IMPROVING HEALTH CARE THROUGH MEDICAL APPLICATIONS RESEARCH

Brookhaven National Laboratory

Suresh C. Srivastava

Tel: (516)344-4459; Fax: (516)344-5962; E-mail: srivast1@bnl.gov

The DOE/BER Program, and its predecessors, have supported research on medical applications of nuclear technology for the past five decades. Research has contributed to better methods for understanding, diagnosing, and treating various disorders including heart disease, neurological illness, and cancer. Each year, about one-third of the 30 million Americans hospitalized are diagnosed or treated with one or more nuclear medicine techniques. Radioisotopes and radiopharmaceuticals (tagged compounds), which are at the heart of nuclear medicine, are used in more than 40,000 procedures every day, and in almost 100 million medical laboratory tests each year. The BER program has supported their development and production at the national laboratories and other institutions, and thus made nuclear medicine what it is today.

After World War II, one of the missions of the national labs was to develop peaceful uses of nuclear science, including medical applications. With nuclear technology came widespread availability of certain radioisotopes generated in nuclear reactors and particle accelerators. Methods for generating technetium-99m, the most widely used diagnostic radioisotope (>85% of all imaging procedures), and the initial development of kit methods (now commercially available) for instant production of radiopharmaceuticals for imaging just about every organ in the body, were carried out at the national labs. Probably second in importance to technetium is thallium-201 which is used widely in stress tests to assess damage to the heart muscle. A number of newer isotopes, for example, copper-67, and tin-117m are being investigated for treating lymphoma and bone pain in cancer patients, respectively. Positron emitters including fluorine-18, and others, are finding increasing use in the exciting area of positron emission tomography (PET). Another technique called BNCT (boron neutron capture therapy), is being tested as a treatment for certain deadly brain tumors. Initial results in 30 patients are very encouraging, and treatments at higher dose levels are to begin soon.

Just as radioisotopes and radiopharmaceuticals are vital to nuclear medicine, so are imaging cameras. BER-supported instrumentation development, including the development of the original Anger camera, and SPECT (single photon emission computed tomography) and PET imaging devices, has been vital for the rapid growth of nuclear medicine. Using PET, which has the capability of measuring in-vivo biological processes, and a short-lived radioactive tracer , typically fluorine-18 fluorodeoxyglucose (FDG), researchers at the national labs and other institutions are studying and improving our understanding of mental disorders such as Parkinson's disease, schizophrenia, Alzheimer's disease, and substance abuse including alcohol and tobacco addiction.

We Are Grateful To The Following Institutions For Providing Information For This Conference:

Lead Laboratory:

