FROM BELOW THE GREAT RIVERS

Frans J. T. Wackers

I was born in 1939 in the south of the Netherlands, in the province of Limburg, in a small town called Echt. As in many other countries, the Dutch are convinced that people of the north are distinctly different from those in the south. In the Netherlands you are either from "above or below the great rivers," that is the rivers Rhine and Meuse. In Dutch stereotypes, people from the north are Protestant, more industrious and successful, and speak "civilized" Dutch, whereas people from the south are predominantly Catholic, more laid-back, less ambitious, and they pronounce the harsh guttural "G" of the Dutch language with a much softer "g" sound.

My family has deep roots in the south. The name Wackers is found as early as 1590 in the town records of Echt. One of my ancestors, a Herman Wackers, is then mentioned as the mayor of the town. Because of its long lineage, our family has been of some interest to regional genealogists. I quote from a recent article:

> The Wackers family is considered one of the most distinguished farmer families in Middle Limburg. Many of its members have served in civic positions in the region, as mayors, aldermen, tax collectors, etc. Thus, through regional authority and landownership this family was capable to maintain its social status and position at the same level for centuries.

My father, Thom Wackers, son of a mayor, was the first of his family to go north and study medicine at the University of Amsterdam. After obtaining his M.D. degree in 1935, he married a girl from Amsterdam, Miep Koopman, and returned to his native Limburg to start a private practice as a family doctor. As happens in Catholic families, six children were born in the next ten years. I was the second child and first son.

On May 10, 1940, the German troops invaded the Netherlands. My dad soon became involved with the Dutch underground and resistance. There are stories about how he helped and treated shot-down pilots, resistance fighters, and Jewish people in hiding. As often is the case, he never talked with us about his wartime experiences. Much later, he was honored by the Dutch government with the Dutch Resistance

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Frans J. T. Wackers, Professor Emeritus of Radiology and Biomedical Imaging, served on the Yale faculty from 1977 to 1982 and again from 1984 until 2012. He received both his M.D. and Ph.D. and cardiology training at the University of Amsterdam School of Medicine. Wackers moved to the United States in 1977, joining the faculty of the Section of Cardiovascular Medicine at the Yale School of Medicine. He served for three years on the faculty at the University of Vermont College of Medicine before returning to Yale. Considered a pioneer in nuclear cardiology, he was the first to inject Thallium-201 in a patient with a heart infarct in Amsterdam. Wackers is the founder of the American Society of Nuclear Cardiology, the Certification Board of Nuclear Cardiology, and the Intersocietal Commission for Accreditation of Nuclear Laboratories. He was principal investigator and chair of a multicenter study on imaging in patients with diabetes mellitus, the "Detection of Ischemia in Asymptomatic Diabetics (DIAD)" study (*JAMA* 2009). Wackers published more than 350 articles on nuclear cardiology and clinical cardiology.

Cross and by the State of Israel with the Yad Vashem medal of the Righteous Among the Nations.

Once the war was over, my father sold his practice and the entire family moved to Amsterdam, where he began training in surgery and urology. After five years the family moved again to The Hague, where he would practice for twenty-five years as a urologist.

When I was twelve years old my parents enrolled me in the Jesuit College in The Hague. I truly hated it from the start. The strict regime, the continuous scrutiny by men in black robes, and the obligatory Mass each morning at 8 a.m., I found very oppressive. The ultimate irony: at the bottom of each homework paper we had to write: "Ad Majorem Dei Gloriam" (For the greater glory of God), the slogan of the Jesuits.

The Netherlands. The blue line indicates the course of the rivers Rhine and Meuse, dividing the country into "above and below the great rivers."

I went to a type of school called "Gymnasium," which is the equivalent of a grammar school. As much as I hated the school, the education was—in retrospect—excellent. Somehow, I believe, I learned critical thinking from the Jesuits. The school curriculum was focused on languages and literature: Dutch, French, Latin and Greek, English, and German. However, the teaching of languages was principally aimed at reading great works of literature, but definitely not to converse with the "man in the street." I did fair in most languages, but French was my favorite, partly because the French teacher, a layman, seemed to be the only one who believed in my intellectual potential. I did like biology as well and found it easy, but mathematics, physics, and chemistry I did not like very much.

