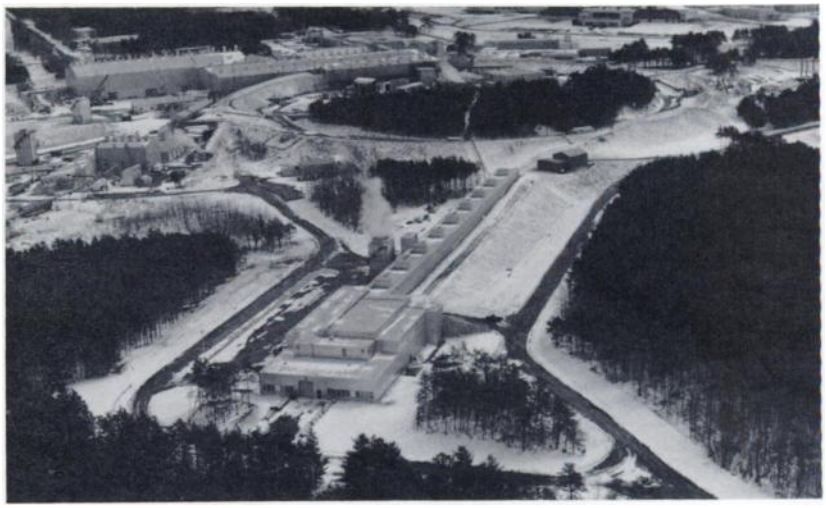
LINAC's Proton Beam Energizes Unique Medical Isotope Producer

BROOKHAVEN, ORIGIN OF TC-99M AND F-18 FDG, OPENS NEW FRONTIERS FOR NUCLEAR MEDICINE

"During our initial forays into the nuclear medicine field, we started making compounds because that's what we could do, and eventually we became more interested in how these compounds could be used and how everything worked. We got more and more interested in physiology and disease syndromes."

During World Wars I and II, United States soldiers trained at Camp Upton on Long Island before shipping out to overseas battle zones. Today, Camp Upton is just a memory, and its army barracks and military hospital stand in the midst of newer buildings that house nuclear reactors, cyclotrons, and high-energy accelerators.

Known today as Brookhaven National Laboratory, this 5,256-acre site with more than 250 buildings lends its immense nuclear research facilities to open new frontiers for nuclear medicine. Brookhaven also provides an international training ground for many scientists in the nuclear medicine field, particularly in the area of radiochemistry. Two departments at Brookhaven have research groups that study nuclear medicine problems.



This aerial view of Brookhaven National Laboratory in Upton, NY, displays the vastly powerful physics research machinery that allows for the production, in a parasitic mode, of radionuclides for medicine. The long narrow structure at the center is the Linear Accelerator's (LINAC) transfer tunnel that accelerates protons to 200 MeV for injection into the Alternating Gradient Synchrotron (AGS), a 0.5-mile-circumference ring. The small dark building at the end of the transfer tunnel houses the Brookhaven LINAC Isotope Producer (BLIP), which harnesses the energy from a deflected portion of the beam to create labels for radiopharmaceuticals.

In the Medical Department, the Nuclear Medicine Group, headed by A. Bertrand Brill, MD, PhD, is working on cardiac perfusion and metabolic studies in hypertension and coronary artery disease. Also in the Medical Department, the Radionuclide and Radiopharmaceutical Research Division, headed by Suresh C. Srivastava, PhD, is working on the development of new radionuclides and tracers, as well as novel methods of labeling blood cells and antibodies.

The Chemistry Department, chaired by Alfred P. Wolf, PhD, has pioneered many breakthroughs in the development of cyclotron-produced radiotracers, and made a major impact on nuclear medicine with the development of fluorine-18 fluorodeoxyglucose (FDG) in the 1970s for positron emission tomography (PET) (*1–3*). Today, the Cyclotron PET Research Group, headed by Dr. Wolf and Joanna S. Fowler, PhD, is unfolding the intricacies of neurotransmitters with receptor-based radiopharmaceuticals and looking at functional enzyme activity in the brain and in tumors. The group is also exploring the use of PET by the pharmaceutical industry as a