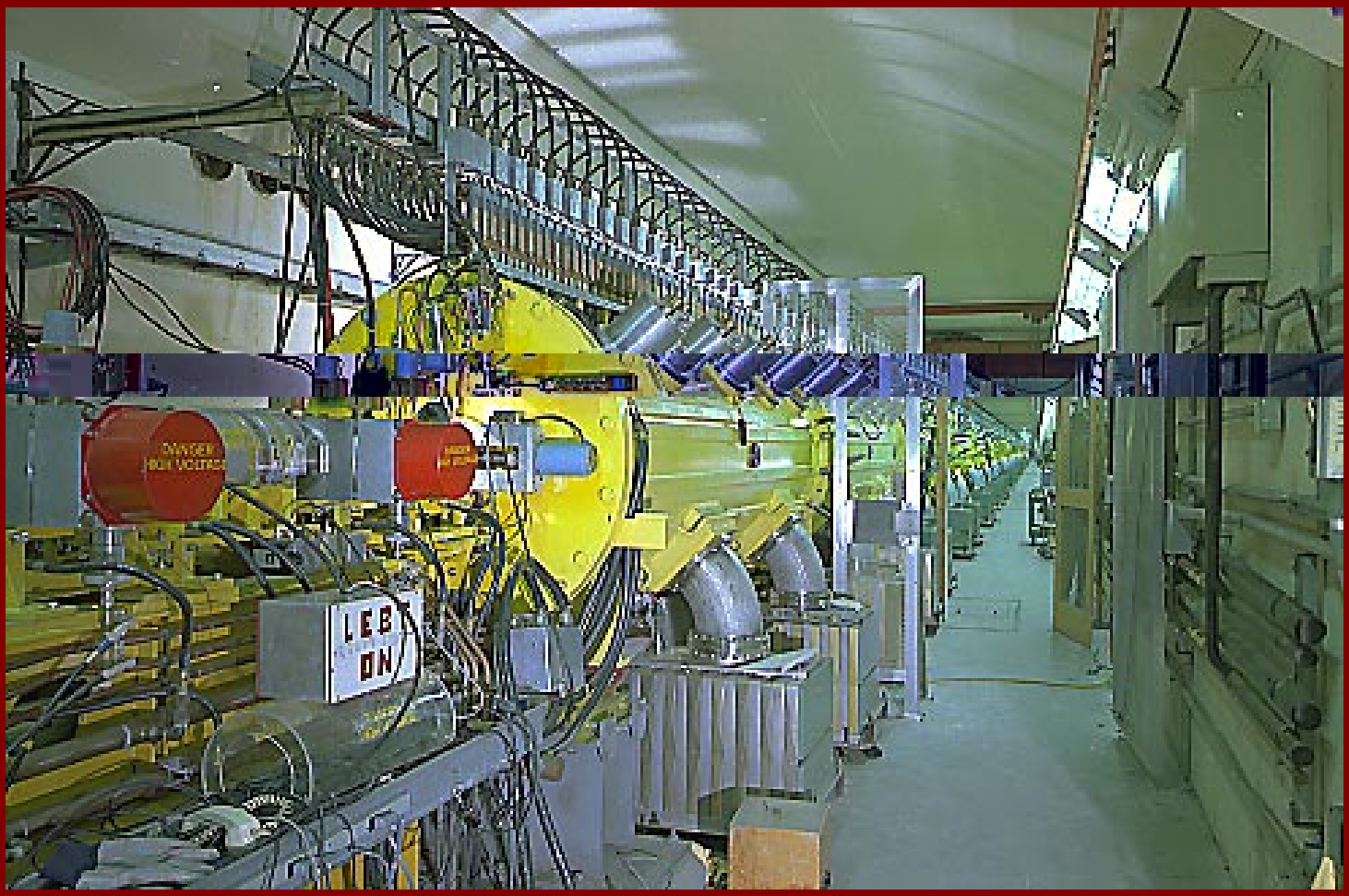
Brookhaven National Laboratory
Dr. Suresh Srivastava, Ph.D.
Building 801
Upton, NY 11973
Tel: 516-344-4459
fax: 516-344-5962
e-mail: srivast1@bnl.gov

University of California-Los Angeles
Mike Phelps, Ph.D.
Department of Molec. and Med. Pharm.
10833 Le Conte Avenue
UCLA Medical School
Los Angeles, CA 90024
Tel: 310-825-6539
fax: 310-206-5084
e-mail: mphelps@ mail.nuc.ucla.edu

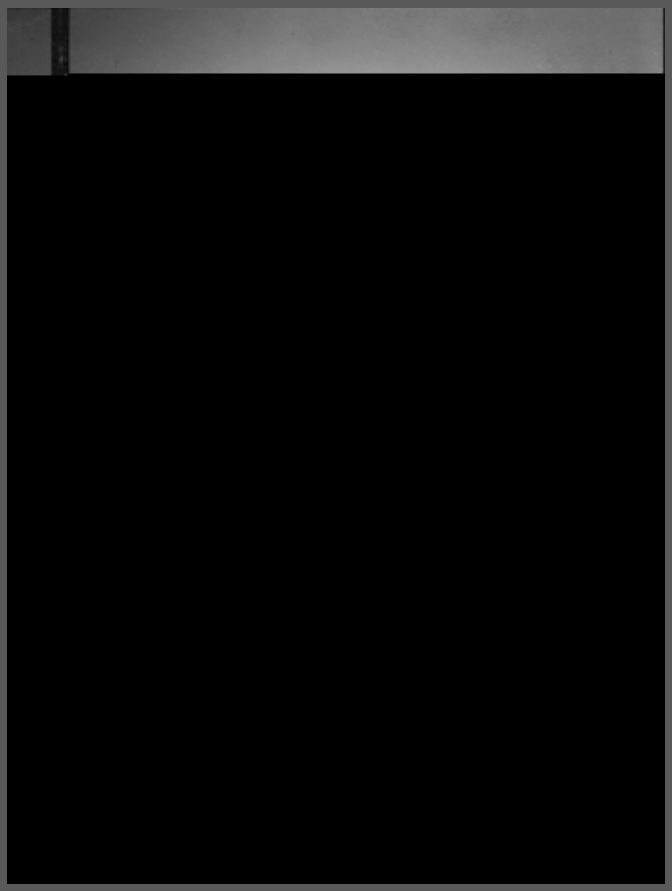
University of Michigan Medical Center
Dave Kuhl, M.D. and Michael Kilbourn, Ph.D.
B1 G505K Box 0028
1500 E. Medical Ctr. Dr.
Ann Arbor, MI 48109
Tel: 313-936-5388
fax: 313-936-8182
e-mail: dkuhl@umich.edu