Totally unexpectedly, my mother passed away after a brief illness when I was sixteen years old. My dad remarried eighteen months later.

I became a little bit of a problem. I rebelled even more against the Jesuit regime. Attending school classes seemed to me a waste of time. I believed that I would study more effectively for the final exam on the beach of the North Sea than sitting in the classrooms. Against all expectations, I passed in 1958 the baccalaureate exam. And thus ended what I still remember as the "most unhappy period of my life."

University of Amsterdam School of Medicine

I had decided to study medicine. I wish it were different, but I do not remember profound reflections or great empathy about becoming a doctor. My dad was a doctor, it seemed a respectable profession, so why not…?

I went also to the University of Amsterdam. I confess that during my first years in medical school I did not study much, but immersed myself enthusiastically in the "student life" of the 1950s in Amsterdam. At medical school I hardly knew the professors by sight when I took the first oral exams. My lack of enthusiasm for studying can

be explained by the fact that most of the lectures (chemistry, physics, statistics, and embryology) seemed to have little to do with my interest, clinical medicine. Perhaps to get myself under control and have more discipline in my life, I took up competitive rowing. Since then, sports – rowing, running, and sailing – have been always a part of my life.

Finally after three years, the lectures became more clinical: lectures with presentations of sick patients and the teaching of pathology. I became a different person overnight. I was excited about medicine. I became a model student, attended all lectures, made meticulous notes, organized study evenings with friends, and passed all exams.

The frustration of the first three years had convinced me that the medical curriculum was totally inadequate. I became an activist in the medical student association and was soon chairing the Medical Education Committee. In 1965 I was the student keynote speaker at a symposium on medical education. On behalf of the Amsterdam medical students I presented a proposal for a revised medical curriculum. The entire text of my speech was published in the *Dutch Journal of Medicine* (1966); this was my first publication.

During the university vacations I often went back home to The Hague to experience "real medicine." My father would take me with him to the hospital, let me "scrub in" and "help" during surgeries. It was in that hospital that I met a young doctor who would have a major impact on my life. Dr. Hein J. Wellens had just returned from the United States after medical internships in Baltimore. He took me under his wing. His enthusiasm was contagious. He gave me my first hands-on experience with patients. He was absolutely passionate about medicine and a great teacher. He intended to specialize in cardiology. From then on, there was no question: I would be heading for cardiology as well. This same Dr. Wellens would later be my professor of cardiology.

With my rekindled interest in medicine, I wanted to get involved with research. I sought and obtained a research position in the pathology laboratory. The professor, Jan F. Hampe, was very popular with the medical students but somewhat eccentric. He was a devotee of the spirituality of the Bhagavad Gita. He had the habit of asking questions that made people uncomfortable. One of his favorite questions was "What is normal?"

This is where my intellectual trajectory starts… However, I believe that my interest in exploring began actually somewhat earlier. At the age of eleven or twelve, I was fascinated by stories about the seventeenth-century Dutch East Indies, the descriptions of long and treacherous sea travels, the discoveries of new lands and people. Through these tales I was imprinted with the notion that a "real" Dutch boy does not stay home with his "mother's porridge pot," as the Dutch expression goes, but he goes out into the big wide world. When I grew older I was disappointed that no new countries were left to be discovered. I believe that I then adjusted my romantic yearning for unknown lands to the more realistic ambition of scientific exploration.

Student Research and Ph.D., M.D.

From 1963 to 1970 I was a research associate in pathology. I learned to perform autopsies and taught pathohistology to students who were just one year behind me. My own research task was to investigate the microanatomy of the female breast in health and disease. In 1966 I received a research grant from the French pharmaceutical company Rhône-Poulenc. I went to Paris and worked for six months in the pathology laboratory of the famed Institut Gustave Roussy. The head of the laboratory, Dr. G. Vogt-Hoerner, gave me a research project that I completed in an amazingly short time. I published my first research paper (in the French language) in *Les Annales d'Anatomie Pathologique* (1967).

Living in Paris was of course a wonderful experience in itself; I enjoyed all aspects of social life of Paris, the theaters and museums. This was definitely one of the best times of my life.

