David E. Kuhl, MD 1929–2017

On May 28, the world lost one of the greatest pioneers in medical imaging, whose contributions set in motion a new and revolutionary approach to the understanding of disease processes at the molecular and cellular levels. The concepts he introduced during his long career have become the bases for development of modern imaging technologies.

David Kuhl was born in St. Louis, MO, in 1929 and grew up in Berwick, PA. During his high school years, he read about and became intrigued by the potential medical uses of radioactive substances. Using uranium compounds found in his high school laboratory, he performed experiments on rats, including postmortem autoradiography. His work was rewarded with a Westinghouse Talent Scholarship, which, in turn, helped him to attend Temple University (Philadelphia, PA).

Eugene P. Pendergrass, MD, chair of the Department of Radiology at the University of Pennsylvania (Philadelphia), learned of David's interests in the radiation sciences and encouraged him to attend medical school. In 1951, after earning an undergraduate degree in physics, David enrolled at the University of Pennsylvania School of Medicine. Soon after enrollment, he began to work in the research facilities of the newly opened William H. Donner Center for Radiology. Under the supervision of physicists, he built his own scintillation counter, attempting to quantitate radionuclide deposition in thyroid tumors from patients treated with ^{131}I. He and his fellow students and mentors built a rectilinear scanner, only a few years after Benedict Cassen, PhD, had invented and introduced the technique. David then constructed the first radionuclide photorecording system, using a glow tube. This resulted in elimination of the standard solenoid tapper display and improved the quality of images generated by rectilinear scanners. David realized that modulated light source projection on photographic film might produce a more controlled image record than the mechanical recorder used in Dr. Cassen's scanner. For this work, David received the Borden Undergraduate Research Award in 1955 on his graduation from medical school.

After a year's internship at Penn, Dr. Kuhl served 2 years in the U.S. Navy, where he directed the Nuclear Medicine Service at the U.S. Naval Hospital in Portsmouth, VA. There he built another scanner–photorecorder system and became interested in the potential of cross-sectional imaging. Soon after completing his military obligation, he was recruited to return to Penn as a research fellow and later faculty member in the Department of Radiology. His interest in cross-sectional imaging continued, and he became the first researcher to advance the concept of tomographic imaging of distribution of radioactive agents in living subjects and to do so by acquiring data from multiple projections using rectilinear imaging techniques and backprojecting the data (Fig. 1). This was the first attempt toward cross-sectional imaging of human bodies and what we know today as the backprojection methodology, currently used for reconstruction in PET, SPECT, CT, and other imaging applications. He and Penn engineer Roy Edwards collaborated on the design of a detector that scanned in a series of tangential traverses, rotating around the patient on a circular path between scan passes. This represented the first true axial tomographic system. This joint effort led to construction of the first single-photon emission tomographic instruments, called the Mark II, III, and IV, completed in the 1960s and 1970s (Fig. 2).

While Kuhl and colleagues were working on the Mark II scanner in 1965, he acquired the first transmission tomographic images of the living human thorax, using ^{131}I and later ^{241}Am. This preceded by more than 5 years the

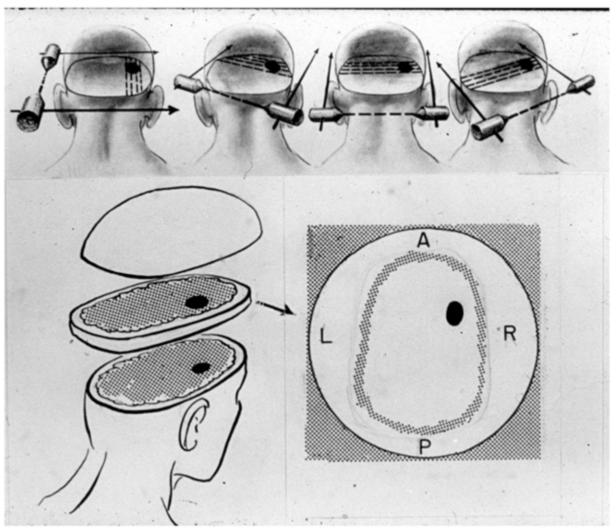

FIGURE 1. Illustrations of original backprojection concept introduced in the 1950s by David E. Kuhl, MD, and colleagues at the University of Pennsylvania. From the authors' collections.

