Nuclear Medicine Pioneers: Henry N. Wagner, Jr., MD

At the close of the twentieth century, the field of nuclear medicine enjoys an opportunity that comes only once in the history of a scientific specialty—the ability to grasp its origins and influences in the living memory of its practitioners. Although the field's forefathers—Glenn Seaborg, Benedict Cassen, Emilio Segrè—have passed away, many of the founders of nuclear medicine as a scientific and medical specialty remain vital and involved.

No one better defines this founding role than Henry N. Wagner, Jr., MD, whose career neatly spans nuclear medicine's "second fifty years," as he termed the period in a 1996 history of the field. Present at the origins of nuclear medicine as a defined sector of medicine, Wagner has sustained the original momentum of discovery begun in the 1950s and 1960s at key U.S. teaching and research centers, like his own Johns Hopkins, where he continues to be professor of environmental health sciences.

Measured by the extent of his personal influence, Wagner has had an enormous impact on the field. This is true in large part because of his 40-year oversight of Hopkins's nuclear medicine program, which has trained nuclear medicine physicians and physicists, pharmacists and technologists, throughout the world, beginning with the "first wave" in the 1960s. He has trained more than 250 nuclear medicine residents and an equal number of radiology residents. Seven SNM presidents received their primary training in nuclear medicine under Wagner, as did two presidents of the SNM Technologist Section, Jim Langan and the late Paul Cole. Of these hundreds of students, nearly half were from outside the U.S. : Eight presidents of the Japanese Society of Nuclear Medicine trained with Wagner.

Yet aside from his influence as a mentor to the field's successive waves of dedicated nuclear medicine physicians, his research endeavors reflect key turning points in the science of nuclear medicine. His work in the applications of nuclear medicine to pulmonary and coronary artery disease and his studies of brain chemistry represent essential research in these fields.

"The Second Best Decision I Ever Made"

Wagner graduated from Baltimore's Calvert Hall High School in 1944 as Allied troops invaded Europe. Like many young men of that graduating class, he went directly into military service, going to the U.S. Coast Guard Academy in New London, CT. At war's end, he enrolled at Johns Hopkins University, graduating Phi Beta Kappa in 1948. He entered Hopkins's school of medicine that year, after a summer working with psychobiologist Curt Richter on measurements of visual response and environmental influences on nervous system function. He received his medical degree in 1952.

Wagner interned and served as a resident at Hopkins, specializing in internal medicine. His research interests concerned the treatment of infectious diseases.

The years from 1955 through 1957 saw the only span in his long career that he served in institutions other than Johns Hopkins. For two years he was a clinical associate with Robert Berliner's group at the National Institutes of Health, and in 1957, he worked in the United Kingdom, at Hammersmith Hospital's endocrine unit.

His travel to Hammersmith hadn't been a foregone conclusion. After his tenure at NIH, "I was invited by Dr. [A.M.] Harvey to return to Hopkins as chief resident in internal medicine," Wagner recently recalled. But there was a slight dilemma: "Another person in my group was also selected. Since there could only be one chief resident, Dr. Harvey said, 'You and Wilbur [Mattison] decide who it's going to be.' We flipped a coin, and I had to 'go second.'"

"Going second" meant going to Hammersmith as a special fellow, which marked a turning-point in his career, although Wagner wasn't aware of this at the time. There, he studied iodine metabolism in the thyroid, and in so doing first began to use radioactive materials.

"Two years before, in 1955," Wagner said, "Hammersmith had just received the first hospital cyclotron, and I saw that the technology of nuclear medicine could solve many of the problems that I recognized existed in medicine."

When Wagner returned to Hopkins in 1958 as chief medical resident, he introduced the newly invented technique of liver scanning. Soon after, when Harvey invited Wagner to join the Hopkins faculty, he asked what field the young researcher wished to pursue.

"I responded 'nuclear medicine.' Although he tried to talk me out of it, I persisted. It was the second best decision I ever

"Best decision": Wagner and wife Anne

made" (his best, Wagner said, was to marry his wife of 48 years, Anne Barrett, in 1951.)