After my return to the Netherlands I continued my research and work in the pathology laboratory. In 1969 I published my second scientific paper in the journal *Cancer* on a rare cardiovascular tumor. For this manuscript I had to do an extensive literature search. I still remember vividly working on this manuscript. The evenings alone in the quiet library of the laboratory, researching old journals and books. I felt like a real scholar!

I finished and defended my doctoral thesis (Ph.D.) in April 1970 at the University of Amsterdam. Around this time I met a student in occupational therapy, my future spouse, Marjan Meijer. Marjan and I disagree about how we met. She claims that I first saw a painting of her made by my artist-brother, Ruudt Wackers. I know that I met her for the first time at the rowing club, where she had coxed a boat. But it is true that my brother urged me to invite Marjan to a formal dinner party with my parents in The Hague. So I did, and from then on she was part of my life.

In June 1970 I passed the M.D. exam. This was a great relief for my dad, who had asked me when I received my Ph.D., "When will you become a real doctor?"

Because the Netherlands still had the military draft, I had now to join the army. To make the best of a bad thing—and being a rower and athletic—I volunteered for the Dutch Commandos, the Green Berets. I went through boot camp and parachute training and I earned the Green Beret. With the commandos, I had my first and useful experiences of being a doctor. I saw a good deal of injuries, emergencies, and common diseases. But I also investigated some of the medical aspects of being a commando. I published an article on the wearing of contact lenses under combat conditions in the *Dutch Military Medical Journal* (1971).

Cardiology Training

Before I went into military service I had assured myself of a place in the University of Amsterdam cardiology training program. It helped that the professor of cardiology, Dirk Durrer, knew me from my activities in the Amsterdam Student Association a couple of years earlier. "Let me know when you get out of military service, I will find a place for you."

In 1972 my military service was over and I was excited to start with cardiology. In those days general internal medicine was still relatively low-tech, mainly based upon patient history, physical exam, and some blood analysis. Diagnoses were often tentative, proven to be right or wrong by success or failure of treatments. The true nature of an illness was often only revealed at postmortem examination.

Cardiology was different… In cardiology one could actually verify diagnoses objectively in the living patient. The electrocardiogram (a Dutch invention) showed the beating of the heart on paper strips and was diagnostic for acute heart attacks and rhythm disturbances. Phonocardiography visualized heart sounds and heart murmurs. Cardiac catheterization had become a routine in the early 1970s, allowing for measuring blood pressures within the heart and visualizing leaking valves and coronary arteries. Thus, for a cardiologist, treating an illness was based on objective evidence, rather than assumptions. This is was what attracted me to cardiology.

The Department of Cardiology in Amsterdam had a mixed reputation. No one questioned that it was probably one of the best cardiology departments in Europe and perhaps in the world. But it was also referred to as the "snake pit of Amsterdam." This was because the training and teaching methods were known to be harsh and demanding. Ignorance was not tolerated, and embarrassment was considered a good motivator for learning.

Two full professors headed the Department of Cardiology: Dirk Durrer, the founder of the department, and Hein Wellens, the doctor who had inspired me as a student, who just one year earlier had become the second professor of cardiology. Unfortunately, the two eminent teachers and scientists were totally incompatible. After only four years Professor Wellens left for the University of Maastricht.

In many of the Intellectual Trajectories, serendipity is mentioned as playing an important role. Mine is not different. A few days after I started in cardiology, I attended a discussion about a research project on patients with unstable angina. Unstable angina is a constellation of clinical symptoms that may be the beginning of a heart attack. Without angiographic confirmation of blockages in arteries, unstable angina remains a tentative diagnosis. The discussion focused on the fact that almost none of these patients had coronary angiography. Thus, the interpretation of results was dubious and potentially flawed.