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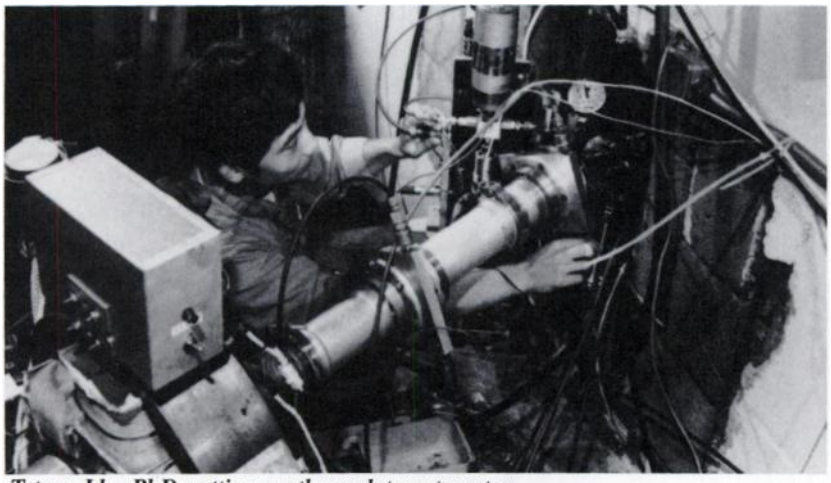
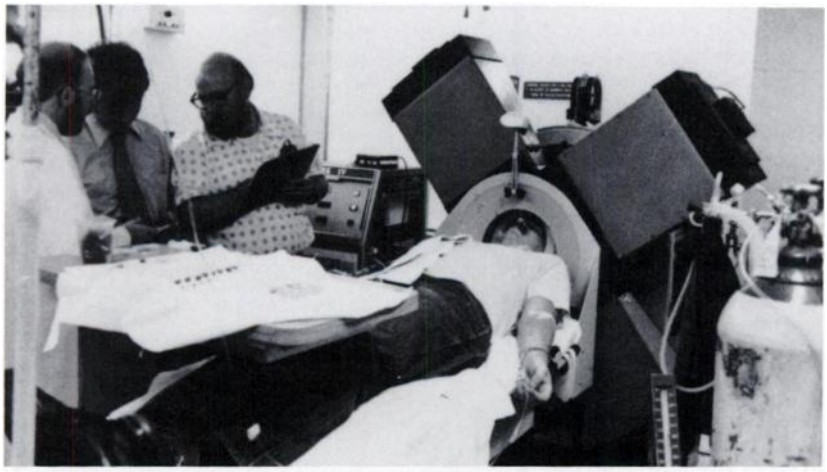
The Story of Fluorine-18 Fluorodeoxyglucose



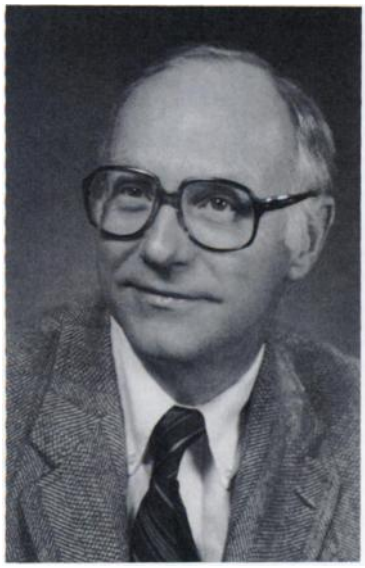
Tatsuo Ido, PhD, setting up the cyclotron targetry.

Fluorine-18 fluorodeoxyglucose landing in Philadelphia.



Investigators (left to right) Joel Greenberg, PhD, Michael E. Phelps, PhD, and Edward ***J. Hoffman, PhD, comparing notes while the subject undergoes a tomographic brain scan.***

In the early winter of 1973, Alfred P. Wolf, PhD, a chemist at Brookhaven, got a telephone call from David E. Kuhl, MD, then head of nuclear medicine at the University of Pennsylvania. As Dr. Wolf recalls, "He said he had a challenging tracer problem, and that we would be interested. On December 19, 1973—I remember the date very clearly, it was a miserable day—we went down there and sat down and talked and that's how FDG [fluorine-18 fluorodeoxyglucose] got started. Abass Alavi was there. Martin Reivich had been a post-doc of Lou Sokoloff's. Sokoloff and Reivich had worked out this deoxyglucose method in rats. Reivich is the head of the Cerebrovascular Institute at the University of Pennsylvania, and he was very much interested in measuring brain glucose metabolism. Dave Kuhl was head of nuclear medicine, and these guys talked to each other. Kuhl said, 'Gee, it would be nice if we could label deoxyglucose with an isotope we can image.' You can't do it with carbon-14, of course, because you can't see it. So he called me. I'd been working in the field for eight years at that time, publishing papers on planar use of positron emitters. I told him, 'I had noticed this in the literature, but we don't have a tomograph.' We sat down and discussed it and he wanted us to make carbon-11 deoxyglucose. I said I thought the way to go was to make fluorodeoxyglucose, which had a sufficiently long half-life to be shipped from Brookhaven to the University of Pennsylvania where Kuhl's tomograph could be used. Sokoloff said we had to show that fluorodeoxyglucose worked the same as deoxyglucose. So we



Alfred P. Wolf, PhD

made carbon-14 FDG, and Sokoloff showed it had similar behavior *in vivo* to carbon-14 deoxyglucose. Then Tatsuo Ido showed up in 1975 and said he wanted to do hot atom chemistry, but I said, 'No, I've got a hot problem for you. Make FDG.' He did both things, and tried a number of syntheses for FDG that didn't work, but we banged away at it, and finally Tatsuo said he had it. 'The yield stinks,' he said, 'but I can make enough.' Then we had to make it sterile and pyrogen-free, so we made it 10, 15, 20 times, then sent it out to independent labs for checking. Finally it was done, so we called Dave Kuhl and said, 'We're ready. Find a victim.' He of course immediately got a medical student and we arranged a date and did a rain dance to make sure we didn't have thunderstorms. On that day, which was a sunny August day in 1976, we all got up early, made the stuff, put it on the plane, they injected it, and that was the first FDG study, and that's the story behind FDG."

