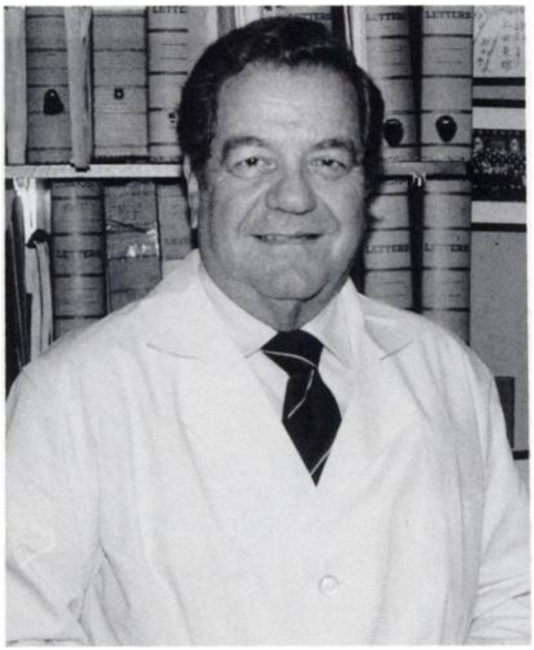
PROFILE

Practical Matters with Henry N. Wagner, Jr., MD



On a rather quiet August morning at the Johns Hopkins University in Baltimore a pair of researchers are preparing to inject a small amount of a radiolabeled tracer into a vein in the tail of a large laboratory rat. The centerpiece of the experiment—a pair of sodium iodide probes that look like secondhand undergraduate physics lab components—is decidedly low-tech equipment in the realm of late Twentieth Century medicine.

Singing the praises of the simple probe set-up is Henry N. Wagner, Jr., MD, a leader for over 30 years in the hunt for new uses of radioactive tracers in medicine and now a bold exponent of positron emission tomography (PET). "I like simple systems that can be used in the practice of medicine," he says proudly as he checks in with the researchers. His smiling features and fleshy face give an impression of kindliness. Professor and the director of two divisions, nuclear medicine and radiation health sciences, he prefers to stay close to the research. Each morning at work he puts on a white lab coat which he wears, even during lunch, until leaving at night.

The goal of this morning's experiment is to see if the probes can be used to measure brain glucose metabolism without resorting to more elaborate and costly camera devices. Using the tracer fluorine-18 fluorodeoxyglucose (FDG), the researchers plan to see how accurately they can measure glucose utilization in a living rat.

"I am very much a follower of a pragmatic approach—you should be only as rigorous as necessary to solve the problem," Dr. Wagner says. "An example is the use of these probes. Some people just can't tolerate such simple measurements. How in the world, when you have a PET scanner, could you possibly want to work with a $30,000 probe system?"

Eventually, Dr. Wagner hopes, doctors will use such probes, with the appropriate tracers, to measure levels of receptor binding to radioligands—to examine neurotransmitter release and the effect of drugs, for example.

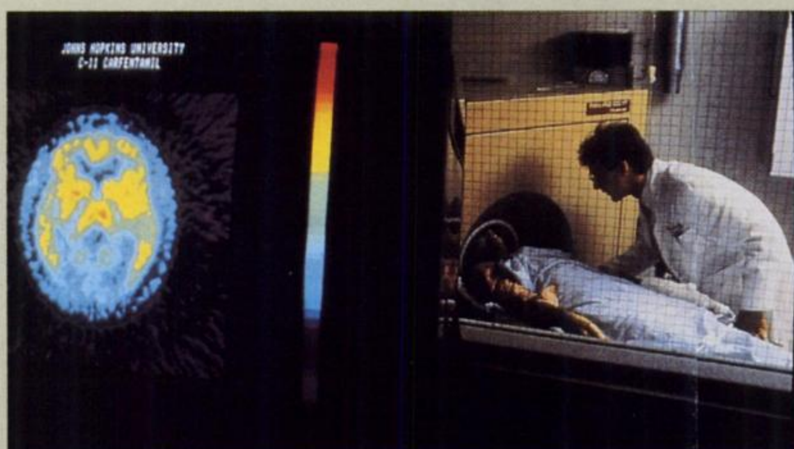
"Consider," Dr. Wagner beckons, "being able to give a psychiatrist the equivalent of a blood-pressure cuff. Try to imagine what it would be like to treat a patient for high blood pressure without being able to measure the blood pressure—that's the equivalent of what psychiatrists do all the time in drug treatment of patients with mental disease." Dr. Wagner believes that simple probe systems like the one being tested today may well be capable of monitoring the brain chemistry underlying destructive human behaviors such as drug addiction. If so, the probes could be used to monitor response to therapy. If an outspoken advocate of clinical PET urging the development of simpler, cheaper surrogates seems contradictory—it's typical of Dr. Wagner. He embodies many opposite qualities.