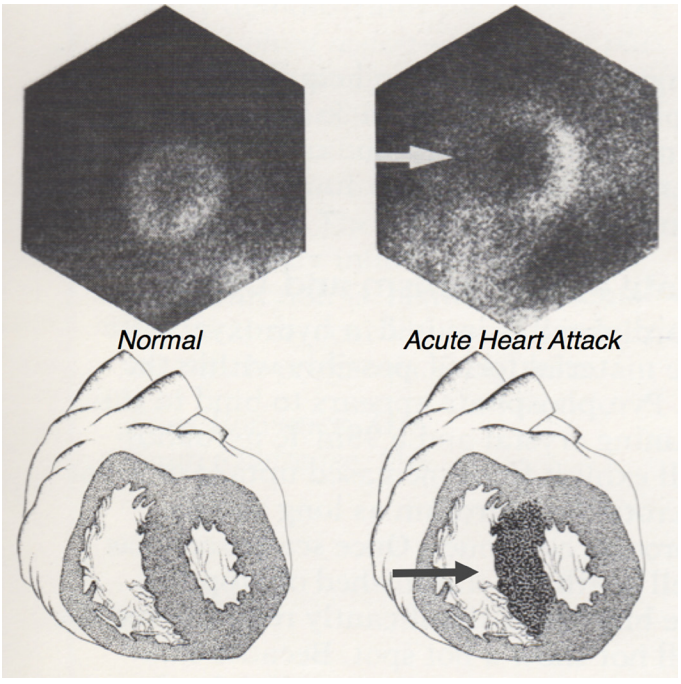
The weekend before starting cardiology training, I had been cleaning out my desk. I went through old issues of the *New England Journal of Medicine* and ripped out articles that were relevant to cardiology. During this discussion on unstable angina, I remembered reading an article by a Barry Zaret on imaging of the heart with radioactive potassium. I mentioned in the discussion that there might be another noninvasive way to confirm the diagnosis of coronary artery disease: by imaging the heart with radioisotopes. Professor Wellens, typically, put me on the spot and challenged me to find out how we could do such imaging in Amsterdam.

I knew the head of nuclear medicine, Professor Jan B. van der Schoot, reasonably well. He was the attending physician of the patient with the rare cardiovascular tumor that I had published about in *Cancer* five years earlier. So I went to talk to him. He told me that it was possible to order potassium-43 from the United States, but that, because of its short half-life, it would be a logistical challenge. "However," he mentioned, "a couple of months ago I was at a nuclear medicine meeting in the U.S. and I saw images of an animal heart using a new and possibly better imaging agent, Thallium-201. I happen to know that Philips-Netherlands is in the process of producing Thallium-201 for clinical use. I will keep you posted." A couple of months later he called to let me know that he had received the first clinical doses of Thallium-201.

Thallium-201 is a radioactive potassium analogue. After injection it will distribute through the body as if it is potassium and go inside the living cells. Regional absence (called a "defect") means either that the cell is dead, or that there is insufficient blood flow to get there.

The first patient we imaged was a man with a two-week-old heart attack. In the 1970s no Human Investigation Committees existed in the Netherlands, nor was written informed consent necessary. I told the patient that we would like to take some pictures of his heart. He had no problems with that. This patient unknowingly had the distinction of being the first patient in the world to be injected with Thallium-201. The images in this first patient were quite spectacular: one-half of the heart was missing! For the first time we saw noninvasively the damaged heart muscle of a living person!

After this encouraging start, I decided to focus on imaging patients with acute heart attacks. However, patients with acute heart attacks are often unstable and therefore in



First Thallium-201 isotopic images of the human heart (1974). On the left: normal heart; on the right: heart with acute heart attack. The arrow points to the damaged heart muscle.

the Coronary Care Unit. It was not considered safe to transport these patients to a nuclear medicine laboratory for imaging. My mentors, Wellens and van der Schoot, made a unique arrangement: one bed in the Coronary Care Unit was removed and in its place came a brand new gamma camera. My task: to investigate the usefulness of radioisotope imaging in patients with acute heart attacks. I started imaging patients with acute chest pain as soon as they were admitted. Most of the imaging I did myself, particularly during off-hours. This way I acquired considerable practical and technical experience with cardiac imaging.

The diagnosis of a heart attack cannot always be made right away: it may take several hours for the electrocardiogram and blood markers to become diagnostic of a heart attack. Could radioisotope imaging be a better method to diagnose a heart attack? How soon after a heart attack are radioisotope images with Thallium abnormal?

