circulatory failure. He was extremely polite and pleasant, but a tough surgeon and, like many great people, had an iron will to succeed. His outstanding attribute was a simplicity and directness of approach, which was also one of Taussig's characteristics. Taussig's greatness was not in the field of science or research, but in the clinical approach. She could remember a child's clinical findings for years and associate them with the personality of the child and the child's family. Being deaf, she relied primarily on visual and fluoroscopic examination. Thus, she formulated disease patterns by simple clinical observation.

It became clear from the beginning that right heart catheterization was to be my main investigative tool. At that time there were mainly two other centers using this new technique: that of Lewis Dexter, MD, at Harvard University Medical School in Boston, Mass, and that of Andre Cournand, MD, and Dickinson Richards, MD, at Columbia University in New York. Blalock was surrounded by brilliant young surgeons, among them, Mark Ravitch, MD, Bill Longmire, MD, Denton Cooley, MD, Henry Bahnson, MD, Frank Spencer, MD, and David Sabiston, MD.

The equipment in the catheter laboratory was archaic. Electronic equipment for pressure measurements did not exist. Instead, pressures were measured with a "Hamilton manometer," using a thin membrane with an attached mirror. Often, at critical moments the system sprang a leak. There was no x-ray image amplification, and fluoroscopy during catheterization was a health hazard because of high radiation emissions.

But it was an exciting period. Cardiac surgery was developing rapidly and the treatment of congenital cardiac defects had made preoperative diagnosis a necessity. Thus, a new specialty was born, pediatric cardiology. By means of data

collected during cardiac catheterization, we could define many congenital malformations according to their physiological pattern. But the most challenging question was how children with congenital heart disease adapt to extremely low blood oxygen tension. After several years, work on congenital heart disease became mainly diagnostic. This was understandable: the chips were down in the operating room where a correct diagnosis determined the operative course.

When the work on congenital heart disease had become routine, we discovered that we could at will catheterize the coronary sinus of the human heart. This opened a new and exciting vista for the study of cardiac metabolism; it enabled us to determine the human heart's consumption of foodstuffs and oxygen. It was difficult to pursue this work at the Johns Hopkins Hospital, because of the heavy diagnostic load of patients with congenital heart disease. Therefore, in 1951, when I was asked to join the University of Alabama School of Medicine in Birmingham as a professor of medicine, I eagerly accepted. The new position would give me ample opportunity to study cardiac metabolism in the human heart.

### **Cardiac Metabolism: Birmingham**

The medical school in Birmingham was just starting to attain excellence; under Tinsley Harrison, MD, in medicine there was a spirit of scientific adventure at the medical school and, more important, the freedom to pursue scientific goals. This was to a large extent due to Harrison, who had always rebelled against stultifying medical traditions. He was a long-standing friend and mentor of Blalock, but preferred to work in an environment that he could build up from the ground, and the University of Alabama was the beneficiary. Everything he did was driven by enthusiasm; and his much read monograph *Failure of the Circulation* was a landmark.

In our study of cardiac metabolism, we discovered that the human heart under certain conditions prefers free fatty acids as fuel and that their metabolism utilizes most of its oxygen. We also found that in myocardial failure, myocardial extraction of foodstuffs is not altered. This directed our attention to the contractile proteins of the failing heart. The 3 years I spent in Birmingham were not only scientifically productive, but also enjoyable for the whole family. I learned that good work flourishes in an environment that promotes freedom and respect for good work.

### **Clinical Medicine: Washington University**

Again, it was a telephone call that set the family on the move. I was offered the position of professor of medicine and director of the Washington University Service at the Veterans Hospital in St Louis, Mo, and accepted because of the extensive clinical opportunities it would provide. At Washington University I encountered a different pattern of academic structure and philosophy. Carl Moore, MD, head of the Department of Medicine, insisted on being addressed by his first name. In Europe this would have been heresy and landed the offender in a psychiatric institution, or worse. But with Moore it seemed natural. His ward rounds were devoid of pomp, and his approach to patients was simple, direct, and friendly. The spirit of Washington University was one of excellence and ambition. The clinical pathology conference and grand rounds were well prepared and formidable forums for learning. Medical research was given high priority and, here too, patient care and teaching flourished in the spirit of

freedom, much to the benefit of the Washington University service at the Veterans Hospital.

Many institutions consider medical research a luxury; others pay little attention to either research or teaching and consider only the daily care of patients to be important. Without question, excellent and compassionate patient care is the cornerstone of medicine. But if medicine is to progress, there must also be a total commitment to research and teaching. If a hospital aspires to become a teaching hospital, it must integrate patient care, teaching, and research.