Friends and colleagues often and in the same breath describe his competitiveness and his generosity. They call him a father figure and praise his boyish love of joke-telling. They emphasize his "strong" personality but his gentle demeanor, his exuberant idealism but his steadfast focus on the practical and achievable. Perhaps the harmonious balance of extremes has helped Dr. Wagner rack up scientific and professional accomplishments. Most recently he became the first nuclear physician to win the Scientific Achievement Award of the American Medical Association for work that started at the beginnings of the specialty of nuclear medicine.

Dr. Wagner is one of the founders of the American Board of Nuclear Medicine. With an illustrious list of students and collaborators, Dr. Wagner helped develop the first nuclear techniques for scanning the kidney, spleen, lungs, and brain neuroreceptors. He is known for the invention of the "nuclear stethoscope," a simple, affordable probe system for measuring left ventricular function in heart patients. His department is responsible for the first exercise heart studies, gated images of the heart, and the use of computers in cardiac imaging. "Somebody has got to be first, it may as well be us," says Dr. Wagner with a good-natured laugh.

As might be guessed of this scientist who boasts about being the experimental subject in the first human lung scan, the first human PET scan of a neuroreceptor, and numerous other less celebrated trials, doing science with Dr. Wagner is seldom a dull affair.

"Henry Wagner came up with ideas faster than we could try them out," says John G. McAfee, MD, an early collaborator of Dr. Wagner and co-founder of the division of nuclear medicine at Hopkins. In one memorable day during Dr. McAfee's tenure at Hopkins, the two conducted experiments with four different new radiopharmaceuticals—an unheard of



On Being a Guinea Pig

"It's really hard to ask somebody to do something that you are not willing to do yourself," says veteran medical researcher Henry N. Wagner, MD. As a consequence of that conviction, Dr. Wagner has been subjected to more probing and prodding than a hard-working guinea pig. Among other feats, he can boast about being the first human being to undergo a radionuclide lung scan, and the first human subject in radionuclide imaging of a brain receptor.

"I can't understand how a person could try something for the first time in normal human beings without having first done it in himself," he says. "There are people doing studies on normal people that they would not do on themselves. Sometimes a rationalization is used: Well, I'm exposed to radiation all the time in my work and therefore I want to minimize my radiation exposure. They're afraid to do the study on themselves." The low levels of radiation used in diagnostic nuclear medicine experiments don't give Dr. Wagner much reason to worry. Says John McAfee, MD, a peer and early collaborator with Dr. Wagner: "I've taken a lot of radiation in my day, and so has he."

Experimenting on yourself has it's advantages. Dr. Wagner says obtaining administrative approvals is easier, and volunteers more readily understand the safety of an experiment if you've carried out the study on yourself.

Possible toxic effects are among the disadvantages. "You do enough animal studies to know the experiment is not going to be harmful to you, but there's always a little doubt that maybe human beings react differently than dogs." says Dr. Wagner. "We had studied 42 dogs before we carried out the first human lung scanning in me, and there was no evidence of the slightest toxicity, but it's conceivable there might be some sort of reflex vaso-constriction or something like that." Similarly, he says, he had some anxiety about being injected with the neuroleptic drug N-methylspiperone for an experiment to capture images of dopamine receptors. "It was conceivable that the human brain could be more sensitive to a neuroleptic drug than an animal would be," Dr. Wagner says.

To obtain images of opiate receptors (shown above), researchers injected Dr. Wagner with a trace amount of radiolabeled carfentanil, which in larger doses is used to tranquilize rhinos and other large mammals in the wild. "It knocks out animals real fast," says Johns Hopkins researcher Robert F. Dannals, PhD.

venture in today's regulatory climate.

