NIH Expands Imaging Research Opportunities

Throughout its 30-year existence, the National Institutes of Health (NIH) has well earned its sterling reputation for basic research. As home to some of the most sophisticated imaging facilities in the world, NIH has continued to reinforce its solid commitment to its imaging sciences research program, funding such state-of-the-art projects as high-resolution PET scanning for small-animal imaging and radionuclide development for gene radiation therapy (See JNM Newsline, March 1997, pp 13N-26N.)

Still, NIH's research focus has traditionally been seen as a step or two removed from the academic hospitals and other clinical research institutions that conduct large scale clinical trials involving hundreds of patients. With its Greek columns and sweeping green lawns, the NIH facility in Bethesda, MD, conjures up images of researchers ensconced in ivory towers. NIH is now encouraging its highly esteemed—if somewhat isolated—researchers to reach beyond their own laboratories to form collaborations with investigators in other institutes within NIH and at other research institutions that have more experience with applied clinical research. The goal is to enable NIH researchers to tap into a larger and more diverse patient population in order to gain experience in a more realistic clinical world than the NIH Clinical Center, which houses only patients who are enrolled in particular research studies. Ultimately, NIH administrators hope that these collaborations will help advance applied research in such areas as substance abuse, diabetes and cancer.

NIH has always served to both dispense government funds for research performed in universities and hospitals throughout the country and to receive government funds to conduct its own research. Traditionally, NIH administrators kept a firm wall between the intramural research program (performed at NIH) and extramural program (funds doled out to other institutions outside of NIH) forbidding NIH researchers to review extramural grant applications and budget allotments. To avoid any appearance of a conflict of interest, "there has been a hesitancy to mix intramural and extramural research programs because extramural grants cannot directly fund intramural researchers," said J. James Frost, MD, PhD, professor of radiology and neuroscience at Johns Hopkins School of Medicine, whose research group has pioneered new types of partnerships between Johns Hopkins and the NIH's National Institute on Drug Abuse (NIDA).

Figure 1. The National Institutes of Health, Bethesda, MD.

Reinforced by congressional initiatives to find better strategies to battle the nation's costliest diseases, the NIH has recently renewed its commitment to coordinate its basic research programs with its clinical research. NIH administrators stress that the separate institutes and the NIH Clinical Center will be more involved in joint research projects; the aim is to bring together researchers from vastly different areas to usher in new treatments or diagnostic tools that can be used in the medical world beyond NIH. "The whole broad field of clinical imaging at NIH will play a major role in our future efforts to translate new scientific discoveries to the larger clinical research arena," said John I. Gallin, MD, director of the NIH clinical center. "Our objective is to recognize the value of the new imaging technologies as they apply to radiology, PET, and nuclear medicine as a whole, rather than as fragmented achievements."

Over the next few months, NIH will begin to award grant money to its researchers in a highly touted program called "Bench to Bedside." Researchers were asked to submit proposals to create a research partnership with other groups at NIH, and those whose proposals are selected will be awarded up to $300,000 in grants from NIH funds to be divided over three years. "The purpose of the Bench-to-Bedside Proposals is to provide incentives to merge basic and clinical research at NIH," said Gallin. Ronald D. Neumann, MD, chief of the NIH Nuclear Medicine

Figure 2. NIH researcher checks sample in a gamma counter.

Department, said he submitted a proposal involving the research program he heads on gamma-emitting triplex-forming oligonucleotides with plans to combine his research with other NIH researchers who are studying the molecular mechanisms of treatments for diabetes and cancer.

Breaking the Barrier Between Intramural and Extramural Research

The need within NIH to find new avenues for collaborative imaging sciences research has resulted in some unconventional NIH partnerships with outside research centers, and this trend is expected to continue, according to Frost. "NIH is forging some new research relationships that are breaking down the traditional barrier between intramural and extramural programs and instead are being designed to promote the scientific and clinical objectives of the particular type of imaging research. What this means is that an NIH partnership today might combine intramural scientific resources and extramural funding, where this was not even considered a decade ago."