Systematic imaging of patients with acute heart attacks showed that the majority of these patients had abnormal Thallium-201 images. But what was most striking: the sooner imaging was performed after the onset of acute chest pain, the more frequently images were abnormal. Thus, Thallium images are abnormal at the very moment a heart attack occurs! We published these results on imaging in 200 patients with acute infarction in the *New England Journal of Medicine* (1976). It was the lead article and generated substantial interest.

We now went back to the initial discussion on patients with unstable angina. Would it be possible to use Thallium imaging to identify patients at high risk of having a heart attack? We found that about one-third of patients with unstable angina had abnormal resting Thallium images. Moreover, those who had complications had more severely abnormal images. Thus, imaging of the heart at rest with Thallium-201 was of value in identifying patients at high risk for future heart attacks.

I was now approaching the end of my cardiology training. I had already published several articles on noninvasive cardiac imaging in premier medical journals. People came to visit me to see how acute cardiac imaging was done. However, I was not sure about my own future in Amsterdam. My mentor, Professor Wellens, was about to leave for Maastricht, and Professor Durrer did not like me very much because I had not made it a secret that I was on Dr. Wellens's side. But, I had no interest in going into private cardiology practice.

The very day our first son was born, I received a letter from the United States, from a Dr. Mueller, chief of cardiology in St. Louis, Missouri, who offered me a position as an assistant professor and to continue my research on cardiac imaging in acute patients. I was understandably very excited about this. However, Professor Wellens suggested that it was probably prudent to look around a little more and see what else was available.

In the fall of 1976 I traveled to the United States with a briefcase full of slides and gave lectures on cardiac imaging in Seattle, San Diego, Baltimore, Dallas, and finally St. Louis. It was clear that I had much more extensive experience in imaging of the

heart than anyone in the United States. At almost every place I visited, I received job offers. Before going home, I presented an abstract on cardiac imaging at the American Heart Association meeting in Miami. I was invited to an informal get-together of about twenty Americans who were involved with imaging of the heart. Everyone was very excited about the new direction imaging of the heart had taken. It was there that I met Barry Zaret, who had recently joined the Section of Cardiology at Yale University.

Back in Amsterdam, I described to Marjan my experiences in the United States, particularly my visit to San Diego and La Jolla – the blue sky, the white buildings, the ocean and palm trees – one of the places where I was offered a research position. I was very tempted…

The next day, while I was imaging in the Coronary Care Unit, I received a call from Barry Zaret asking whether I was perhaps interested in coming to Yale. I knew about Yale crew and Yale locks, but not much about Yale Cardiology. One of the following weekends I went to New Haven. I landed at JFK after dark and found the small Pilgrim Airlines plane with running engines on the windy platform. I was the only passenger. I remember vividly how after takeoff the plane banked sharply to the left and I saw through the window the full moon over Long Island Sound. I believe that at that very moment I decided that I liked New Haven.

Yale Cardiology

So I agreed to go to Yale. On June 17, 1977, Marjan, our ten-month-old son, Michiel, and I arrived in New Haven.

The first months at Yale were not easy. Although my English was reasonably good, I remember being tired after an entire day of speaking in and listening to English. I was now an assistant professor and had to adjust myself to a different medical and academic culture. I had clinical responsibilities, seeing patients and teaching fellows in training. Particularly, the switch from being taught to teaching was difficult and intimidating.

Barry Zaret and I had agreed to a commitment for at least two years with the understanding that I would return to the Netherlands. But my family and I settled down gradually in New Haven; we had bought our first house in Hamden; we had our second son, Paul, and made new friends and acquaintances and started feeling at home. In 1979 I obtained the Connecticut medical license, and our H-1 visas were converted to permanent resident visas. It had become clear to me that two years was too short to complete any meaningful research.