Washington University Medical Center
Michael Welch, Ph.D.
Professor of Radiology
Director, Div. of Radiation Sciences
510 S. Kings Highway
St. Louis, MO 63110
Tel: 314-362-8436
fax: 314-362-8399
e-mail: welch@mirlink.wusl.edu

An aerial view of the high-energy physics complex at Brookhaven National Laboratory. The LINAC (linear accelerator) injects 200 million-electron-volt protons into the Alternating Gradient Synchrotron (AGS), where they are accelerated further to an energy of 33 billion electron-volts. Excess protons that are not needed by the AGS (≥ 75% of total) are fed into the BLIP (Brookhaven Linac Isotope Producer) for production of radioisotopes for medical use. The Relativistic Heavy Ion Collider (RHIC) is presently under construction. The BLIP and the LINAC have been refurbished for year-long isotope production at higher beam currents.



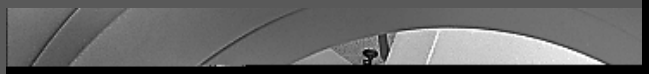
An inside view of the LINAC (linear accelerator) tunnel, almost 600 feet long, showing nine accelerating stations (magnets) used for the acceleration of protons to provide a 200 million-electron-volt energy beam, for various applications, including isotope production at BLIP.



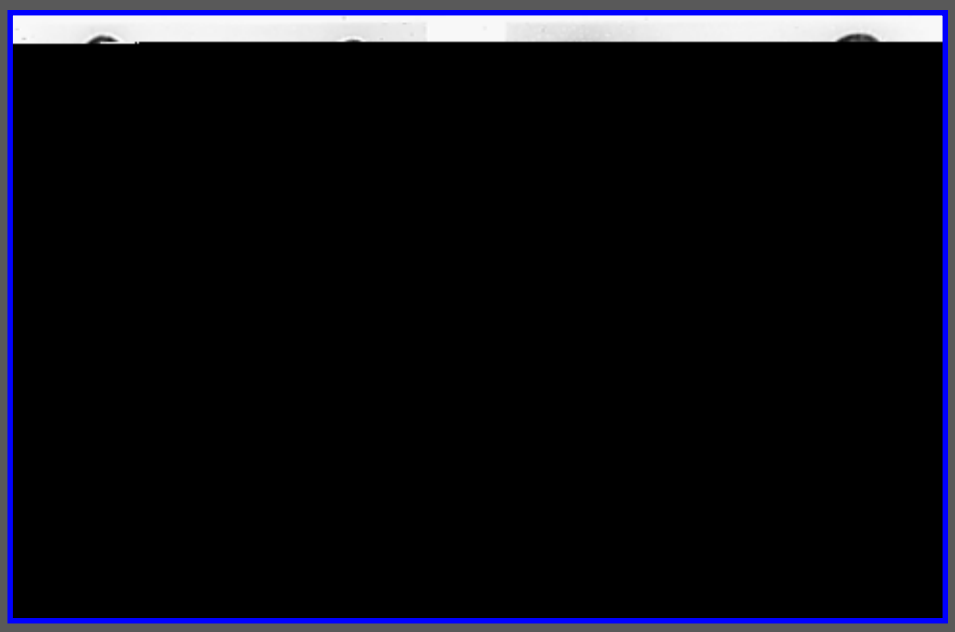
The first technetium-99m generator, developed at BNL circa 1958 (shown here without shielding). Technetium-99m is the most widely used radioisotope for nuclear medicine imaging (about 36,000 examinations every day in the U.S. alone).

Two of the Brookhaven National Laboratory scientists involved in the earliest development of technetium-99m