Although the bold approach led to some stunning successes, a few ideas are remarkable as fabulous flops. For example, Dr. McAfee, now a professor of radiology at George Washington University Medical Center, recalls, "We thought we had a great idea for demonstrating gastrointestinal bleeding using xenon gas." The idea: Have the patient inhale xenon-133 until labeled red blood cells pass into the lumen of the digestive tract at the sight of bleeding. Upon stopping the input of xenon, the tracer would exit circulating blood but remain trapped at the sight of bleeding.

To test the idea, Dr. McAfee persuaded Dr. Wagner to let him insert a plastic tube through the nose, down the throat, past the stomach to the duodenum so that they could scan the distribution of the radioactive gas in Dr. Wagner's gut. They found to their chagrin that the piped-in xenon gas diffused rapidly through the intestinal tract, rendering the scans useless for revealing "bleeding."

Seminal work on lung imaging with David C. Sabiston, MD, in contrast, proved a dramatic success. Dr. McAfee credits Dr. Wagner with seizing the insight that led the way in 1963 to a long-sought method to diagnose life-threatening blood clots in the blood vessels of the lungs. Inspiration came from results presented by George Taplin, MD, who was using radioactively labeled albumin aggregates to study the reticuloendothelial system in dogs. "Dr. Wagner immediately saw the application to studying pulmonary embolism," says Dr. McAfee. "As soon as we got home from the conference Dr. Wagner tried macro-aggregated albumin labeled with iodine-131 and obtained very clear images of lung blood flow." After trying the procedure on 42 dogs with experimental pulmonary embolism, Dr. Wagner became the first human subject of the lung scan.

Dr. Wagner and Dr. McAfee met at Hopkins in 1958, shortly after Dr. Wagner returned from the Hammersmith Hospital in London, England, brimming with visions of the untapped promise of using radioactive tracers to diagnose and treat human illness. After medical school, an internship, and residency at The Johns Hopkins University School of Medicine and Hospital, Dr. Wagner went to work at the National Institutes of Health, then took a one-year fellowship at the Post-Graduate Medical School of Hammersmith Hospital (after losing a coin toss with a colleague to decide who would first assume the chief resident spot on the Osler Medical Service at Hopkins—hence Dr. Wagner's fondness for saying that the flip of a coin landed him in nuclear medicine). When he returned from England, Dr. Wagner became chief medical resident.

James William Fulbright (seated) with Henry Wagner, MD and Prof. Michio ***Okamoto, Kyoto University, Japan.***

When Dr. McAfee met the ambitious chief resident, nuclear medicine hadn't earned many enthusiasts. The radiology department provided the use of a small room, about ten feet square, Dr. McAfee recalls, in which they set up a "sort of hodgepodge" rectilinear scanner. Dr. Wagner conducted experiments on the makeshift equipment at night after completing his rounds at the hospital. "He did all this stuff for a year, literally doing it by himself at night," says Dr. McAfee. "He was tireless."

Dr. Wagner says that he is driven by curiosity, but also by the need for recognition. Sibling rivalries and boxing matches from a childhood in Baltimore before WWII surface in a conversation about his competitive nature. The stern and demanding Christian brothers of his Catholic schooling instilled a sense of duty and the importance of hard work and accomplishment. "We were rewarded for compliance. We were punished for disobedience," Dr. Wagner says. He remembers the Catholic brothers as "excellent role models" and values the self-discipline they taught him, though he no longer considers himself religious. "Discipline is necessary for freedom," he says. "If you are disciplined then you are free, the more you learn the more you discipline yourself, the freer you can be."

Subsequent experience would teach the young man the necessity of challenging authority. Near the end of WWII, Henry Wagner turned 18 and faced conscription into the U.S. Army. He chose to apply to the Merchant Marine and Coast Guard Academies; each accepted him and he entered the latter in July, 1945. A month later U.S. forces dropped the atomic bombs on Hiroshima and Nagasaki, Japan and the war in the Pacific ended.

The Coast Guard taught Dr. Wagner to abhor blind obedience to authority and disillusioned him of faith in authority unless it was earned —a characteristic that he says benefits him as a research scientist. In a rueful incident that remains with Dr.

