# Illuminating Cardiac Function

## Heinz Schelbert Talks with Heiko Schöder and Johannes Czernin About a Pioneering Career in Nuclear Cardiology

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Heiko Schöder, MD, MBA, chief of the Molecular Imaging and Therapy Service in the Department of Radiology at Memorial Sloan Kettering Cancer Center and professor of radiology at Weill Cornell Medical College (both in New York, NY), and Johannes Czernin, MD, editor-in-chief of *The Journal of Nuclear Medicine* (*JNM*) and a professor at the David Geffen School of Medicine at the University of California Los Angeles (UCLA), spoke with Heinrich (Heinz) Schelbert, MD, PhD, about his groundbreaking career in nuclear cardiology. Dr. Schelbert is a Distinguished Professor Emeritus of Pharmacology and Radiologic Sciences and former chief of the Nuclear Medicine Service at UCLA.

Dr. Schelbert received his medical degree and doctorate from the University of Würzburg School of Medicine and completed his residency at Fitzgerald Mercy Catholic Medical Center of Southeastern Pennsylvania in Philadelphia. In 1976 he joined the active and innovative early PET program at UCLA, with a personal focus on cardiac applications of the new technology. Among his many major research achievements has been the development and validation of noninvasive radionuclide imaging techniques for investigating cardiovascular function and their application to the study of functional and metabolic consequences of coronary artery disease. He is credited with identifying specific patterns of blood flow and metabolism in chronically dysfunctional myocardium that are predictive of potential reversibility and with development and validation of PET-based techniques for measuring regional myocardial blood flow in absolute units using $^{13}$N-ammonia.

From 2004 to 2011, Dr. Schelbert served as editor-in-chief of *JNM*, successfully modernizing the journal while continuing long traditions of broad inclusiveness and high editorial standards. During his editorship, the journal's manuscript submission and review transitioned from a paper-based to an electronic process. He oversaw the redesign of the journal and introduced online prepublication of manuscripts and the availability of complete past issues in an improved online database, with consistently high annual impact factors.

Throughout his career, Dr. Schelbert has been recognized with numerous scientific, educational, and service awards and honors, including the Georg Charles de Hevesy Nuclear Pioneer Award for distinguished contributions to nuclear medicine by SNMMI and the Georg von Hevesy Prize (twice) from the World Federation of Nuclear Medicine and Biology. In 2012, he received the Distinguished Lifetime Achievement Award from the American College of Cardiology, which called him "a giant in the field of cardiology," adding that "with a plethora of seminal achievements as a pioneer in the development and application of PET and other nuclear cardiovascular technologies, he is a rare researcher who can truly claim the honor of witnessing the direct application of his experimental research to clinical care and improved patient outcomes during his lifetime."

**Heinrich R. Schelbert, MD, PhD (Courtesy of Mei Tian, Hangzhou, China)**

***Dr. Czernin:*** *Dr. Schöder and I were both students of cardiovascular imaging in your group in the 1990s and late 1980s, respectively. You have been a leader in cardiovascular imaging for a long time. Your initial training was in Germany, but your career took off in the United States. What prompted your move here?*

**Dr. Schelbert:** After finishing medical school and a 1-year internship in Germany, I wanted to see how medicine was practiced in other countries. I ended up in the United States in a community hospital outside of Philadelphia through an internship program for foreign medical school graduates. After that I trained in internal medicine, which was very intense but also very good. A German cardiologist in Philadelphia, Otto F. Müller, MD, made cardiology exciting and attracted me to the field. I soon began to read electrocardiograms and was fascinated by the amount of information that could be derived from ECGs. I also became involved in echocardiography, which began to enter clinical cardiology at that time.

Before returning home, I wanted to learn something in cardiology that would be unique in Germany. The leading cardiology group in the United States was headed by Eugene Braunwald and John Ross, Jr., at the NIH. I applied, was accepted, and after the group had—unexpectedly for me—moved to San Diego, I started there in the fall of 1968. My research tasks were to find ways to improve contractile function in infarcted myocardium and, in another project, to explore the possibility of myocardial perfusion imaging with radiolabeled microspheres administered into the coronary circulation.

