30 Years of Nuclear Medicine at the NIH

Despite his frenetic pace as chief of the nuclear medicine department at the National Institutes of Health (NIH), Ronald D. Neumann, MD, steals a few moments to gaze out his office window at the clusters of trees on the 306-acre campus in Bethesda, MD and reflect on why he likes working at the NIH. Being able to perform sophisticated research protocols without the hassles of writing grants is the biggest job benefit. However, he also finds there are quality of life issues: "The physical setting is very pleasant, and I can't complain about my 15-minute commute." A child's fingerpaintings hang on the wall behind him. "I also loved having my son near me in the on-site daycare center," he said. "The salary shortfall is definitely offset by a lot of the pleasantries of my lifestyle."

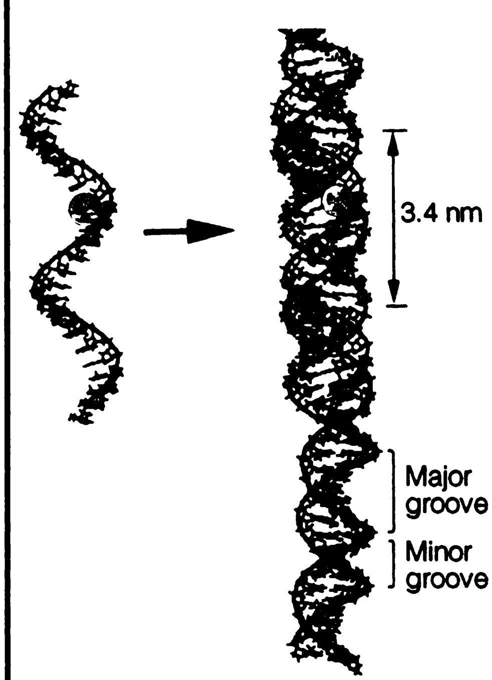
Symbolically, at least, these quality of life issues sum up the differences between the nuclear medicine department at the NIH and the nuclear medicine departments at every other hospital and university in the country. Nuclear physicians at NIH are free to pursue research without the hassles of grant writing or the day-to-day burdens of reimbursements for procedures. Everything is funded by the government—including the salaries which are at the 50 percentile of AAMC salary survey figures for medical school faculty.

Focus on Research

Nuclear physicians who choose to work at the NIH have particular motivations: the need to perform cutting-edge research and the need not to be too distracted by clinical procedures driven by reimbursements. Indeed, patients at the NIH Clinical Center are scarce. Only about 150 patients presently occupy the 540-bed hospital, and they must fit into specific research protocols. The Intramural Program, which funds the internal research studies at the NIH, allows nuclear medicine researchers to take on "risky projects that look at mechanistic questions—not just clinical utility," said Neumann. (About 90% of the NIH budget goes into its Extramural Program to fund grants to investigators at hospitals and universities outside of Bethesda.)

Since its establishment over 30 years ago, the nuclear medicine department has stood alone, different from those at most universities and hospitals. Consider the five nuclear physicians on staff. None are radiologists. Four are internists board-certified in nuclear medicine with subspecialties in other fields such as cardiology and endocrinology. Neumann, himself, is a pathologist board-certified in nuclear medicine with additional training in oncology. "I found anatomic pathology too fixated on anatomy and histology, whereas nuclear medicine is physiology-dominated and is now moving into molecular biology. It flows with the dynamism of medical research and science," he said.

Unlike most hospitals, nuclear medicine at the NIH is a separate department from diagnostic radiology. In fact up until last year, NIH radiologists were paid under separate contracts and had no research funding. (See box on page 15N) "Since we practice independently from the department of radiology, we tend to pursue different interests," Neumann said.



NIH researchers are using triplex-forming oligonucleotides to deliver radiation to break a particular DNA sequence. An iodine molecule is attached to the oligomer which attaches itself in a spiral on the DNA. If successful, the radiation gene therapy technique could be used against certain cancers.

PET: A Separate Entity

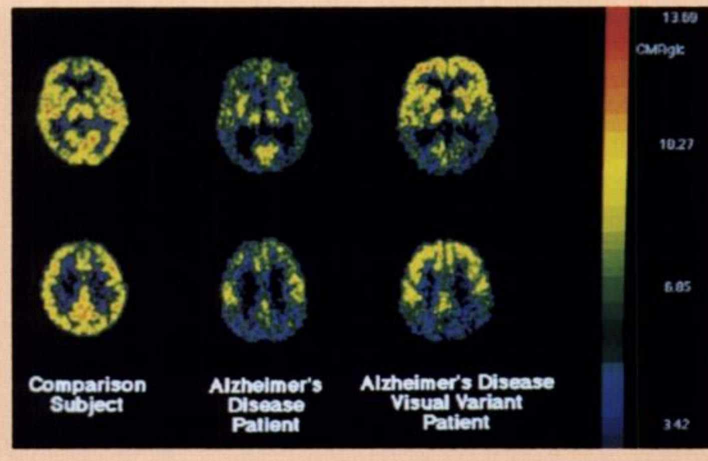
Perhaps the most novel thing about the nuclear medicine department is what it does not have: a PET group. PET has been a separate department with its own budget for the past four years. The 33-person staff, headed by William Eckelman, PhD, performs 1400 PET studies per year. "We had to manage PET at the NIH almost the way an astronomy observatory is managed for astronomers from different universities," said Neumann.