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tool for identifying target organs and measuring the pharmacokinetics of new drugs.

Improved Biodistribution Studies

"We think that if PET were to become a more widely used tool in the pharmaceutical industry, investigators could find what they need to know by performing a smaller number of studies with fewer animals to determine the short-term pharmacokinetics, target organs, and excretion patterns of new drugs," said Dr. Fowler.

"If the drug industry used PET, one could look at the whole body of an animal, or a person, with tracer doses of the labeled drug and get this information very rapidly," said Drs. Wolf and Fowler, adding that the Ciba-Geigy pharmaceutical company plans to acquire a PET unit at its research center in Switzerland for this purpose. In addition, Dr. Wolf's group has started a collaboration with Hoffman-LaRoche, Inc., using PET to assess the dynamics of a newly approved anesthetic in the brain.

Dr. Fowler noted that the use of PET in drug development would expedite the introduction of new drugs into medical practice because PET can provide information, such as measurements of blood-brain barrier permeabilities and short-term kinetics, that is difficult or impossible to obtain with other methods.

"Radioisotopic Cows"

Two decades before the development of fluorine-18 FDG, the Department of Nuclear Engineering at Brookhaven created a device that profoundly influenced nuclear medicine—the molybdenum-99/technetium-99m generator.

Walter D. Tucker, a chemical engineer in the Manhattan District Project, joined Brookhaven in 1947, the same year that the research center was established to provide a state-of-the-art physics research facility for several universities (mostly Ivy League) in the eastern United States. Warren E. Winsche, PhD, a chemical engineer at the Oak Ridge National Laboratory in Tennessee, also came to Brookhaven that year to take charge of the engineering aspects of designing the new graphite reactor. He later became Deputy Director of Brookhaven.

"Warren had been involved in some radioisotope work at Oak Ridge, making triggers for the atom bomb, and he felt that a reactor should have a hot lab with it, so he volunteered to design, construct, and operate the hot lab we have here now," recalled Mr. Tucker, who headed the Radioisotope Development Group from 1949–1961.

"Warren also had the idea of being able to produce short-lived isotopes by getting a parent that you could milk, finding an isotope pair where the daughter had a shorter half-life than the parent. This way, you could have short-half-lived isotopes available at distances from the production site," said Mr. Tucker.

Mr. Tucker and Louis G. Stang, head of the Hot Laboratory Division from 1947–1981, came up with a tellurium-132/iodine-132 generator. "Iodine-132 had great acceptance in Europe, but very few physicians in the United States would touch it, partly because Oak Ridge had done a terrific job in making iodine-131 available," said Mr. Tucker.

The first generator had other problems, he recalled, because small amounts of tellurium, which causes strong garlic breath, contaminated the iodine-132 injection, "the patients revolted against that. This problem was solved by the development and patenting of the aluminum oxide generator, giving a much purer product."

A customer detected another impurity in one of the generators—technetium-99m. Investigating the problem led to the discovery that the chemistry of the molybdenum/tech-

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netium parent-daughter pair was similar to that of tellurium/iodine pair.

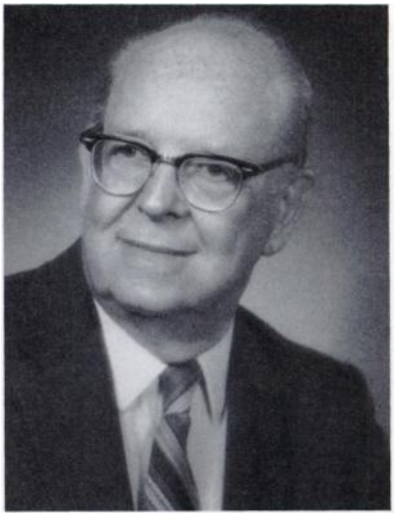
Margaret W. Greene, a chemist at the hot lab, and Mr. Tucker decided to adapt the aluminum oxide generator for the production of technetium-99m. "The isotope was perfect, with a single gamma, no beta, and a six-hour half-life. The Anger camera was coming out then, and the technetium-99m gamma had an ideal energy level to work with the scintillation camera," noted Mr. Tucker.

In 1960, the first issue of *The Journal of Nuclear Medicine* (*JNM*) included an abstract entitled "Radioisotopic Cows," on the technetium-99m generator, presented at The Society of Nuclear Medicine's (SNM) Southwestern Chapter Meeting (*4*).

Also in 1960, Mr. Tucker transferred to another division, and Powell (Jim) Richards took charge of radionuclide research and production. "Jim was a genius at seeing a practical medical use for these radionuclides," said Harold L. Atkins, MD, who headed the Nuclear Medicine Division at Brookhaven from 1963–1979.

On an airplane flying to Rome in 1960 for the 7th Nuclear Congress, Mr. Richards met Paul V. Harper, MD, of the Argonne Cancer Research Hospital in Chicago, and told him about technetium-99m. "At that time, we couldn't get anyone to use the stuff, but Harper contacted me a year later and we worked jointly on the first clinical evaluations of technetium-99m agents," said Mr. Richards, who retired from Brookhaven in 1983.