During the next four years at Yale I published fourteen original articles, not only on Thallium heart imaging, but also on assessing the pump function of the heart with radiotracers. Although things seemed to go reasonably well, I was not certain about my future at Yale, where I worked in the long shadow of Barry Zaret. I felt strongly that I needed to create my own environment and prove my own worth as an independent investigator. I had to move on…

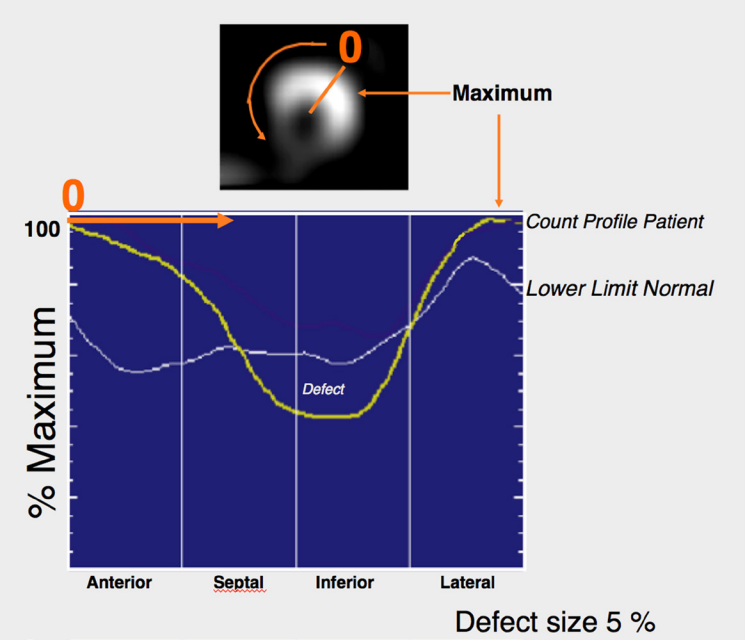
Vermont Nuclear Cardiology

In July 1981 we packed up and moved to the University of Vermont in Burlington, where I became an associate professor and director of nuclear cardiology. Prior to my arrival in Vermont, radionuclide cardiac imaging, or nuclear cardiology as we called it, was virtually nonexistent. The fellows in training for cardiology needed a lot of teaching. The interpretation of cardiac images at that time was very subjective and depended heavily on experience. I wondered how to teach the fellows to read cardiac images.

I found out that one of the technologists in Vermont was also a computer programmer. Together we developed software that mimicked the mental process of image analysis. Abnormal radiotracer uptake was graphically displayed as a percentage of normal uptake using circumferential profiles. By comparing abnormal to normal profiles, one could not only objectively determine the presence of an abnormality, but also quantify its extent.

This software turned out to be an excellent teaching tool. It was expanded over the years and adjusted to new radiotracers and new imaging equipment. It greatly improved the consistency and reproducibility of interpretation. This software has been used in the Vermont and Yale laboratories day in, day out, for over thirty years.

In the short two and a half years I was at the University of Vermont, six original research projects were completed and published, not only on radiotracer imaging but also on electrocardiography and clinical cardiology. I always insisted that research projects should have clinical relevance and have an impact on patient care.



Quantification of the size of a heart attack using circumferential radioisotope profiles. Software developed in the early 1980s.

Back to Yale

In fall of 1983 Barry Zaret called to ask me whether I was interested in coming back to Yale. My time in Vermont had boosted my self-confidence and I would have liked to go back to Yale. However, I was in a somewhat awkward situation, because just at that time I was considered for early promotion to full professor with tenure at the University of Vermont. I thought that this would give me a good bargaining chip. However, Yale would not make me full professor two and a half years after leaving as an assistant professor. As a compromise we settled for associate professor with tenure, with the assertion that I "soon" would be promoted to full professor. This promise was kept, as I became full professor two years later.

One of the reasons I was asked to come back to Yale was that Yale Cardiology had been selected as one of the clinical sites in a large NIH-sponsored multicenter trial of acute heart attacks, known as the TIMI trial. Yale was also charged with the task to organize a Central Core Laboratory to assure uniform data quality and processing. This challenge was right up my alley. As a core laboratory, Yale established a reputation for excellence. During the subsequent twenty years the core laboratory remained involved in numerous other multicenter trials.

Founding a New Professional Society

In the early 1990s nuclear cardiac imaging had become a routine part of clinical cardiology. This was in no small part thanks to clinical research performed by cardiologists. However, technically they depended on collaboration with nuclear physicians. At Yale I had a dual appointment in Medicine and Diagnostic Radiology, which assured a good collaborative relationship. However, in many other institutions this relationship was rather strained by nasty turf battles. Many cardiologists felt that because of this schizophrenic situation it was difficult to advance the field of nuclear cardiology to its full potential.