Yet the busy PET department still feels the pressures of researchers' demands. "Our major challenge is coordinating 60 research protocols from the 13 institutes," said Eckelman. He points to a sign-up sheet for the PET cameras with every two-hour increment filled in for the next month. "We've started performing PET studies on Saturdays to give everyone access." This month, a new whole-body PET scanner will be installed in the department, adding to the two PET cameras for brain studies and an older whole-body PET camera.

The biggest change in the PET department, according to Eckelman, has been the expansion into a variety of receptor binding ligands and monoclonal antibody fragments. Although ^{15}O-water and FDG continue to be the most commonly performed studies, at least a dozen other PET radiopharmaceuticals are being developed and tested in preclinical and clinical studies at any given time. "The PET department [was] started mainly for neurology research, but the whole-body scanners have allowed us to expand into other areas such as the diagnosis and treatment of cancer," said Eckelman.

The World's Smallest PET Scanner

In the basement of the Clinical Center, in a dimly lit room without windows, nuclear physicist Michael Green, MS, unveils one of the Imaging Physics Lab's works-in-progress: an experimental PET camera that can image a mouse's organs. The miniature apparatus rests on a small table—about one-tenth the size of a standard whole-body PET camera which can fill an entire room. "So far we've been able to get a 1.3-mm resolution, not bad for PET," said Green. Standard PET cameras have a 4–5-mm resolution, and some scientists had thought that a resolution better than 2 mm could not be reached. Green and his NIH colleagues are still working on methods to improve the resolution still further, to below 1 mm, and modifications are being made to the camera and to the three-dimensional reconstruction software to reach this goal. Once perfected, the camera should be able to accurately measure organ function in small rodents and will be used in a wide range of biological studies.



Brain imaging constitutes 75% of the PET studies performed by the PET department at the NIH. In this particular protocol, Pietro Pietrini, PhD, and colleagues at NIH's National Institute on Aging used PET scans to identify a rare form of Alzheimer's disease, which causes visual impairment rather than memory loss. Individuals with the visual variant of Alzheimer's displayed a markedly lower glucose metabolism in areas at the back of the brain, including the primary visual cortex. The same individuals showed relatively normal activity in other regions, including some of those associated with memory. Areas of low glucose metabolism appear in blue and purple in these PET cross-sections of the brain of a healthy volunteer (left), a person with typical Alzheimer's disease (center) and a person with the visual variant of Alzheimer's (right).

Green and his colleagues are also working in collaboration with researchers at the National, Heart, Lung and Blood Institute at the NIH to perform gated blood-pool imaging on genetically altered mice expected to develop hypertrophic cardiomyopathy. They are using a pinhole collimator containing a single opening 1 mm in diameter compared to the thousands of 2-3 mm holes found in a standard SPECT collimator. The investigators want to determine if the mouse heart does indeed express this defect and, if so, to identify the evolving functional consequences of this genetic manipulation.

On a computer screen, Green clicks on an image of a beating mouse heart. "You would never know you were looking at a heart the size of a fingernail beating at a rate of 300 per minute," he said. "We can measure ejection fraction and produce a left ventricular volume curve, just like in human studies." He circles the left ventricle with the computer mouse and within moments the computer produces a curve. Green predicts that PET, SPECT and planar imaging methods will find increasing use, particularly in small animal studies. "A lot of modern biomedical research is directed toward understanding the relationship between genes and organ function," he said. "Nuclear medicine techniques offer a powerful tool for exploring this connection and help investigators answer these kinds of questions."

From Auger Emitters to Osteoporosis

If performing PET and SPECT on palm-size rodents is not high-tech enough, consider the research underway by Neumann's team. "We're looking at nucleic acids to ultimately see if we can develop radiopharmaceuticals that can do gene radiation therapy," Neumann said. He came up with the idea for this project about five years ago after researchers failed to achieve good therapeutic results with monoclonal antibodies against solid tumors. NIH colleagues were experimenting with treating cancer cells with alpha particles or beta electron emitters attached to antibodies in an attempt to create lethal breaks in the cell's DNA. "The trouble was the electrons were emitted from outside the cell membrane, which is like trying to throw a strike from centerfield 350 feet away," said Neumann. "Our goal was to get closer to the DNA."