Mr. Richards' group developed technetium-99m-labeled sulfur colloid, pertechnetate, diethylenetriaminepentaacetic acid (DTPA, the first instant kit), and the red blood cell kit (*5–8*). During the SNM 1964 Annual Meeting in Berkeley, CA, Mr. Richards organized the first meeting of the Technetium Club.



Walter D. Tucker, who worked with Margaret W. Greene to develop the first technetium-99m generator.

When Dr. Atkins joined the laboratory, his group also evaluated the clinical uses of these new technetium-99m compounds at the 40-bed Brookhaven hospital, which was then an inpatient facility. In 1966, commercial manufacturers took over the production and distribution of the generator.

Elliott Lebowitz, PhD, a Brookhaven chemist, heard a discussion on the possible use of thallium for myocardial imaging, presented by a group at Argonne during an SNM Annual Meeting in 1970 (*9*). There was a need for something to replace potassium-43 for cardiac imaging because its high energy made it unsuitable as a scanning agent.

Dr. Lebowitz took on the challenge of developing the new heart agent, and presented a paper on this work two years later at the SNM meeting (*10*). In 1975, a report was published in *JNM* stating that "thallium-201 merits evaluation for myocardial visualization, kidney studies, and tumor diagnosis because of its physi-

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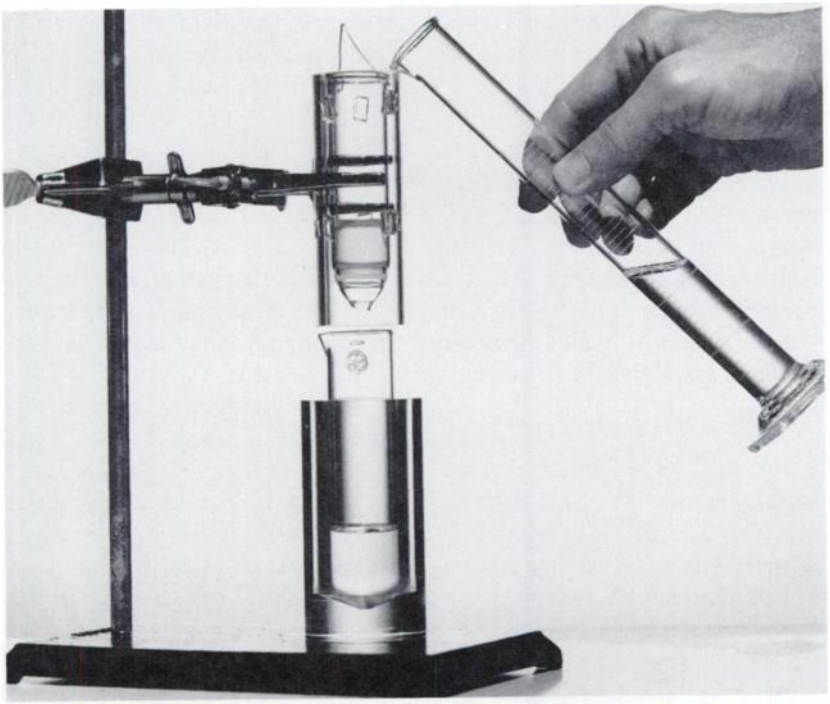

In 1958, the head of the Brookhaven Patent Office said that he and Atomic Energy Commission (AEC) officials were "not aware of a potential market for technetium-99m great enough to encourage one to undertake the risk of patenting..." In 1982, the market for technetium-99m products was estimated in excess of $100,000,000 per year. **(Reprinted with permission from Richards P, Tucker WD, Srivastava SC: Technetium-99m: An historical perspective. *Int J Appl Radiat Isot* 33:793–799, 1982)**

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cal and biologic properties." (*11,12*).

BLIP Produces Xenon-127

Paul B. Hoffer, MD, Paul V. Harper, MD, and other investigators at Argonne reported in 1973 that xenon-127 produced higher quality lung and brain images than xenon-133 (*13*). The Chicago group could not produce enough xenon-127 in their cyclotron, however, to conduct extensive studies.

About the same time, Brookhaven was making plans to deflect the high-energy proton beam from its Linear Accelerator (LINAC) to make radionuclides for the Medical Department. "Jim Richards thought that we could make xenon-127 with the BLIP [Brookhaven LINAC Isotope Producer] because the procedure required a high energy," said Dr. Atkins.

The Brookhaven group published a comparison of xenon-127 and xenon-133 for ventilation studies in 1977, and concluded that xenon-127 appears to be preferable because of the higher counting rates, lower patient radiation dose, and longer shelf life (*14*).

Xenon-133 today is still used much more often than xenon-127 for ventilation imaging, however, because it is less expensive and more readily available. "The primary advantage of using xenon-127 is that you can do a ventilation study right after a technetium-99m perfusion study because the energy level of the gas is high enough to prevent the first study from interfering with the ventilation image, although you do need a high-energy collimator," explained Dr. Atkins.