While I was in San Diego in 1975, UCLA had established a new PET research program and had recruited David E. Kuhl, MD, who had developed the first SPECT device at the University of Pennsylvania, and Michael Phelps, PhD, who had built the first PET device in St. Louis, MO, together with Edward Hoffman, PhD, and Henry Huang, DSc. At that time, PET was applied mostly in neurology but very little in cardiology. The UCLA group invited me to come to explore the use of PET for cardiac applications.

***Dr. Czernin:*** *Can you talk about the environment, atmosphere, and spirit of this group at the time? Was this team both running the nuclear medicine clinic and doing research?*

**Dr. Schelbert:** I was of course very excited to join this unique group of young, aggressive, and highly resourceful investigators at UCLA. There was a tremendous level of comradery and excitement to explore what seemed like an unlimited potential of this new

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technology for studying human biology. The research group did not run the nuclear medicine clinic; we had clinical appointment in nuclear medicine. The amount of time spent in research or clinical service depended on the amount of research support we had generated.

***Dr. Schöder:*** *How did you settle on $^{13}$N-ammonia as a blood flow tracer? Was that simply because it was available, or had you already realized that this might be the best perfusion tracer to answer your questions?*

**Dr. Schelbert:** Yes, because it was available. $^{13}$N-ammonia was used for brain imaging at that time. I thought, let's try it for the heart. I explored this in canine experiments and found that it produced high-quality flow images. We then worked out the tissue kinetics of $^{13}$N-ammonia, with the goal of quantifying myocardial blood flow.

***Dr. Schöder:*** *When and how did you translate the technique to humans?*

**Dr. Schelbert:** The $^{13}$N-ammonia images we obtained in dogs were of superb diagnostic quality. We then explored effects of coronary stenoses on myocardial perfusion images in chronically instrumented dogs, which Lance Gould brought from the University of Wahington in Seattle to UCLA. Once we had received IRB approval, we validated the technique against coronary angiography in humans and confirmed its high sensitivity and specificity.

***Dr. Schöder:*** *You also extensively studied cardiac metabolism. What was the hypothesis there?*

**Dr. Schelbert:** At that time, Lionel Opie had demonstrated that mild reductions in coronary flow produced an increase in glucose utilization in the affected myocardium. We wondered whether this observation could be demonstrated noninvasively with $^{18}$F-FDG and $^{13}$N-ammonia. And indeed, we saw an increase in $^{18}$F-FDG uptake in the region of diminished myocardial blood flow downstream of an experimental coronary stenosis.

We asked whether a similar flow–metabolism pattern existed in humans and could be shown with PET. We studied a patient with chest pain at rest as a sign of acute ischemia. In fact, we found a perfusion defect downstream of a left anterior descending artery stenosis that was associated with an intense increase in $^{18}$F-FDG activity; in other words, we saw a blood flow–metabolism mismatch that we had already seen in dogs with experimentally induced acute ischemia. I said, "If that's acute ischemia, then let's study a patient without clinical signs of ischemia. We should not see a mismatch pattern!" We expected to now find a matching flow–metabolism defect, but what we saw was another mismatch.

***Dr. Czernin:*** *When you initially came out with these data and the associated publications, there was a lot of skepticism from the cardiac SPECT community.*

**Dr. Schelbert:** People didn't know what to do with quantitative myocardial blood flows. Also, PET was perceived as a direct competitor of SPECT perfusion imaging. The viability issue was different; it had direct clinical implications and thus was accepted.

***Dr. Schöder:*** *You created a large and leading cardiovascular research program. How did you recruit postdoctoral fellows from all over the world?*

**Dr. Schelbert:** Word got around that PET was useful not only in brain imaging but also in cardiology. That, of course, attracted many young people. I received applications from Europe (Germany, Austria, Italy, The Netherlands. Denmark, Sweden, and others) and from Asia. Our postdoctoral fellows were all highly qualified and truly interested in and committed to research. More than 50 postdoctoral fellows attended our research program.

***Dr. Czernin:*** *There is now a resurgence of clinical PET with the expected commercial availability of $^{18}$F-flurpiridaz. How do you see the future of PET myocardial perfusion imaging?*

**Dr. Schelbert:** You asked an interesting and important question, because the number of stress/rest perfusion imaging studies over the past 10 years has and continues to decline. This may be for several reasons; one is the use of appropriateness criteria. Another is referral of high-risk patients directly to invasive coronary angiography. Also, reimbursement for nuclear perfusion imaging studies has declined.