In the inspiring environment at Washington University our research was directed to investigating the role of contractile proteins in myocardial failure. The technical means were primitive, but medical developments are limited by the status of the mother sciences, physics, chemistry, and molecular biology, and benefit from their progress. Myocardial failure is a good case in point. I recall heated discussion at the meeting of the Association of American Physicians in Atlantic City, NJ, in early 1950 over whether a low cardiac output was the hallmark of congestive heart failure, or whether a "white raven," that is, an increase in resting cardiac output, was compatible with this condition. Later came the period of accurate hemodynamic measurements, and myocardial failure was defined in terms of cardiac contractility.

With refinements in our approach to cardiac metabolism, we could explore changes in the chemistry and function of subcellular structures and particularly the role of calcium. Finally, molecular biology has lent new tools for the study of certain types of myocardial failure. Altered gene expression or downregulation of certain receptors can cause a decline in myocardial function. The computer has also invaded medicine and with it, to my regret, has come canned information and a superficial approach to the broader aspects of medicine. Rarely does the data search go back more than 10 years!

#### **Chairman, Department of Medicine, Wayne State University**

I always wanted to be chairman of a department of medicine. It was an ambition kindled by my European background, where a departmental chairman, or *Ordinarius*, is considered next to the deity. In reality nothing is further from the truth. A good chairman does not have an easy life. He must subjugate his personal interests to those of his institution and department. He must be a father figure, a political wizard, and set an example. Should administrative powers decide to interfere, he will be powerless to achieve his goals. To succeed, the departmental chairman and the school's administration must show mutual good will, without which every slight misstep will result in a painful fall.

In 1959 I accepted the appointment as chairman of the Department of Medicine at Wayne State University in Detroit, Mich, a university located in a poor, inner-city neighborhood. The Receiving Hospital, the main teaching hospital at that time, was also located in the inner city, which added a tremendous burden on the staff and administration. As in an underdeveloped country, the niceties of university life, such as basic or clinical research, often appeared frivolous in the face of the number of people needing urgent attention. In the clinical department, patient care was the most pressing concern. Research cannot flourish in an environment where it is considered a mere luxury. Even good patient care is difficult when funds are lacking.

Being chairman of a department of medicine also demands

complete devotion to clinical duties. I faithfully made ward rounds three times weekly and met with the house staff every morning. But I was not an astute administrator. There are medical schools where the department heads and the dean's office work closely together, and with good will on both sides, many difficulties can be overcome. There are also schools where the department chairmen and the administration are at odds. In my case, add to this a recurring conflict: despite my devotion to clinical teaching I always had an eye on research. Given the burden of daily patient care at Wayne State, research had, I felt, assumed a secondary priority.

In 1956 I was approached by some scientists interested in cardiac metabolism, among them George Rona, MD, and Eors Bajusz, MD, to help found a professional society that would focus exclusively on fundamental cardiac research. I was asked to serve as the first president of the International Society for Heart Research as well as editor-in-chief of the society's new publication, the *Journal of Molecular and Cellular Cardiology*. Being responsible for editing a new journal was a unique experience. To guarantee its financial survival, we had first to attract enough subscribers. Fortunately, this posed no problem, as the society soon had enough members.

An editor responsible for a new journal is wise to look primarily at the overall scientific value of the papers submitted and less at the details of a submitted paper. It is always bad policy to review a paper for publication with the purpose of finding its weak spots. Also objectionable is for a journal to value itself according to the number of papers it rejects, a practice similar to judging a country's judicial system by the number of executions. Many excellent papers, containing material that later proved seminal, have been rejected.

#### **Coda: California**

After 10 years as chairman of medicine, the family moved to California, where, thanks to the kindness and generosity of friends, I am still deeply involved in research on the role of the endothelium, on coronary and cerebral microcirculation, and on isolation of immunologically active cells. California has been an unusual but rewarding experience. I started a residency training program at the Huntington Memorial Hospital in Pasadena and joined the Huntington Medical Research Institutes, where I am currently working. Although the institute has no direct university connections, it shares with the California Institute of Technology a range of excellent research projects that are carried on in a cooperative spirit.

I have been especially fortunate in having both a loving family and a second career in music. I have composed more than 250 works for chorus or chamber ensembles, some of which have been performed and recorded. Music has smoothed many of the rough edges of my life and made personal loss endurable.

When I envision the future of medicine I see the art of medicine persisting, even in the face of profound social changes. But what of medical research, the science of medicine? Here the future is less certain. The tremendous medical advances made during the last 50 years have been largely due to knowledge derived from the fundamental sciences. To guarantee the future of scientific medicine, I believe we must teach its importance to medical students and house staff: this is our best guarantee for the future of medicine. Let us hope that the combined voice of the physician, the scientist, and the artist will never be stilled.