Wagner, an upperclassman at the Academy punished him for daring to do things appropriate only for cadets of higher rank, or being "ratey" in the argot of the academy. The militaristic hierarchy ran counter to his notions of equality. In spite of his love of ships—and a psychological profile that said he would make a good gunnery officer—he returned to Hopkins after 18 months in the Coast Guard.

The competitive aspects of science appealed to the Johns Hopkins undergraduate, so did the process of discovery. Dr. Wagner reveled in the atmosphere at Hopkins; the system rewarded originality and results rather than compliance with the arbitrary rules and regulations of the military. Once in medical school the decision to pursue a research career became an easy one. "I've always been a curious person," says Dr. Wagner, "so it didn't take much to turn me on to scientific studies—I liked it, and was genetically inclined that way, and I was in an environment where it was encouraged."

Over the years Dr. Wagner has managed to preserve an idealistic view of the scientific enterprise. He frequently cites Karl Popper, the traditional philosopher of science, and passionately espouses the ideal of free and open exchange of scientific knowledge. He enjoys competition and spirited debate, and insists that science need not be a contentious business between rivals. "I feel that I have gotten more out of being very open than I have lost. The free exchange of ideas is much more helpful than being secretive. I'm very open with scientific results," says the winner of more than a few scientific foot races. "I think that healthy competition is useful and fun. It's like a sport."

In 1983 the race was on between labs in England, France, and the U.S. to capture PET images of neuroreceptors in the living human brain: Researchers had proven the existence of a number of brain receptors by then and were working to unravel the way receptors processed information in the brain. Dr. Wagner remembers describing at a conference on PET in Stockholm, Sweden his success using N-methylspiperone labeled with carbon-11 to image dopamine receptors in a baboon—important beginnings for understanding schizophrenia and the action of antipsychotic drugs.

He recalls his displeasure when the next presenter at the meeting announced that the only possible way to image receptors *in vivo* was to use a fluorine-18 labeled ligand. "Apparently he didn't even listen to my talk," Dr. Wagner says. "At that time I made up my mind that we were going to do a human study as soon as possible. I knew it was really important."

On May 25, 1983, Johns Hopkins researchers performed the human study on Dr. Wagner, an achievement he now downplays—"Just to image receptors is nothing. You really want to find out the role that they play. You want to come up with a way of looking at how receptors encode information, how you remember things, how you are carrying your past experience."

Fellow researcher Robert F. Dannals, PhD, associate director for nuclear medicine research at Johns Hopkins, points out that before their success, many researchers argued that the specific activity of carbon-11 was too low for use in PET imaging of brain receptors. Dr. Wagner, he says, urged them to proceed full speed ahead. "Sometimes he's a bull in a china shop," says Dr. Dannals. (To image the opiate receptor in 1984, the researchers injected Dr. Wagner with radiolabeled carfentanil, a wild animal tranquilizer, which was, Dr. Dannals likes to joke, "appropriate for use on Dr. Wagner.")

Since demonstrating the use of PET to image brain receptors, researchers in Dr. Wagner's department have made several observations with weighty implications for the treatment of mental disorders. The number of dopamine receptors, for example, decreases dramatically as a person ages, in men more so than women. Many schizophrenic patients have abnormally high numbers of dopamine receptors. Opiate receptors proliferate at the site of onset of focal epilepsy. And in patients with bi-polar illnesses, the number of dopamine receptors increases if the patient has psychotic phases. The most obvious implication is the potential for using PET to monitor patients with these illnesses to measure the effects of therapy on the progression of the disease.

Given advances such as these, Dr. Wagner's fanciful idea of giving psychiatrists the equivalent of a blood-pressure cuff seems less far-fetched, however far away such a device may be. This morning, in particular, the advance of science has ground to a halt because a scheduled cyclotron run has fizzled, leaving the lab without FDG to conduct the probe experiment.

Undaunted, Dr. Wagner advises the young researchers, one still an undergraduate, to carry out the experiment with a "dummy" injection, which would give them practice working with a live rat and other unpredictable components of the study. "You have to be able to distinguish starting points from stopping points," says Dr. Wagner. The phrase is one of the many teaching maxims he brandishes frequently.

"A loser is somebody who looks for acceptable excuses," is another maxim familiar to Hopkins nuclear medicine trainees. "I'm not interested in effort," Dr. Wagner says. "I don't want them to work hard, I want them to get results. Minimize the work, maximize the results, I tell them." The students of Dr. Wagner credit this emphasis on the practical.