Most importantly, the clinical presentation of coronary artery disease has been changing from obstructive disease with acute events to a more diffuse nonobstructive disease associated with fewer acute events but a rise in heart failure hospitalizations. Quantitative myocardial blood flows will remain important in these changing scenarios of nonobstructive disease because the myocardial flow reserve as the ratio of hyperemic to baseline flows provides important diagnostic and prognostic information and will continue to be important for risk stratification, especially in patients without perfusion defects.

***Dr. Schöder:*** *What do you think was the influence of the rubidium generator, which obviated the need for a cyclotron for cardiac PET imaging—an advantage or disadvantage overall?*

**Dr. Schelbert:** Unlike the cyclotron, the generator system is available all the time, and you can use it as many times as you want. The diagnostic quality of rubidium perfusion images is not as good as that of $^{13}$N-ammonia, but they are diagnostically adequate. The ready availability of the rubidium generator has been a major driver of the clinical use of PET perfusion imaging.

> "When I looked at what was happening in the field—the exciting imaging technologies and radiotracers, such as those targeting prostate-specific membrane antigen—it became clear to me that the future was and is bright for nuclear medicine."

***Dr. Schöder:*** *What is the future of molecular imaging as it relates to cardiac imaging and also to the general development of new probes?*

**Dr. Schelbert:** I think quantitative flow measurements will stay with us because they're important. Other conditions that are likely to benefit from new and emerging molecular probes include myocardial inflammation and nonischemic cardiomyopathies. This will be especially important in patients with heart failure with preserved ejection fraction and in patients with inflammatory disorders of the myocardium.

***Dr. Schöder:*** *Let's talk about* JNM *for a moment. You had a highly successful run as editor-in-chief. What prompted you to apply for the editorship?*

**Dr. Schelbert:** I saw an opportunity to become editor. So, I applied; I thought this was an interesting challenge, which I wanted to take on!

***Dr. Schöder:*** *You had a vision, and obviously you changed the journal and improved the quality. How did that happen?*

**Dr. Schelbert:** In applying for the editorship, I presented a plan for what needed to be changed or innovated. At that time, the number of manuscript submissions to *JNM* had markedly declined. The whole review system was a mess, and I proposed what I would change and improve. I also addressed content and introduced several

new series or types of publications that I thought would be of interest to the *JNM* readership and that I believe became quite successful.

***Dr. Schöder:*** *We are in the era of artificial intelligence (AI) and very different means of communication. What do you think is the future of a traditional journal such as* JNM*?*

**Dr. Schelbert:** I have no doubt that traditional journals such as *JNM* will continue to exist. Yet, there will be more brief communications and letters to the editors for quickly communicating research findings. Paper publication will disappear; everything will be online. I do believe that social media will play a greater role although I am concerned about the superficiality of reports and communications. And I do think that AI will have a role, not so much in the scientific content or its assessment but rather for quality control as well plagiarism and data fabrication. Although more science will be disseminated through social media (we see that at *JNM*), I think the basic time-tested more rigorous format of research papers, with introduction, rationale, methods, results, and discussion, will stay with us, at least for the most important manuscripts.

***Dr. Czernin:*** *If the data are correct and the author wants to use an AI tool, for example, to write the paper so that it's stylistically sound and better, would you object to that?*

**Dr. Schelbert:** If it is limited to style and grammar, it is OK.

***Dr. Czernin:*** *Many groups have graphic designers who provide figures, and the figures are usually of much higher quality than those the authors themselves could create. Isn't that comparable to having a* manuscript *written by AI?*

**Dr. Schelbert:** I don't know the answer to that. I agree that AI could create figures that are much better in quality; if we allow those we're sort of on the border. I can't quite tell where the border is between creating figures and writing text. It's a difficult area.

***Dr. Schöder:*** *What will be the role for investigator-initiated versus industry-driven research, where we are basically executing whatever a company is pushing for? Can investigator-driven research survive in this era of company pressure?*

**Dr. Schelbert:** Investigator-driven research will persist. The NIH and other funding agencies reward new ideas and the development of new concepts. I always wonder about the big trials that are company-sponsored, but those large trials are important. When you look at cardiology—at coronary artery or inflammatory disease, for example—you can answer effectiveness questions on new drugs only through large trials. So, they are necessary.