During a sabbatical at the National Cancer Institute, Neumann learned about triplex-forming oligonucleotides that can form a triple helix within a particular DNA sequence and deliver the Auger electrons to the DNA directly. "They bind by similar chemistry to the Watson Crick spiral, so if we know the sequence of a target we can make a triplex oligomer that will slide right in," Neumann said.

"We can then attach iodine to the oligomer, which would bring it within striking distance of the DNA, allowing the electron decay to break the DNA at exactly the site we want."

In an article published in the Scandinavian journal *Acta Oncologica* (1996;35:817–823), Neumann and his colleague Igor Panyutin, PhD, found that the decay of ^{125}I in bound triplex-forming-oligonucleotides could indeed cause sequence-specific breaks in the DNA. After one half-life of decay accumulation, approximately one-quarter of the DNA plasmid molecules contained double-strand breaks in a particular sequence. "This is potentially applicable to any gene that we know the sequence of and that meets the rules for triplex binding—meaning it contains runs of purine bases," said Neumann.

In addition to the gene radiation therapy research, the nuclear medicine department is currently expanding its research efforts to areas of interest to the federal government. For instance, women's health and diseases have become a major priority, so the department is evaluating PET imaging for breast cancer. NIH researchers are creating software displays that will allow a surgeon to get an anatomic representation of the axillary lymph nodes as seen during surgery instead of transaxial views. Bone densitometry has also taken on added importance, not just for the diagnosis of osteoporosis in women, but also for evaluating growth problems in children accompanied by low levels of bone mineralization. "DXA constitutes almost a third of our daily practice," said Neumann. Two categories of studies the nuclear medicine department does not do: Phase III clinical trials (universities and pharmaceutical companies have better resources and more patients to do these) and cost-effectiveness studies (costs for NIH procedures are completely funded by the government).

Bureaucratic Realities

When asked to name the biggest drawback of working at the NIH, Neumann responded without hesitation: "The federal bureaucracy." Since NIH is part of the government, it must abide by all government rules. For example, the nuclear medicine department can only purchase imaging equipment according to federal procurement rules. Medical devices not only must be already approved by the Food and Drug Administration (FDA) but must have several working models in the field. "We cannot easily bring in prototypes, for example, which means we never get the first of anything unless we build it ourselves," said Neumann. For this reason, the PET department did not get a whole-body three-dimensional PET camera as quickly as they would have liked, according to Neumann. The first whole-body three-dimensional PET camera was not installed until 1994, while some universities had the camera in 1993.

The nuclear medicine department also had to deal with the month-long Federal government shutdown at the end of 1995. "During that time, we couldn't

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An Overview of 30 Years

The Department of Nuclear Medicine at the National Institutes of Health (NIH) was established in 1966 to meet the needs of investigators from the various institutes who were requesting radionuclide procedures. Since then, NIH nuclear medicine researchers have developed several major advances that have entered the clinical setting at hospitals throughout the country. The following is a list of NIH Nuclear Medicine Department chiefs through the decades and highlights of groundbreaking research.

Jack D. Davidson, MD, 1966-1971

He founded the department and originated the use of the tetrascanner made from four gold/tungsten collimators.

Gerald S. Johnston, MD, 1971-1983

While department chief, list-mode cardiac imaging was invented and became the standard for several years until multigated imaging came into widespread use.

Steven M. Larson, MD, 1983-1988

Monoclonal antibodies became the major research focus of the department. The work has seen been turned over to universities and radiopharmaceutical companies for clinical trials.

Ronald D. Neumann, MD, 1988-present

Under his direction, investigators are radiolabeling nucleic acids to use as potential radiopharmaceuticals. Whether this research will have clinical usefulness is still unknown.

New Opportunities for Radiology Researchers

Radiologists, among whom many nuclear physicians count themselves, have until recently had a somewhat detached arrangement with the National Institutes of Health (NIH) Clinical Center. The radiologists on staff have been hired on independent contracts to avoid the salary shortfalls of government physicians. What they had gained in salaries, however, they lost in research opportunities. Up until last year, Clinical Center radiologists were not funded to do intramural research at the NIH. Nuclear physicians, on the other hand, could do research but earned less than Veterans Administration (VA) nuclear physicians who are also employees of the Federal government.

All this changed at the end of 1995 when the salaries of both nuclear physicians and radiologists at the NIH were put on Title 38 funding, which means they will be on approximately the same pay scales as VA physicians, according to Ronald D. Neumann, MD, chief of the nuclear medicine department at the NIH. In essence, radiologists can now perform research using NIH intramural funds. "Radiology has become part of the imaging sciences group with a laboratory of diagnostic radiology research," said Neumann. The lab received funding by Congress about five years ago as a result of lobbying efforts by academic radiology organizations. The aim is to centralize diagnostic radiology research for the NIH within the department of diagnostic radiology.