"He has taken a group of young investigators and given them the opportunity to prove themselves under his guidance," says Dr. Dannals, who as an undergraduate at Hopkins in 1974 had the chance to work in Dr. Wagner's lab at the Medical Institutions. "He taught me how to develop hypotheses, how to develop interesting research, and how to design experiments," says Dr. Dannals. "He's similar to a father to a bunch of young investigators. He's put a lot of trust in us to be successful in our careers."

Despite the administrative demands of running two divisions, Dr. Wagner has found the time generate productive research ideas. And he can be quite convincing in urging a researcher to take up an idea. "He has a strong personality," says Dr. Dannals. "He's persuasive by gentle persuasion, by explaining his point of view and how the results, if successful, would benefit medicine on a large scale."

A prolific writer, Dr. Wagner has written or co-written hundreds of scientific articles and numerous books. He has written for popular audiences, as well, battling the ignorance that clouds debate about the uses of radioactivity. (He helped found the Center for the Advancement of Radiation Education and Research at Hopkins, a national resource center for objective expert information and educational books and pamphlets about radiation.) He is editing an entirely new version of the classic book *Principles of Nuclear Medicine,* to be published 25 years after the first edition.

Winding through the teaching and work of Dr. Wagner is a firm belief in dealing with human illness at the level of chemistry, the interaction of biological molecules. The strength of nuclear medicine, he says, is its ability to visualize and measure *in vivo* chemistry. The original allure, he says, was the potential to use nuclear techniques to examine biochemistry in living human beings. With the array of radioactive tracers now available to the nuclear physician, he says, the field has evolved to the level of a major medical specialty. The field is now molecular medicine, he pronounced in his 14th consecutive presentation of the highlights of the annual meeting of The Society of Nuclear Medicine.

Whatever discouragement or uneasiness that may sweep through the ranks of nuclear medicine under the mounting burdens of regulation and medical cost-cutting, Dr. Wagner seems immunized against it, enthralled by the power he sees in the technology, "the fundamental fantastic nature of the technology," to use his phrase. "Molecules are a fundamental unit," Dr. Wagner elaborates. "The only field that can really study molecules interacting from one part of the body to another in living human beings is nuclear medicine. We have the unbelievable ability to measure these interactions that integrate our behavior. It's the unbelievable specialty. It's sensational. The reason I am excited constantly about nuclear medicine is the fundamental power of the technology."

The problem with "molecular medicine" is defining diseases at the molecular level. Diseases present, after all, at the level of coughs and sneezes. "To develop a molecular approach on a whole-body scale is going to take decades if not centuries," says Dr. Dannals. But he points out that researchers have found "molecular handles" for a some illnesses, such as schizophrenia, drug addiction, and Parkinson's disease.

It is not surprising, then, that the chemistry of the brain is what commands Dr. Wagner's interest. He considers *in vivo* brain chemistry the most important direction in brain research. While acknowledging the importance of the arrangement of neuronal arrays, he emphasizes chemistry. "Maybe there's a mosaic of neurons that encode experience, but the color of the mosaic is painted on by various chemicals."

Convinced by the advances he has seen in brain research and the power of technology, Dr. Wagner goes so far as to profess a faith that science may enable humanity to understand and eliminate violence and war. "My present research," he has written, "is concerned with investigating the chemical reactions constantly taking place inside the human brain, and how these reactions affect how we think, feel, and act. . . how they affect whether we are afraid, violent or destructive. . . Perhaps we will be able to learn enough about the brain chemistry of fear, violence, and destructiveness to save ourselves from the problems of interpersonal violence and war."

Although when Dr. Wagner turns 65 next year he is required by the rules of his institution to give up his administrative jobs, his plans include further research and writing. The NIH recently renewed for five years a training grant and two major research grants—one in its 30th year. "I was attracted to nuclear medicine because I saw tremendous opportunity for using radioactive tracers to measure human physiology," Dr. Wagner says. "The advances in PET, SPECT and new radiotracers are what keep nuclear medicine unbelievably exciting. I think nuclear medicine has an unbelievable future —the potential is tremendous."

J. Rojas-Burke