In 1959, Wagner and John McAfee, MD, founded the Johns Hopkins Division of Nuclear Medicine, with Wagner becoming division chief in 1963 when McAfee accepted an appointment as chair of radiology at Syracuse University.

The "Natural History" of the Discipline

In a 1984 article marking Wagner's winning of the de Hevesy Prize, James Adelstein, MD, noted that he was "struck by" the ways in which Wagner's career "paralleled the natural history of our discipline over the last two decades." His "stewardship" of the Johns Hopkins program, Adelstein said, "led the field in new directions and helped to elaborate on fields opened up by others."

Throughout his career, one quality of Wagner's scientific discoveries has been that they exceed the simple proliferation of new tests, expanding the scope of basic nuclear medicine science itself. In the late 50s and early 60s, for example, Wagner, along with McAfee and D.C. Sabiston, Jr., MD, created the first lung scanning procedure for diagnosing pulmonary embolism. His use of macroaggregated albumin and xenon gas, and their application in pulmonary disease, in turn led directly to more efficacious use as new thrombolytic agents developed via multicenter trials. In addition, in a pattern of scientific repercussion that would be repeated throughout Wagner's career, this research led directly to offshoots, such as the demonstration that aggregated albumin particles could be used to detect regional hypoxia and lung cancer as well.

In the early 1960s Wagner and McAfee also investigated relative kidney function by showing the rate of arrival of Hg-203 chlormerodrin, and extending use of the agent to measure differential renal function, in studies involving the young Richard Reba, MD.

Reba was one of two original fellows in the Hopkins nuclear medicine program (the other was Wil B. Nelp, MD, University of Washington). In the late 1950s, a fellow resident at the University of Maryland got Reba interested in radiotracers, letting him know that the recently opened Hopkins program might be seeking applicants. Once in the program, Reba was soon joined by fellows from Japan, Korea and Egypt.

From the start the Hopkins program in nuclear medicine had an international flavor, commented Reba. Another pungent ingredient present from the program's inception was Hopkins's well-known openness, its lack of pretense.

"I came from a more traditional environment," Reba said. "When I got to Hopkins, everyone was on a first-name basis. They drew you in: You were a member of a family."

One practical outcome of this was Hopkins's "open-door policy" throughout the School of Medicine.

"Henry used to say that at Hopkins anything anyone wanted to do could be done," said Reba. "If you had a problem to be solved, there was always someone with whom to talk it through. Henry could always marshal resources."

Along with work in thryoid, pulmonary and renal nuclear medicine, Hopkins researchers were publishing on a wide variety of other areas, like the use of pertechnetate for brain scanning, peripheral vascular and congenital heart disease, and measurement of cardiac output.

The catholicity of Wagner's own research during the 1960s is reflected in a random survey of his published papers during that period. He was lead author on articles whose subjects ranged from "the effect of age on reticuloendothelial function in man" to "radiomercurials in the study of renovascular hypertension." Much of his research continued to concentrate, however, on pulmonary circulation.

As a resident at Hopkins in the early and mid-60s, Donald Tow, MD, worked closely with Wagner and McAfee in their applications of nuclear medicine to lung studies. For Tow, the research resulted in seminal work on pulmonary embolism, which in turn may have contributed to the shift in the way the field was perceived by general medicine.

"I think that lung scanning," Tow said in a recent interview, "helped to propel nuclear medicine into a clinical specialty in the early 70s. It was the first time that an area of nuclear medicine dealt so directly with the management of patients."

A Golden Age

Nuclear medicine was thriving at Johns Hopkins, as it was at certain other key research centers. These acted as foci for

the explosion of the discipline in the late 60s and early 70s and set the stage for dynamic educational efforts soon to come. Nevertheless, "in those years," Donald Tow noted, "Hopkins was the center—there was no competition. It was the vanguard of nuclear medicine research."

Judy Buchanan, Wagner's long-time editor, logistical coordinator, and friend, pointed out that formation of the nuclear medicine program was truly a joint undertaking, with McAfee insisting on an "exacting" attention to detail and Wagner stimulating a breadth of intellectual freedom.

"They were a good combination," Buchanan said. "The program wouldn't have started as it did without their partnership."

With McAfee's departure in 1963, Wagner undertook sole directorship of the program.