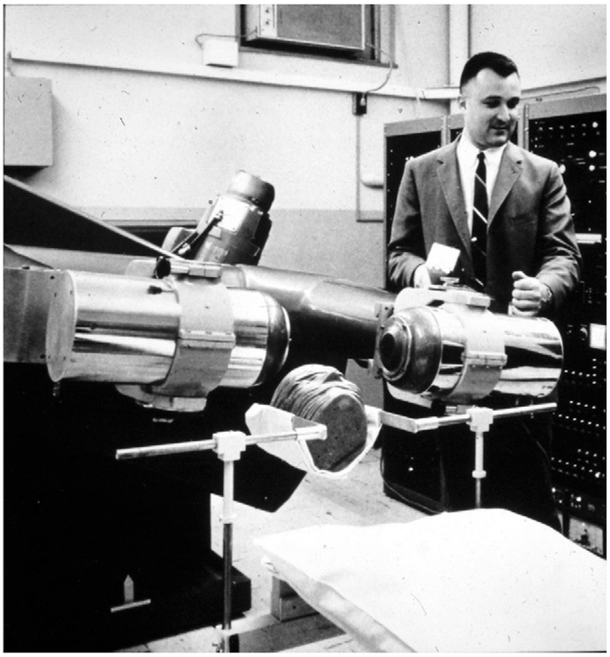

FIGURE 2. Dr. Kuhl with the Mark II scanner, which was used to perform both emission and transmission tomography.

introduction of X-ray CT by Godfrey Hounsfield in 1971. Kuhl was, therefore, the first to demonstrate the feasibility of transmission tomography with radioactive sources. Although the Mark II device was designed to image the whole body, the Mark III and IV were focused on brain imaging. Early images were used to detect blood/brain abnormalities resulting from tumor or stroke (Fig. 3). In 1972, Dr. Kuhl, along with Penn collaborators Abass Alavi, MD, and Martin Reivich, MD, initiated novel techniques for measuring blood volume in the brain using radiolabeled red blood cells in monkeys and humans. They were able to demonstrate response to hyperventilation and administration of CO_2 in nonhuman primate experiments. Further attempts to measure blood flow with ^{123}I tracers met with some success.

The introduction of CT in 1971 and the success of iodinated contrast agents for evaluation of brain disorders were major challenges to continuing research based on breakdown of the blood/brain barrier with conventional radionuclides (^{99m}Tc, ^{123}I compounds). Around this time, Louis Sokoloff, MD, and colleagues from the National Institutes of Health (Bethesda, MD), along with Dr. Reivich from Penn, had shown that ^{14}C-deoxyglucose (DG) was successful in mapping regional brain metabolism and correlated well with regional function in animal experiments. The investigations showed that DG crosses the blood/brain barrier through the transporter system and is phosphorylated to DG-6-phosphate, much like glucose, in contrast to glucose-6-phosphate, which is rapidly metabolized to CO_2 and water. DG-6-phosphate remains intact for an extended period of time. These early experiments were conducted using autoradiography, which requires the sacrifice of animals 45 minutes after administration of the compound and the use of brain slices and radiographic films to demonstrate the concentration of DG in the brain. It became increasingly clear that the use of DG as a noninvasive imaging technique for brain function would require labeling the compound with radionuclides that could be imaged externally in vivo. In December 1973, Drs. Kuhl, Reivich, and Alavi discussed the possibility of labeling deoxyglucose with ^{18}F-fluoride. This led to the synthesis of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) at Brookhaven National Laboratory (BNL; Upton, NY), where a cyclotron was available for production of FDG. By 1976, the efficacy of FDG as a biomarker for glucose metabolism was well established by Kuhl's group and BNL, and plans for human studies were underway. The Mark IV collimators were designed to image 511 keV emitted by positron decay. In August 1976, the first human studies were carried out at Penn by transporting FDG on a private plane from BNL to Philadelphia. The resulting studies included both tomographic images of the brain and rectilinear scans of the whole body. This research launched a new era in medical imaging that continues today. Its impact is as great as any other