Since research priorities both within and outside of NIH now emphasize writing treatment protocols for major diseases such as diabetes and stroke, imaging sciences researchers are increasingly faced with the dilemma of finding large groups of study patients and sites to treat these patients. As a result, the Clinical Center and various institutes at NIH have become increasingly interested in partnerships with outside hospitals that provide access to a larger patient population in a more realistic clinical setting in exchange for NIH's providing scientific consultation, funding, and technological support. "The classic NIH clinical trial population is managed under a medical subspecialty and represents only a small fraction of the patients and scenarios in real clinical practice," explained US Navy Captain David Harlan, MD, head of the Immune Cell Biology Department at the Naval Medical Research Institute. Harlan is currently working on a collaborative research project involving islet cell transplantation with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). "On the other hand, clinical depart-

Presidential Award Given for PET Research

In recognition for a lifetime achievement in the field of nuclear energy, President Clinton named Michael E. Phelps, PhD, as a winner of the Enrico Fermi Award on February 18, 1999. Phelps is chairman of the Department of Molecular and Medical Pharmacology at the University of California at Los Angeles School of Medicine. He contributed to the invention and use of positron emission tomography (PET) and specifically contributed to PET's use in research and patient care in neurological disorders, cardiovascular disease and cancer. He also established and directed the first PET clinic for patient care. Clinton also announced that the award would be given to Maurice Goldhaber, PhD, a nuclear and particle physicist and distinguished scientist emeritus at Brookhaven National Laboratory in Upton, NY, who was the first person to accurately measure the mass of a neutron.

"It is a privilege to honor these scientists and their pioneering research," said President Clinton. "Dr. Goldhaber's work has contributed significantly to our understanding of the way the world works. Dr. Phelps made possible an innovative technology that has improved medical research and health care." Phelps and Goldhaber will each receive a gold medallion and a $100,000 honorarium from U.S. Energy Secretary Bill Richardson during an awards ceremony on April 16 in Washington, D.C.

Phelps earned his PhD in chemistry from Washington University, St. Louis, in 1970. His early work applied nuclear physics, chemistry and mathematics to biomedical imaging. Goldhaber earned his PhD in physics at Cambridge University. He is the former director of Brookhaven and since his retirement has continued the study of neutrinos, most recently as part of the international collaboration of scientists who found evidence that neutrinos have mass.

The Fermi Award is the government's oldest science and technology award and was first given in 1956. It honors the memory of Enrico Fermi, leader of a group of scientists who achieved the first self-sustained, controlled nuclear reaction at the University of Chicago in 1952. Among the first recipients were physicists Robert Oppenheimer, PhD, Hans Bethe, PhD, and Ernest O. Lawrence, PhD.