"People came from so many different backgrounds," noted Buchanan. "Not only medically but culturally."

Their experience working under Wagner and McAfee led physicians from Asia and Europe to encourage their colleagues to travel to Baltimore.

"During my time at Hopkins," reminisced Michael Maisey, MD, now of Guy's, King's and St. Thomas' School of Medicine, London, "probably at least fifty percent of the fellows were from outside the U.S.—Japanese, New Zealanders, Britishers, Canadians and Australians—from everywhere."

Like many international fellows, Maisey returned to his home country not only educated in the state of the art but also with a firm idea of how a nuclear medicine program should be organized. When he returned to Guy's Hospital, he set up that institution's first nuclear medicine program. "I lifted it almost verbatim from Hopkins," he said.

Arguably, entire national medical communities were influenced by how nuclear medicine was practiced at Hopkins. Nowhere is this better symbolized than in Japan, where Hideo Ueda, MD, and Masahiro Iio, MD, were among the original fellows in nuclear medicine at Hopkins in the early 1960s. Then, with their encouragement, more than 70 Japanese physicians followed, among whom was Yasuhito Sasaki, MD, now director general of the National Institute of Radiological Sciences, Chiba.

As a resident Sasaki had worked under Iio, who encouraged him to study at Hopkins, where the former began his fellowship in early 1969, remaining there nearly two years. His work centered on the microsphere distribution technique for measurement of cardiac output and the use of C-14 breath tests in the study of adult lactase deficiency. In the latter research area, Wagner introduced Sasaki to members of Hopkins's gastrointestinal unit, and like many other fellows, Sasaki found that interdepartmental collegiality within the School of Medicine was far-reaching.

"Most of the studies I did were performed in cooperation with specialists in different fields," Sasaki recently noted, "which was, I believe, an important element in the way Dr. Wagner achieved such outstanding results. I've tried to follow the same principle."

"When I returned to Japan," Sasaki added, "I felt that I'd been among the top group in the world of nuclear medicine, and I was very proud of that."

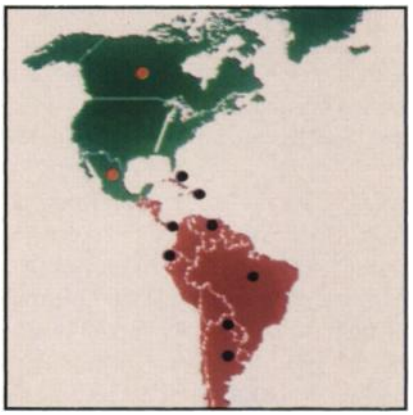
This was, by some accounts, the "golden age" of the Johns Hopkins program in nuclear medicine, the period that trained many of the men and women who would lead the field in the 1970s, 80s, and 90s.

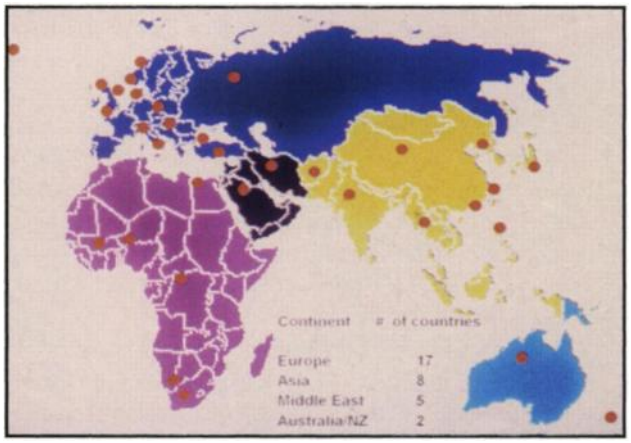
For many the highlight of Hopkins nuclear medicine program during this time was the morning conference, when Wagner, faculty members, fellows, and nearly anyone else who was interested, would study and, usually, debate individual cases. Those who attended the conferences in the early 70s recall that the atmosphere on those mornings was a heady blend of elation, intellectual challenge, occasional frustration, and, throughout, great excitement.

"The environment was magic," H. William Strauss, MD, one of the "generation of 1970," recalled of the conferences. "Henry kept the pot stirring. He created an atmosphere that allowed people to be their best."