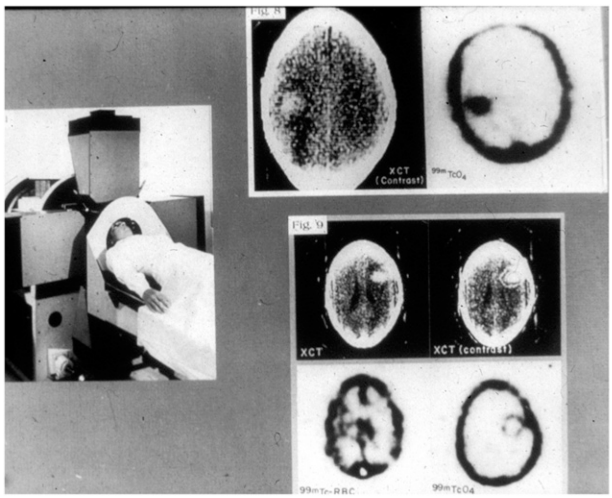

FIGURE 3. The Mark IV scanner (left) and images (right) acquired in 1976 comparing recently introduced CT imaging with radionuclide scanning with the Mark IV. Top: CT with contrast (left) and ^{99m}TcO^{4} imaging. Bottom: CT without and with contrast (top) and Mark IV imaging with ^{99m}Tc-red blood cells and ^{99m}TcO^{4} in a patient with an intracerebral hemorrhage. Before the arrival of a prototype CT machine at Penn, SPECT imaging with the Mark III and IV were heavily employed for assessing a variety of central nervous system disorders. For a period of time, the group was performing almost 10 such studies each day. However, this pattern of referral rapidly shifted in favor of CT soon after its installation at the institution. This had a dramatic impact on ongoing radionuclide research and clinical activities in the laboratory. It was the Penn group's relentless and successful efforts in moving the FDG project forward that saved the complete elimination of radionuclide-based brain imaging, then and for the foreseeable future. Even at the most active centers today, including the University of Pennsylvania, the number of daily radionuclide-based brain scans does not match that of Kuhl's group in the early 1970s.

imaging technique, including CT and MR imaging, and it served to reinvigorate the field of nuclear medicine and provided the tools for new generations of molecular imaging.

Soon after these experiments in 1976, Dr. Kuhl moved to the University of California at Los Angeles (UCLA), where an onsite cyclotron was available for research. There he established the first PET center at UCLA, which became one of the most successful radionuclide-focused research groups in the world. He initiated multiple research studies in the brain with FDG, including pioneering work on stroke, epilepsy, normal aging, Alzheimer disease, and movement disorders. He was the first to demonstrate that temporal lobe metabolism in epilepsy is an effective preoperative guide for surgeons performing lobectomy for seizures. He also was the first to show hypometabolism in the caudate nucleus in patients with Huntington disease prior to clinical manifestations of the disorder.

In 1986, Dr. Kuhl transferred to the University of Michigan (Ann Arbor) and remained on the faculty until his retirement in 2011. He was chief of the Division of Nuclear Medicine, director of the PET Center, and a professor of Internal Medicine and Radiology. He continued his research in brain imaging, with emphasis on age-related disorders such as Alzheimer disease and movement disorders. He built a strong research team that included a large number of basic scientists and physician–scientists in nuclear medicine and molecular imaging as well as engineering, chemistry, and other related fields. His group and their colleagues at Michigan made extraordinary contributions to the field, including pioneering work in neurochemical imaging of the brain, introduction of SUV as a metric, invention of diagnostic statistical mapping of the brain, neuroendocrine imaging and therapy, new PET and SPECT probes, new advanced image reconstruction, cardiac imaging software, and others. Many of these technologies and discoveries are now in widespread clinical use and continuing research development. His research received strong and continuous funding support, from his earliest efforts throughout his career, from a diversity of sources, including the U.S. Department of Energy, the National Institutes of Health, and public and private foundations.

Dr. Kuhl trained numerous talented individuals from many countries, many of whom now occupy leadership positions in universities and scientific institutions around the world. He published more than 300 peer-reviewed articles, and his publications on emission tomography and novel quantitative techniques have become classic references for research and clinical applications of PET and SPECT imaging. He was one of the founders of the American Board of Nuclear Medicine and served as the inaugural chair of the Residency Review Committee. He received numerous national and international awards, including the Ernst Jung Prize for Medicine (1981), election to the Institute of Medicine of the National Academy of Sciences (1989), the SNM Cassen Prize (1996), the SNM Georg Charles de Hevesy Nuclear Medicine Pioneer Award (1995), the Charles F. Kettering Prize for Outstanding Contribution to the Diagnosis and Treatment of Cancer (2001), and the Japan Prize (2009).

It is noteworthy that in 1976 Dr. Kuhl was named as the Nuclear Medicine Pioneer of the Year by SNM. In describing his pioneering contributions, author Frederick J. Bonte, MD, wrote: “There are rare individuals who by their very presence in a certain endeavor not only impart to it a significant intellectual momentum but confer upon it dignity and stature as well. Such a man is David E. Kuhl.” At the time, Dr. Kuhl was only 47 years old; he would continue to contribute to nuclear medicine and allied fields for more than 35 years, with a legacy that would influence the work of thousands of physicians and scientists and that will be extended well into the future to benefit countless patients around the world.

He is survived by his wife, a son, and 2 grandchildren.

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