Xenon-127 is only one of several radionuclides produced in the BLIP (*15*), which can bombard several targets at once with a 200-MeV proton beam. The beam's energy is reduced as it goes through each target, allowing targets to be placed selectively in positions that receive different energy levels ranging from 0–200 MeV. The portion of the beam that is not deflected to the BLIP travels straight to the Alternating Gradient Synchrotron, which accelerates the protons in a 0.5-mile orbit to 30 GeV for high-energy physics experiments.

The BLIP also produces iodine-123, strontium-82 (used as the parent in rubidium-82 generators), and germanium-68 (the parent in gallium-68 generators), as well as other radionuclides. "The ability to have a stack of multiple targets that are hit with different energies is unique. There's no other facility like this in the world," said Leonard F. Mausner, PhD, head of BLIP operations.

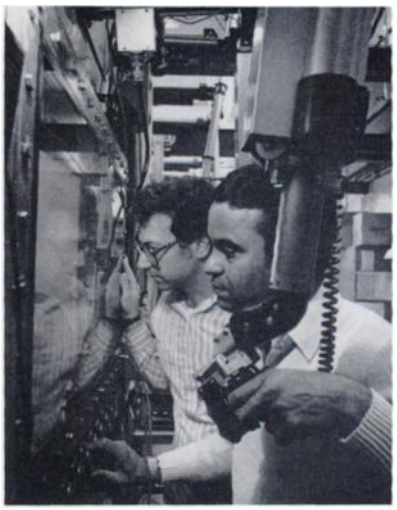
New Labels for Antibodies

Drs. Srivastava's group is using the BLIP to search for better labels for therapeutic monoclonal antibody procedures. "The diagnostic radionuclides presently available (iodine-123, technetium-99m, and indium-111) give good antibody images. There's no crying need for any new isotopes in that area," said Dr. Mausner.

"I feel that using iodine-131, which has an eight-day half-life, for therapy is not ideal in all cases, however, and we're looking at making new radionuclides that might be more appropriate," he added. The first one the group studied was copper-67, which has a 2.8-day half-life.

"Most antibodies in research application now concentrate in the tumor within one to three days, and stay there for one or two days. You need to tailor your half-life to those biologic kinetics, otherwise you're adding to the patient's whole-body dose without doing anything therapeutically," explained Dr. Mausner.

The Radionuclide and Radiopharmaceutical Research Division is also planning to assess the potential use of scandium-47, palladium-109, and samarium-153 for antibody therapy. Samarium-153 can also be produced in Brookhaven's reactors, and won't have to depend on the BLIP schedule. Currently, the Accelerator Department operates the LINAC about eight months out of the year at a cost of $100,000/week.



Suresh C. Srivastava, PhD (right), and Leonard F. Mausner, PhD, standing in front of the hot cell where radionuclides from the BLIP are processed. The targets are transferred from the BLIP by fork lift in lead casks which are connected to the hot cell through trap doors.

In the diagnostic area, work is being done to develop antiplatelet antibodies. "There is a need for this approach in cell labeling to make it possible to label specific types of cells in samples of whole blood or *in vivo*. Then clinicians could avoid cell separation procedures, which are time-consuming and also damage cells," said Dr. Srivastava. His group has labeled the antiplatelet 7E3 antibody, developed at SUNY Stony Brook, with indium-111 and iodine-123 (*16*).

Working with investigators at Stony Brook and in Albuquerque, Prantika Som, PhD, of Brookhaven's Medical Department, investigated another antiplatelet antibody, 50H.19, labeled with technetium-99m. Dr. Som and her colleagues have used it to detect thrombi in dogs, and she said that human studies are to begin soon (*17*).

"There is also a tremendous need for technetium-99m-labeled white blood cells," said Dr. Srivastava. Although indium-111 oxine is better for

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measuring cell survival and kinetics, he explained, technetium-99m would be much better for imaging sites of inflammation and occult abscesses.

The group is also developing an improved red-blood-cell labeling kit for use with 1-ml whole blood samples (*18*).

Tin-117m for Bone Cancer

While studying the effect of tin on technetium-99m for cell labeling, the Brookhaven group observed that various tin compounds localized in the bone (*19*). "We decided to look into that in more detail," said Dr. Srivastava, "and found that one chelate, tin (IV)-DTPA, had exceedingly high bone uptake and very low soft tissue uptake, which gave us the idea that it might be suitable as a therapeutic agent."

The Brookhaven group has recently started to evaluate the ratio of bone tumor to normal bone in the uptake of tin-117m. "That ratio needs to be high so that we don't overdose the whole skeleton," explained Dr. Mausner. "This procedure looks promising, and we're giving it a lot of attention now," he added.

PET and SPECT Heart Imaging

Brookhaven has been collaborating with Oak Ridge on the evaluation of hypertension with thallium-201 and iodine-123-labeled fatty acids. Autoradiographic results in rats indicate that hypertensive heart disease impairs the myocardium's ability to metabolize fatty acid before it impairs blood flow (see *Newsline*, Feb. 1986, pp. 155–157). Fluorine-18 FDG studies show "that the heart switches from its usual proclivity for using fatty acid to a preference for glucose as its major energy source," said Dr. Brill (*20*).