"Henry wasn't an old-school medical school professor," Donald Tow said. "Morning conferences were the place to be—discussions were often heated. Everyone was encouraged to give an opinion."

Sasaki, too, had trained in a traditional environment: "I envied the fact that young doctors could hotly debate with our 'boss.' But at the same time, I used to sympathize with Dr. Wagner, who had to walk around the conference room looking for an eraser for the chalkboard. That would never have hap-





Maps above show worldwide distribution of former fellows in Johns Hopkins nuclear medicine program (courtesy of Richard Reba, MD).

pened to a professor in Japan. The eraser, or anything else, would have been brought to him instantly."

"He had placed a sign over the viewbox—'Data Not Dictum,'" Reba recalled. "That summed up the atmosphere."

The conferences also marked a sea change for nuclear medicine, from a research-bound field of medicine to a more clinically based discipline, a transition that would soon lead, on the organizational front, to incorporation as a specialty. Although Wagner had long since set his course as a medical researcher and teacher, his roots in clinical medicine, begun at Hopkins itself, ran very deeply. Wagner noted that it was his earlier training under Harvey that contributed to the concentration on the individual patient stressed during those conferences.

"The morning conferences were building nuclear medicine into medicine through their emphasis on patient management," Maisey remarked.

The twice-weekly seminars introduced at this time, and organized by Buchanan, also had as one aim a clinical "product." Meanwhile, the late 60s saw a proliferation of general textbooks aimed at the clinical practitioner. One of these was Wagner's *Principles of Nuclear Medicine* (1968). Later, in 1986, with Buchanan's editorial aid, Wagner published *Diagnostic Patient Studies* (1986), a volume based on the morning conferences.

Wagner's strengths as a writer and communicator were integral to the success of the Hopkins nuclear medicine program, and graduates still recall the importance he lent to clear expression.

"He taught a whole generation how to communicate with referring clinicians," said Maisey. "At the morning conferences, he paid great attention to the actual words used in the interpretation of nuclear medicine studies."

Strauss said simply, "For Henry, clarity of expression was clarity of thought."

As the 1970s moved on, Wagner and Joseph Ross, MD, pressed for consolidation of the field into a medical specialty,and with others, they formed the American Board of Nuclear Medicine in 1971, solidifying nuclear medicine's stature as an independent specialty distinct from radiology and other allied disciplines. Wagner, who was SNM president at the time, was instrumental in fighting for the fledgling board at the American Medical Association (AMA) and other medical groups. "The formation of the ABNM with Merle Bender and the other founders was our greatest accomplishment," Wagner noted.

At the same time, Wagner's research was centering on cardiac studies. His research on myocardial perfusion resulted in seminal advances in coronary blood flow studies and new therapies for coronary artery disease. One outcome of these studies had been a 1970 paper on radionuclide angiography in cyanotic congenital heart disease: A co-author was a young H. William Strauss, MD, who would four years later perfect the cardiac stress-rest test.

Wagner was the presiding spirit over most activities taking place at Hopkins. Strauss's work in cardiology, for example, was facilitated by his day-to-day association with people working in parallel fields and assembled by Wagner. Barry Zaret, MD, had stressed the need to measure ventricular function. Knowing of software created by R.J. Natarajan, which allowed "stop motion" imaging of the heart, Strauss posed the problem to him: As a result, the two connected the gate to a gamma camera, resulting in the gated scan.

Spotting the Signal in a Sea of Noise

As physicians and scientists like Strauss, Peter Kirchner, MD, Leon Malmud, MD, and others formed a diaspora of Wagner-trained nuclear medicine adepts, a new generation of men and women entered the Hopkins program in the late 70s and early 80s. One of these was scientist Jonathan Links, PhD. Links had come to Hopkins from UC Berkeley, where he had worked with nuclear medicine pioneer Thomas Budinger.

"He doesn't put labels on people," Links noted. "Everyone gets full access to projects. Even as a first-year graduate student, I was on a research team. In 1982 he put me in charge of the PET scanner."