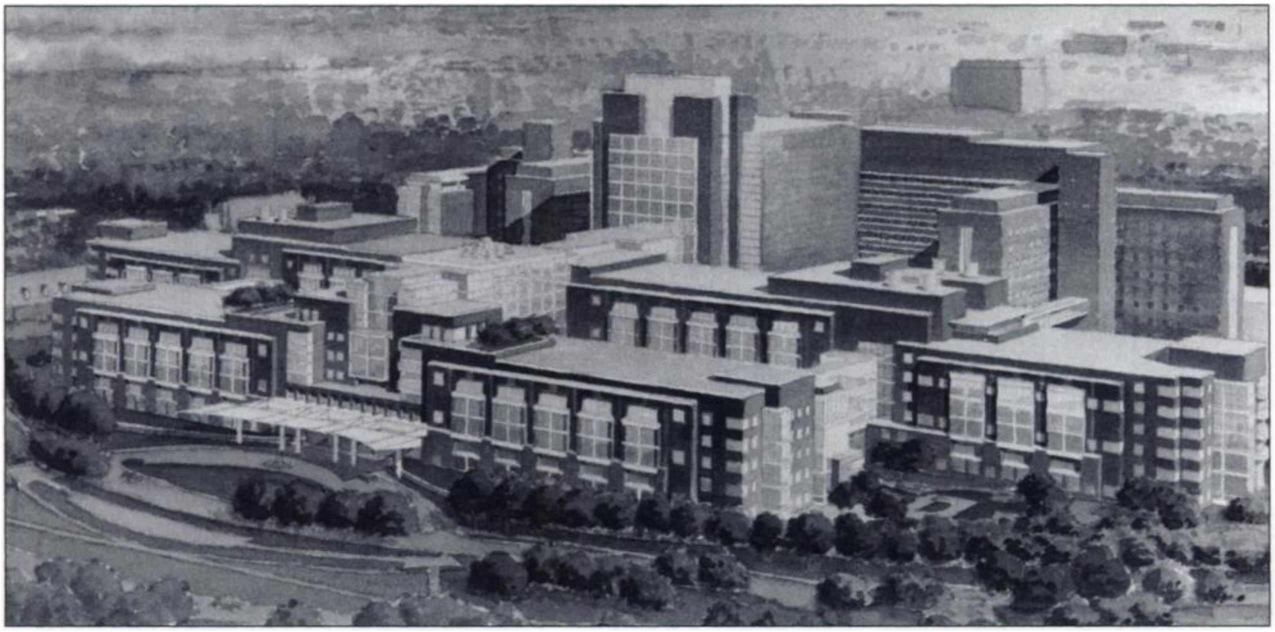

Figure 3. Artist's rendition of Mark O. Hatfield Clinical Research Center, under construction at the NIH.

ments at academic hospitals, which house the patient cohorts of interest, just don't have the money to do pilot trials any more. It may take 2 or 3 years for a grant application to come through, and third-party payers cannot be called on to reimburse experimental treatments. NIH doesn't face those types of financial pressures."

R. Nick Bryan, MD, PhD, director of diagnostic radiology and associate director for Radiologic Imaging Sciences at the NIH Clinical Center has been heading up the effort to forge new types of imaging research partnerships with the Johns Hopkins School of Medicine, where he served for 10 years as director of the Neuroradiology Division before joining NIH in January 1998. He believes the two institutions can form a symbiotic relationship where NIH can draw from Johns Hopkins's patient population base and clinical facilities, and Johns Hopkins can use NIH funding and new imaging technologies developed at NIH to springboard into new clinical protocols. Elias Zerhouni, MD, PhD, chair of radiology and a professor of biomedical engineering at Johns Hopkins School of Medicine, who is working with Bryan to establish the partnership, concurs. "At Johns Hopkins, we realize that while we have the ability to see large groups of patients, identify clinical problems and areas of opportunity for treatment, and even develop new concepts for using imaging, we don't have the funding to capitalize acquiring advanced imaging technologies," Zerhouni said. "NIH has the mandates and funding from the government to acquire new, expensive imaging technologies and can afford the risks of being a test-bed for unexplored clinical applications with such technologies."

A current problem that the NIH partnerships would solve involves testing new radiopharmaceuticals developed at Johns Hopkins. "We have a world-class radiochemistry laboratory to create radioactive compounds, but we don't have the imaging capabilities that NIH has to keep up with testing these new compounds," Zerhouni said. "Although we're at the forefront of radiochemistry for PET applications to specific clinical problems, we need NIH funding, imaging expertise (such as the small-animal PET imaging program), or both, to help us to address these clinical problems."

Using PET to Evaluate Treatment for Substance Abuse

One of the first initiatives that Johns Hopkins researchers took in establishing a new type of partnership with NIH researchers involved using PET to study the neurochemical effects of opioid abuse. "I though that intramural investigators at NIDA would be terrific scientific collaborators with our group," said Frost, who received the first extramural grant for the collaboration about three years ago. Since then, the researchers have been collaborating to study the how brain opioid receptors change when substance abusers undergo drug withdrawal treatment programs. "PET scans have proven to be invaluable for comparing changes in opioid receptor binding from baseline through the period of drug withdrawal and treatment," said Frost. "By comparing the timeline of these changes to changes in patient abuse patterns, we can in turn essentially predict time to relapse."