These findings are similar to the observations of other investigators studying coronary artery disease, where blood flow is impaired and the myocardium lacks sufficient oxygen. "In the hypertensive animals with normal blood flow, however, the heart should have enough oxygen, and we are doing studies in hamsters with severe cardiomyopathy—the type for which patients receive heart transplants—to try to understand the metabolic basis for the switch in energy source," explained Dr. Brill.

In the hamster model, Dr. Brill's group found that the alteration in fatty acid and glucose metabolism can be blocked by calcium-channel blocking agents. "This finding suggests that this form of therapy, if started early in the development of cardiomyopathy, may be of importance," said Dr. Brill. "We're also evaluating new tracers to see which is most efficacious in making the correlation between disease and normal states, and to understand the pathophysiology of the disease," he added.

Next April, investigators from Stanford University are planning to use the Synchrotron Light Source to generate monoenergetic X-ray beams for coronary angiography. "The beam will be very narrow, just above and just below the peak absorption of an iodine contrast agent given intravenously," said Dr. Brill. "We hope that these studies will demonstrate that, with very sensitive detectors and computerization, this procedure will give physicians the same kind of information on coronary artery abnormalities that is now obtained with catheterization," he explained.

His group plans to evaluate the functional capacity of the myocardium in those patients found to have a flow obstruction with a simultaneous PET and SPECT [single-photon emission computed tomography] procedure, using injections of fluorine-18 FDG and iodine-123 fatty acid.

With a multiwire proportional chamber, developed at CERN [European Nuclear Research Center] for PET imaging, two 30 × 30 cm area detectors 180 degrees apart will rotate around the patient, similar to a SPECT system. Two SPECT cameras, mounted on the same system, 180 degrees apart and at 90-degree angles to the PET detectors, will also rotate around the patient.

"We would expect to find increased fluorine-18 FDG uptake in regions of the heart with decreased blood flow, and decreased iodine-123 fatty acid uptake in those same regions," said Dr. Brill. His group also plans to assess the value of these metabolic imaging procedures in comparison to coronary angiography, radionuclide angiography, and thallium-201 studies.

PET Chemistry

Brookhaven's Chemistry Department began studying the chemistry of positron emitters in 1954, and has provided most of the basic data that is used in the field today. It obtained its first grant from The National Institutes of Health for nuclear medicine research in 1974.

"During our initial forays into the nuclear medicine field, we started making compounds because that's what we could do, and eventually we became more interested in how these compounds could be used and how everything worked. We got more and more interested in physiology and disease syndromes," recalled Dr. Wolf.

"We started working with Hal Atkins in the Medical Department, and that's basically where we cut our teeth in the nuclear medicine field," said Dr. Wolf, who was evaluating the planar imaging uses of positron emitters in the early 1970s.

Dr. Atkins was interested in adrenal imaging agents at that time, and Dr. Wolf's group made some carbon-11-labeled compounds, such as carbon-11 dopamine for collaborative studies with the Medical Department. "We also made iodinated compounds, and got into the astatine-211 business, an alpha emitter for therapy, with Jim Adelstein at Harvard," said Dr. Wolf.

After fluorine-18 FDG was devel-

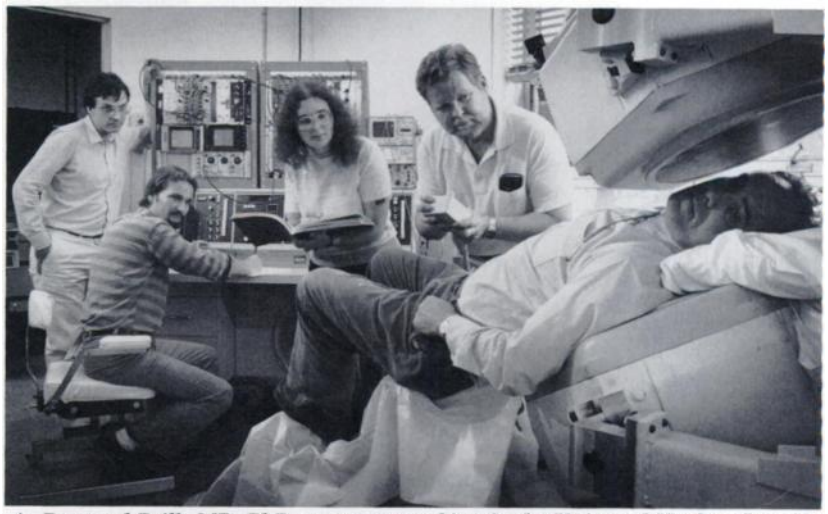
oped, Drs. Wolf and Atkins wanted a PET machine. "At that time, there were no commercial PET units, but Michel Ter-Pogossian was building another machine in his series, and he wanted to get rid of his PETT III. We bought his machine for about $75,000, transported it up here and stationed it in the Medical Department," said Dr. Wolf. His group worked with the PETT III from 1977–1981. In 1979 the Brookhaven Chemistry Department, jointly with the New York University (NYU) Department of Psychiatry, received a grant from the NIH to build the PETT VI.