In 1992 I was the president of the Cardiovascular Council of the Society of Nuclear Medicine (SNM). At this time the frustration among cardiologists had reached a boiling point. I decided to take the initiative to start our own professional society. In March 1993 the American Society of Nuclear Cardiology (ASNC) was incorporated. Being still president of the Cardiovascular Council of the SNM, I chose not to be the first, but second president of the ASNC.

When my term as ASNC president was over, I founded the Certification Board of Nuclear Cardiology to create a subspecialty exam. Subsequently I founded the Intersocietal Commission for Accreditation of Nuclear Laboratories.

Now twenty years later, nuclear cardiology is a mature subspecialty, and the ASNC is a thriving professional organization with 5,000 national and international members, its own *Journal of Nuclear Cardiology* (of which Barry Zaret was the first editor-in-chief), and well-attended annual scientific meetings. More than 8,000 physicians worldwide are currently certified in nuclear cardiology, and more than 3,000 U.S. laboratories are accredited.

My Swan Song: The DIAD Study

Nuclear cardiology was no longer a technical innovation but a useful tool for addressing clinical problems. In the late 1990s there was increased focus in cardiology on the interaction between diabetes and heart disease. The notion was popularized that having diabetes was equivalent to having coronary artery disease. It was believed that more than one-half of patients with diabetes had silent heart disease and that heart attacks could strike at any time and out of the blue. Doctors would refer patients for coronary angiography, not because of symptoms, but just because they had diabetes.

No studies had been done that justified the appropriateness of such indiscriminate screening. Having been involved in many multicenter studies as an investigator, I felt it was now time to start my own multicenter study and to investigate the problem of silent heart disease in patients with diabetes. With my co-investigators in cardiology and endocrinology, Drs. Zaret, Young, and Inzucchi, we designed the DIAD study, which stands for Detection of Ischemia in Asymptomatic Diabetics. We recruited over 1,100 asymptomatic patients with diabetes in fourteen clinical centers in the United States and Canada. They were randomized to screening with stress cardiac imaging or no screening. The questions to be answered were:

1. How many asymptomatic patients with diabetes do have silent heart disease?
2. Does screening improve clinical outcome?

The DIAD study, which ran from 2000 to 2007, proved conventional wisdom to be wrong. The prevalence of significant silent heart disease was much lower than expected and was found in only 6 percent of asymptomatic diabetic patients. Furthermore, having diabetes was not a dreaded sword of Damocles: the rate of cardiac complications was actually quite low, less than 1 percent per year. And the outcome was not different in patients who had screening compared to those who had no screening. Thus screening of asymptomatic people with diabetes is not justified. These results were published in 2009 in the *Journal of the American Medical Association* (*JAMA*).

Several studies have now confirmed the findings of the DIAD study. Nevertheless there are still those who believe that screening must be done and that the DIAD study was flawed. For a man with a hammer, everything looks like a nail…

Looking Back

I have now come to the end of my intellectual journey. For me personally, the decision to retire was not a simple one. It took me years to get used to the idea. The notion of deliberately marking the end of one's professional life was unsettling, even when you realize that it is the transition to a wonderful new phase of life. Once the decision is made, there is no going back! One should hope that when you look back, you are pleased. Well, I am delighted: I proved the Jesuits wrong. I achieved more than they ever could imagine.

I did have my share of good luck, but I worked hard and had focus. Perhaps more important, I had sufficient imagination to see questions that deserved to be answered.

The course of one's life is very much determined by the people you meet. Also in this respect I have been very fortunate. First of all, I should mention Marjan. She has been amazingly supportive. It is no small challenge to transplant a family to a foreign country. She did it, and I am grateful for that. We are now married for forty-one years. Someone asked us recently how we stayed married for so long. I answered, "Marjan is my best friend." And that is the truth.

Meeting Dr. Hein Wellens was a crucial turning point in my life; he motivated me enormously and remained a role model. Barry Zaret, who recruited me to Yale, became a good friend, colleague, and collaborator for more than thirty-five years, and that by itself is remarkable.