Both Johns Hopkins and NIDA researchers

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have benefited from the partnership by drawing from each other's strengths. NIDA, based in Baltimore, has set up a preliminary PET program and has no way to produce PET tracers since it is fairly isolated from the PET department located on the main NIH campus an hour away. Johns Hopkins, however, has a strong PET program that specializes in the production of receptor-specific PET tracers. Its researchers rely on NIDA investigators for their experience working with a particular patient cohort and NIDA resources to recruit and characterize drug-abuse patients. "The hard part at the time that we submitted the first grant proposal was convincing the NIDA Intramural Research Program to provide principal investigators to collaborate with us on the study, because our funding was to come from an extramural NIH grant," said Frost. "Finally, it was decided that the NIDA investigators could serve as full scientific collaborators without receiving additional pay for the project."

In order to conduct the study, hospital inpatients were shuttled from the NIDA facility to the adjacent Johns Hopkins University Bayview Campus hospital for baseline PET scans and follow-up scans. In the fall of 1998, NIH awarded a $1.3 million grant to Frost's research group for a follow-up collaborative study to use PET to assess changes in brain opioid receptors in addicts receiving outpatient treatment, which is a much more realistic clinical scenario than that of the first study.

Getting NIH Technologies into the Outside World

As part of the effort to encourage the sharing of new research, NIH administrators have been encouraging a "cross-fertilization" of sorts, allowing outside investigators to spend a great deal of time at NIH and vice versa. The intermingling has been particularly strong with Johns Hopkins since the two facilities are located fairly close to each other. "Many of our researchers here at Johns Hopkins spend half of their time at NIH, and likewise NIH researchers split their time between NIH and Hopkins," said Zerhouni. "NIH is not only a source of facilities and funding for us in these partnerships but it also serves as an important training ground for our researchers."

The fruit of these collaborations could come in the form of a small-animal PET imaging facility which would be built at Johns Hopkins to be modeled after the one that already exists at NIH. The tiny PET imager that is capable of taking scans of genetically engineered mice and other small animals was built by Michael Green, MS, a nuclear physicist in the NIH Imaging Physics Lab. "The idea for the Johns Hopkins project started when Dr. Zerhouni, Dr. Bryan, myself, and researchers from other academic centers met in February 1998 to discuss the prospect of developing molecular imaging centers across the country," explained Martin G. Pomper, MD, PhD, assistant professor of radiology at Johns Hopkins School of Medicine. "NIH subsequently issued a Request for Applications inviting institutions to apply for grant funds from NIH to help build a small-animal PET imaging facility. Our grant proposal is still pending, but we hope to hear something within the next several weeks."

In the meantime, William Eckelman, PhD, chief of the NIH PET Department, recently agreed to forge a collaboration with Pomper to do advanced PET research, including a potential partnership between Pomper and Green using his small-animal imager. The first collaborative experiment involved PET scans on a single transgenic mouse—developed at Johns Hopkins—that overexpresses c-Myc, a gene associated with lung, breast and occasionally colon cancer.

Reaching Out from Within

As a bastion for basic research, NIH has, in the past, left studies on clinical problem-solving largely to those institutions that have large, diverse patient populations. However, NIH recently decided to reverse this trend. As managed care executives and congressmen alike focus on the need for outcome studies, NIH has decided to expand its own clinical facilities in order to utilize specialized clinical settings (intensive care units, operating rooms, and emergency rooms) to study how advanced imaging technologies can be used most effectively in these settings.

In two years, NIH plans to open the Mark O. Hatfield Clinical Research Center. The new 250-bed hospital, which will replace the existing 325-bed Clinical Center, will have closely linked research and clinical facilities. "The new NIH hospital will become very important in supporting joint initiatives between basic and clinical research throughout the Institutes, including in the imaging sciences," says Gallin.

In terms of medical imaging, the ultimate goal for the Clinical Center across NIH research departments is to determine ways to accommodate more testing of imaging techniques in increasingly diverse clinical settings. For instance, one project in the works for the new Clinical Center will be to install an imaging program in intensive care units. "Traditionally at NIH, we do not have much access to patients in this setting," said Bryan. "We are already negotiating the details of finding space for our PET, CT, and MR machines in the intensive care units of the new NIH hospital, including specialized beds and modified instruments that would allow us to study acutely ill patients around the clock."

—Jill Katz