In the 1980s, the group used PET to explore the dopamine receptor system with carbon-11 and fluorine-18-labeled neuroleptic drugs (*21*). In 1985, the chemists concluded that fluorine-18 N-methylspiroperidol (NMS) was the ligand of choice for dopamine receptor studies in humans (*22*).

"We're using this tracer to probe the site of action of antipsychotic drugs, such as haldol, and to measure the duration of the drug's binding to the dopamine receptor," said Dr. Fowler. The half-life of fluorine-18 allows for clearance of non-specifically bound tracer and optimal delineation of receptor-rich areas of the brain, she added.

Members of the chemistry group are now labeling the actual antipsychotic drugs (such as haldol), rather than analogues, to measure short-term pharmacokinetics of the drug itself and to study other questions as well. Fluorine-18 haldol exhibits a much higher uptake than NMS, said Dr. Fowler, but it is released from the receptors more rapidly.

"There's some evidence that this characteristic may be an advantage in some ways. We may be able to get a handle on how much endogenous dopamine is in the brain, for example, because if the labeled haldol binds less tightly to the receptor, endogenous dopamine may displace it from the receptor," explained Dr. Fowler.



A. Bertrand Brill, MD, PhD, serves as a subject in the Universal Nuclear Imaging ***Construct (UNICON), a camera with flexible mounting and the capacity to detect both single-photon and positron emitters. Yves Bizais, MD, and George Zubal, PhD, observe from the console, while Wanda Rowe, PhD, takes notes and Gerry Bennett, PhD, positions the camera.***

In collaboration with NYU and Stony Brook psychiatrists, the Brookhaven group is working toward using PET dopamine receptor studies to determine the optimal antipsychotic drug dose for schizophrenic patients (*23*).

Functional Enzyme Activity

There are established PET methods to assess glucose and oxygen metabolism, receptor activity, blood flow, and other parameters. The chemistry group is now using a new approach to study neurochemistry with PET—tracers that map patterns of enzyme activity (*24*).

At the 1986 SNM meeting, the Brookhaven group, in collaboration with the University of Uppsala, presented work on carbon-11 L-deprenyl to map and measure the synthesis of monoamine oxidase (MAO-B) in a baboon brain (*25*). "We've begun human studies with this tracer, which could provide significant new information for patients with Parkinson's and other neurologic and psychotic diseases," said Dr. Fowler.

Patients with Parkinson's disease have a deficiency of endogenous dopamine. Administration of L-DOPA, a precursor of dopamine that crosses the blood-brain barrier, is one of the therapies for Parkinson's disease. MAO, however, works against the treatment by metabolizing dopamine.

In a large clinical trial in Europe, patients with Parkinson's disease were treated with both L-deprenyl, which inhibits the activity of MAO, and L-DOPA. "The life-span of the patients was significantly increased relative to patients treated with L-DOPA alone," noted Dr. Fowler.

In addition to treating these patients, it has been speculated that L-deprenyl could eventually be used to prevent Parkinson's disease. Studies of methylphenyltetrahydropyridine (MPTP), a toxin that produces a syndrome very similar to Parkinson's disease, show that pretreatment with L-deprenyl before injecting MPTP prevents the neurotoxicity.

Investigators in the United States are planning to conduct a clinical trial to treat people at risk for Parkinson's disease with L-deprenyl. There is a theory that Parkinson's disease may be caused by an environmental toxin which, when oxidized by MAO, pro-

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duces a neurotoxin which causes Parkinson's disease, explained Dr. Fowler, and L-deprenyl may be able to prevent the onset of the disease.

One advantage of these studies, said Dr. Fowler, is that the approach—using a labeled suicide inhibitor, or a tracer that crosses the blood-brain barrier and reacts to label the enzyme—can potentially be adapted to other enzyme systems.

The Brookhaven group is looking at ornithine decarboxylase, an enzyme which converts ornithine to putrescine, one of several polyamines synthesized in large quantities in tumor cells. "We have labeled putrescine with carbon-11, and its uptake appears to be related to the degree of malignancy," said Dr. Fowler (*26–28*).

"We'd like to label some of the suicide inhibitors of ornithine decarboxylase because it might allow us to interfere with the metabolic machinery of the tumor. We're giving this project a high priority," she said, adding that oncologists have already used some of these inhibitors as chemotherapeutic agents.

Dr. Wolf's group and colleagues at NYU are setting up a protocol to scan patients with carbon-11 putrescine before and after chemotherapy or radiation treatment. By determining whether the uptake is decreased or increased, the procedure could provide a tool to monitor that treatment, he explained.

Future of PET

Dr. Wolf sees first-hand the growth of PET as he continually trains scientists who are sought after by academic PET programs. The number of PET papers presented at the SNM Annual Meetings has grown exponentially, he noted. "The physicians are beginning to see that PET has clinical application. Now they're getting excited, and that's why more hospitals are showing interest, and that's why the Veterans Administration is going into PET," he said. Every university hospital can now think seriously about installing a clinical PET center, said Dr. Wolf. "The community hospitals are not ready yet for PET, but I think it's coming," he added.