***Dr. Czernin:*** *You did translational and translatable research long before these terms existed. What do you see as your most successfully translated and impactful research?*

**Dr. Schelbert:** I think it is the assessment for myocardial viability. The concept of chronically increased myocardial glucose utilization was a new one. No one really knew at that time whether chronic ischemia existed (and it still isn't ischemia). "I would not touch chronic ischemia with a 10-foot pole," a colleague said when I asked him about chronic ischemia. Today it seems more like an adaptive change in myocardial substrate metabolism, perhaps "a recapitulation of the fetal metabolic program," as it has been referred to, in the adult heart.

***Dr. Czernin:*** *We still do quite a few viability studies, so this has staying power. Obviously, there's a clinical need.*

**Dr. Schelbert:** No matter what some clinical trials have concluded, I believe viability assessments will persist. This is what I hear from colleagues in nuclear medicine and nuclear cardiology and what I see happening at UCLA at present. Our own initial experience with viability imaging was derived from patients with end-stage coronary artery disease considered for surgical revascularization vis-à-vis cardiac transplantation. It is, I believe, in this very challenging clinical situation that viability testing was used at the time we started out and still does contribute to the clinical decision-making process.

***Dr. Schöder:*** *Tell us a little about your interests outside of medicine. How did you balance these interests with your highly successful career? What did your work/life balance look like?*

**Dr. Schelbert:** Often when you're very busy you do not have time for those things you really like to do. My hobbies are classical music and, of course, reading, mostly history. At times we're all extremely busy writing grant applications or pursuing new ideas. But after some time, I always go back to spending more time with music or reading. I do believe you need to set aside time to do what you really like and to "rebalance" yourself.

***Dr. Czernin:*** *At the time when people (including me) had doomsday predictions for nuclear medicine, you kept telling me that we should not promote such defeatist attitudes and that the specialty would survive and actually grow. You were right. What made you so optimistic for the future of nuclear medicine?*

**Dr. Schelbert:** When I looked at what was happening in the field—the exciting imaging technologies and radiotracers, such as those targeting prostate-specific membrane antigen—it became clear to me that the future was and is bright for nuclear medicine. Just seeing these many opportunities made me very optimistic. I remember the time when CT arrived, prompting many to believe that nuclear brain imaging was out (that was with CT and MRI), and yet today we do even more brain imaging than before.

***Dr. Schöder:*** *My wife asked me to ask whether you would you do it all over again? Or what would you do differently?*

**Dr. Schelbert:** Yes, I would do it all over again. The question, however, is, *could* I do it again? Could I repeat it? Probably not, because life brings a series of opportunities, and those opportunities are not the same and change with time. Another thing is whether one grabs those opportunities when they appear. I was very lucky. Looking back, I would say: yes, I would repeat it, but I'm not sure that it is repeatable.

***Dr. Czernin:*** *What kind of advice do you have for the younger generation, the colleagues who enter the field of nuclear medicine or medicine?*

**Dr. Schelbert:** I think the most important element is attracting young people to our field and stimulating our younger colleagues. This requires presenting the field as exciting and with a future that motivates them to research, emphasizing that it's important to find new things. So, I would go that way. Based on my own experience, that's what I would do.

***Dr. Czernin:*** *As a follow-up to an initial question, who was your most important mentor?*

**Dr. Schelbert:** My initial mentor was Otto F. Müller, the German cardiologist in Philadelphia, whom I mentioned earlier. He made cardiology exciting and brought me into it. Other mentors who affected my professional life were Eugene Braunwald, who introduced me to the research side, and Franz Loogen, the chief of cardiology when I trained in clinical cardiology in Düsseldorf, Germany, who taught me the human side of medicine. There is also Sherman Mellinkoff, the dean of the UCLA Medical School when I joined UCLA, whom I deeply admired for his intellect, honesty, curiosity, kindness, and integrity.

***Dr. Czernin:*** *Thank you very much, Heinz, for all your accomplishments and contributions and for the time spent with us and our readers.*