As a physicist, Links holds a slightly different perspective on Wagner's strengths than physician colleagues:

"He's a true scientist, a superb critical thinker," Links said. "And as a scientist, he's extraordinary in two ways. He has factual knowledge greater than anyone I know, and his ability to abstract—to see the signal in a sea of noise. That's why he's good at spotting trends."

One such perceived trend may have been the general movement within medical research to interest in brain function. "He was early in his understanding how PET could be used to study brain chemistry," commented Strauss.

In May 1983, Wagner and his colleagues were the first to

"Wagner created an atmosphere that allowed people to be their best."

Wagner as a child: "He kept the pot stirring".

image dopamine neuroreceptors in the brain of a living human being, that of Wagner himself. (Wagner has often been an experimental subject in the course of his own work, such as in the early pulmonary studies.) The Hopkins group was also the first to image the opiate receptor in a living subject, once again Wagner. He characterizes his research in neurology since then as "his most significant work." His in vivo studies of brain chemistry have since 1983 led to significant expansion of information on cerebral neurochemistry.

It's apparent that Wagner's ability to discern patterns in nature, noted by numbers of his students like Links, carries over to discernment about colleagues. "He sees the potential in everyone," Links said, giving voice to an insight widely shared by successive waves of Hopkins students and colleagues.

"He Always Knows What Everyone Is Doing"

Wagner's current research efforts focus on neuroscience and oncology. His 40-year National Institutes of Health program-project research grant for nuclear instrumentation and chemistry in medicine is now in its 38th year. Wagner plans to apply for its renewal when the funding period ends.

Although now retired from the Johns Hopkins School of Medicine (he still serves as director of Radiation Health Sciences), Wagner continues to teach and to provide the wide view he's lent to the field for 40 years. Perhaps the most highly visible form of this is his "Highlights" talk given yearly at the SNM Annual Meeting since 1976.

One long-time physician colleague remarked that "Henry always knew what everyone was doing... That's why the 'Highlights' talks work."

Others interviewed for this profile agreed, pointing out that the same ability to "discern the signal in a sea of noise" also stands Wagner in good stead as he extracts common themes for each year's group of scientific sessions. "Henry's very good at framing questions," Strauss noted. "And he's very good at dissecting a great deal of data."

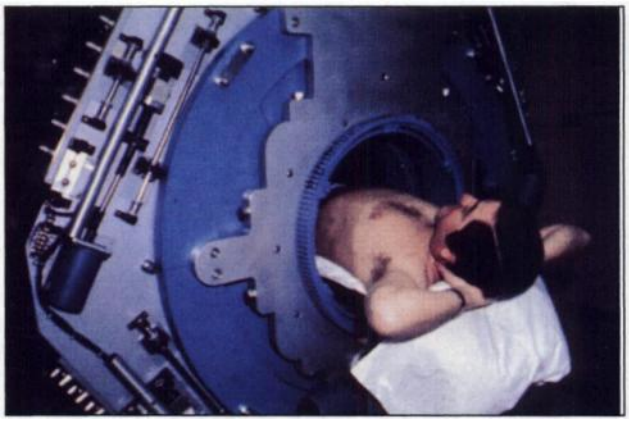
As he surveys the field at the very end of the twentieth century, Wagner remains a proponent for a variety of initiatives to attract new practitioners to the field. "Nuclear medicine is a primary specialty field whose increasingly obvious worth will lead many bright young people into the field. Other specialists—endocrinologists, oncologists, neuroscientists—will also see, as I did, that nuclear medicine can solve many biomedical problems better than any other approach."

Wagner's view of himself is pragmatic, reasonable, slightly self-effacing. In contrast, many observers of nuclear medicine emphasize his unique and sustained influence on the field through seminal research contributions, the quanitity and quality of his scientific endeavors. Yet literally hundreds of students and fellows, now colleagues and peers, cite his teaching, his mentorship, his leadership, as his most lasting gift to the profession.

In this context, Wagner is himself fond of a remark made by American philosopher, physician, and teacher William James (himself beloved of generations of his Harvard students):

"What doctrines students take from their teachers are of little consequence provided they catch from them the living, philosophic attitude of mind, the independent, personal look at all the data of life, and the eagerness to harmonize them."

—John Childs and Eleanore Tapscott



Wagner as researcher:
He was often an experimental subject in his own work.