Dr. Wolf also foresees major changes in the instrumentation and a reduction in price. "Now Phillips and Siemens are in the PET business, and once they see a market for more than 30 or 40 machines, I think they're going to convert the digital circuits to chips, which might bring the cost down to less than $1 million," he predicted.

Cardiology is a significant growth area for PET. Manufacturers are building "Cardio-PETs," which are less expensive than whole-body scanners, in anticipation of the availability of rubidium-82 generators. Japan Steel Works has also introduced a "baby baby cyclotron" that produces only oxygen-15 for cardiac studies. "PET could become a routine tool in nuclear cardiology, like an ordinary stress test," said Dr. Wolf.

The PET revolution did not come in time, however, for the Brookhaven "head shrinker," the first ring-detector PET system, designed in 1960 by James S. Robertson, MD, PhD and Lucas Y. Yamamoto, MD. Without the mathematical algorithm developed in the 1970s by the inventors of the X-ray computed tomography (CT) scanner, the early PET machine could not adequately reconstruct tomographic images. It was sent to the Montreal Neurological Institute in 1974, where it was eventually used for brain studies of tumors, epilepsy, and stroke.

At Brookhaven, scientists have worked for almost 40 years on ideas that merge radiation chemistry, physics, and biology to expand the horizons of nuclear medicine. Victor P. Bond, MD, PhD, the world-renowned radiation biologist, has seen many) of those ideas succeed or fail during his 30 years at the research center.

Dr. Bond joined Brookhaven in 1955. He served as chairman of the Medical Department from 1962-1967, after which he was appointed associate director of Brookhaven for biology, chemistry, medicine, health physics, and safety. In 1984, he relinquished all administrative responsibilities to devote his time once again to biomedical research.

Neutron Capture Therapy

During the late 1950s, Dr. Bond worked with Lee Farr, MD, and associates on neutron capture therapy for patients with glioblastoma and

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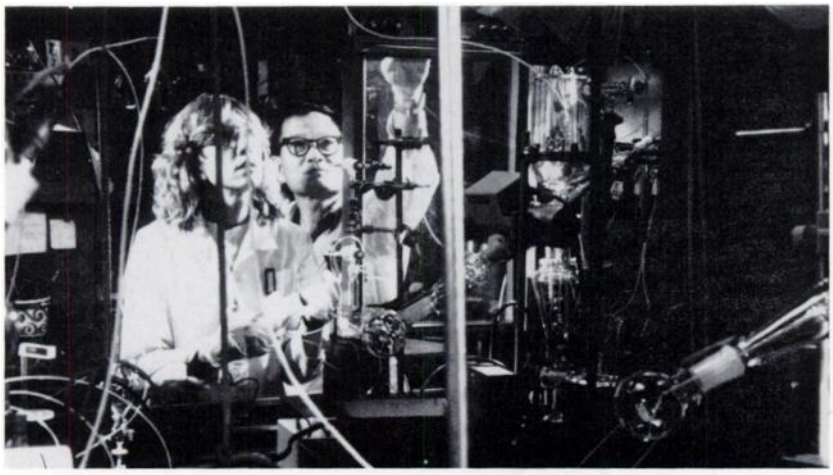

Joanna S. Fowler, PhD, and Chyng-Yann Shiue, PhD, working in a hot cell equipped for the synthesis of positron-emitting radiotracers.

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multiforme. "The clinical trials were a total failure," he said, because the treatment did not benefit the patients and it caused serious side effects.

"So the approach languished for a number of years, but it didn't die, and over the years it became known why the clinical trials had failed. We had used inorganic boron, which did not localize very well in tumors, and by the time it was at maximum levels in the tumor, it was also at a very high concentration in the blood, so you were irradiating the sides of the vessel walls," explained Dr. Bond.

The concept has been revived under the direction of Ralph Fairchild, PhD, who is now working with Dr. Bond and colleagues to evaluate several organic compounds labeled with cold boron that are taken up by tumors. The group has also developed an "epithermal beam," which is in fact a degraded fission spectrum.

"As the beam travels through the tissue, it thermalizes further and reaches a peak, substantially higher than the entrance dose, about 3 cm into the tissue," explained Dr. Bond. With the original technique, the beam lost energy as it traveled through the tissue, resulting in too much irradiation of the normal tissue and not enough of the tumor.

Although nuclear medicine is defined in several ways, usually as a field that deals mainly with diagnosis and somewhat with treatment, Dr. Bond said that, in a broader sense, at least some forms of experimental radiotherapy fall under the umbrella of nuclear medicine.

"When I began in this field, I thought that radioisotopes would play a much larger role in therapy. With the outstanding exception of radioiodine thyroid treatment, though, we still don't have the isotopes that will selectively go to tumors in high enough concentrations to control them," said Dr. Bond.

With respect to the other applications of nuclear medicine, "the field has turned out to be much more important and valuable than even my most optimistic expectations. The future of nuclear medicine, which lies in metabolic studies, has unlimited possibilities," said Dr. Bond.

Linda E. Ketchum

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