A long-term goal envisioned by U.S. radiologists as well as nuclear medicine leaders is to establish a separate institute for funding imaging research at the NIH and the outside community. This would be a dedicated "home" for all research grants in both nuclear medicine and radiology doled out by the extramural program. This dream, however, will not become a reality anytime soon.

N E W S L I N E

Government Relations Update

(Continued from page 24N)

based on information received late in the rulemaking on the subject of duplicative regulation by the NRC and EPA on this issue. While collecting information on this topic, the EPA granted a stay from the regulations, but this order was overturned in court. As a result, the EPA implemented subpart I regulations on November 16, 1992. The Clean Air Act of 1990, however, included a provision for the administrator of the EPA to rescind regulations if a determination that the NRC's program adequately protected public health and safety was made. The delay in recission resulted in the NRC having a 50-mrem standard which was higher than the 10 mrem set by the EPA.

For several years, the ACNP and SNM worked with both the EPA and NRC to develop a dose limit that would satisfy both agencies. The EPA, however, was insistent on the 10-mrem level originally set. Eventually, the NRC made changes to their regulations, including lowering the level to 10 mrem, and published a final rule effective January 1, 1997. Based on the implementation of these new regulations, the EPA has also published a final rule rescinding subpart I of 40 CFR Part 61. This means that as of December 30, 1996, NRC licensees will have to comply only with NRC regulations and not with both the EPA and NRC in this area.

TECHNOLOGIST SECTION

Pew Commission. In December 1995, the Pew Commission Taskforce on Health Care Workforce Regulation issued a set of principles, recommendations and policy options for reform to improve the state-based system of health professions regulation. The report, according to the Pew Commission, has received national attention and has been successful as a vehicle to stimulate and encourage debate and discussion of the issues identified therein. In order to further that discussion, the Pew Commission is seeking comments on the initial report to produce a follow-up report in the Fall of 1997.

The SNM-TS reviewed the 10 recommendations regarding workforce regulation and submitted comments to the Pew Commission. These comments focused on the need for multiskilling and lowering the current barriers that prevent this from happening, reducing the regulatory burden on healthcare workers and creating a uniform system that would be applicable in all 50 states.

For a copy of any of the documents mentioned in this report, please contact Leonard Getzin at (703) 708-9773 or via e-mail at lgetzin@snm.org.

—David Nichols is the associate director of the ACNP/SNM government relations office

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30 Years of Nuclear Medicine at the NIH

(Continued from page 15N)

Fast Facts About the NIH

- The National Institutes of Health (NIH) nuclear medicine department has eight SPECT cameras and only one non-SPECT gamma camera. In 1987, the department had only one SPECT camera; the rest were of the non-SPECT type.
- The recent addition of a whole-body PET scanner brings the total number of PET cameras at the NIH to four. Two cyclotrons on site produce PET radiopharmaceuticals.
- Approximately 50% of nuclear medicine patients are cancer patients, and 25% are cardiovascular disease patients. The rest are from the various other institutes. About 75% of patients who receive PET studies have neurologic or psychiatric diseases, or are studied to map normal brain function. About 15% of patients have cardiovascular disease and 10% have cancer.
- The annual combined budget for both the nuclear medicine and PET departments is about $7 million. Approximately $5 million is for operational costs and $2 million is for capital such as new imaging cameras.
- A staff of nearly 60 runs the nuclear medicine and PET departments at the NIH. An additional 30 post-graduate fellows conduct research projects in both departments.

order certain supplies nor perform laboratory studies," said Neumann. All in all, though, the department has never experienced crippling delays in getting what they need. "We don't feel impeded in our ability to do our work," he said. "We're probably the best equipped nuclear medicine department in the U.S."

Although the NIH is owned by the government, it must deal with the FDA and Nuclear Regulatory Commission (NRC) just like any private facility. The NRC has been particularly stringent with the NIH after an incident in 1995 in which a pregnant research fellow at the NIH ingested ^{32}P. The event occurred in a National Cancer Institute lab, which is not housed in the Clinical Center. Nevertheless, the nuclear medicine department has had to contend with NRC sanctions and stricter security rules. Laboratories containing radiopharmaceuticals are locked at all times unless a researcher is present. Moreover, an armed security guard sits all day in the patient waiting area keeping watch over the radiopharmacy.

Overall, Neumann finds the pleasantries of working at the NIH far outnumber any inconveniences: "We are able to interact with the best scientists in the world and to see a variety of diseases that we would never see at a more traditional hospital," he said. Moreover, he can walk down the hall and meet his wife, who is chief of surgical pathology at the NIH, for lunch. In his mind, there's not much room for discontentment.

—Deborah Kotz