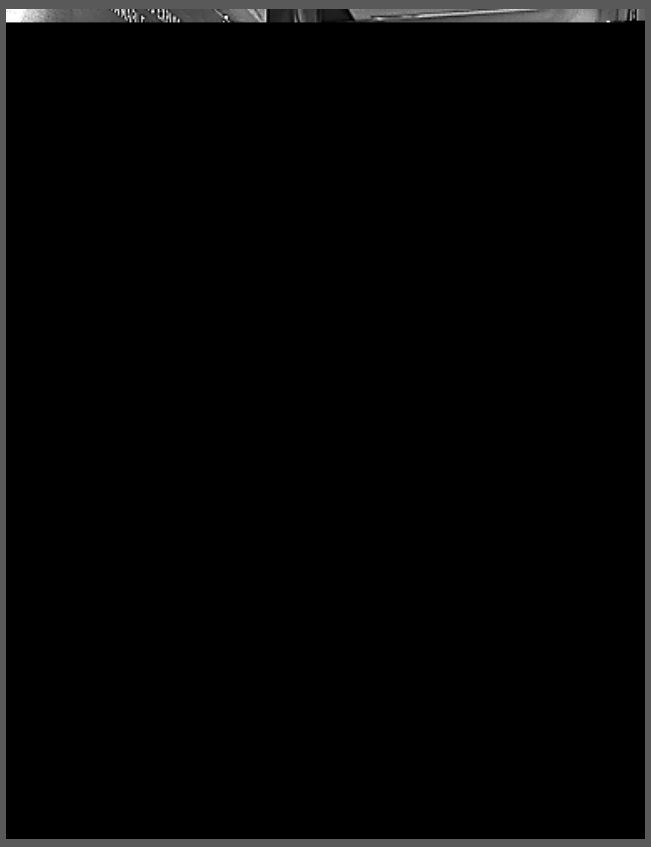
Brookhaven scientists preparing **copper-67** for the clinical trial for treatment of lymphoma in patients at the U.C. Davis Medical Center.



Shown here is a patient being imaged under a **SPECT** (single photon emission computed tomography) camera. Patients are administered with the BNL-developed **tin-117m DTPA**. This has, in initial studies, in 47 patients, shown considerable promise for the treatment of pain resulting from the spread of prostate, breast or lung cancer to bone. An extended phase 3 trial is to begin soon.

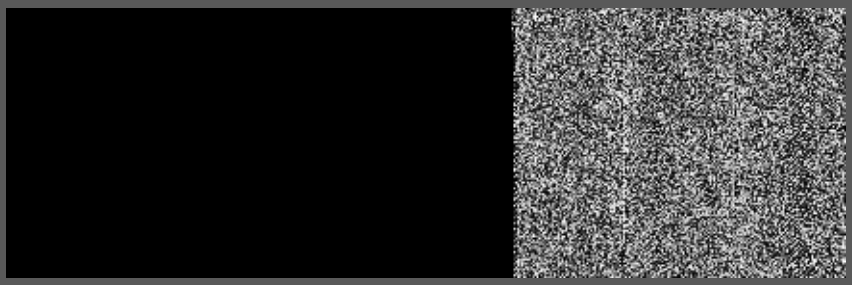


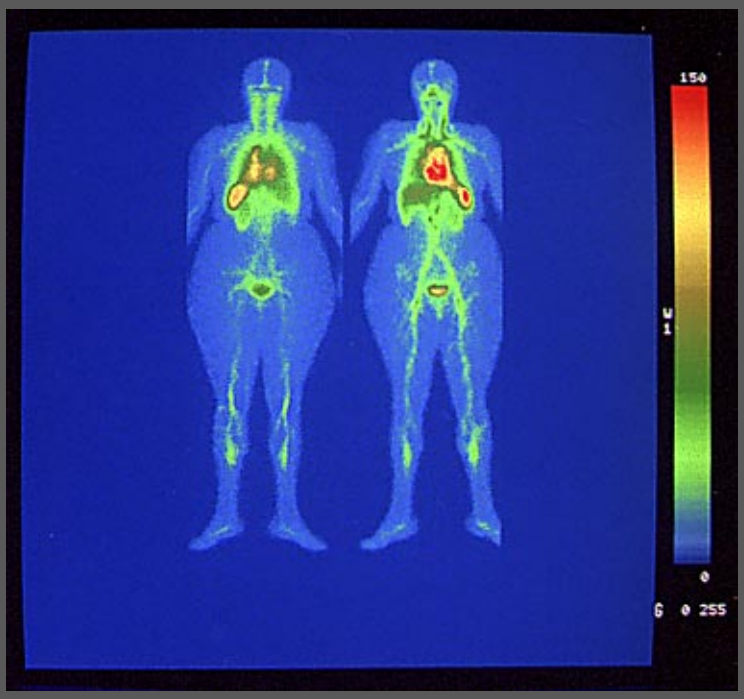
Bone scans in a prostate cancer patient, with the cancer spread to bone. On left are the posterior and anterior views obtained using the common bone scanning agent, technetium-99m-MDP. The right panel shows whole body anterior and posterior images in the same patient following the administration of **tin-117m-DTPA**.



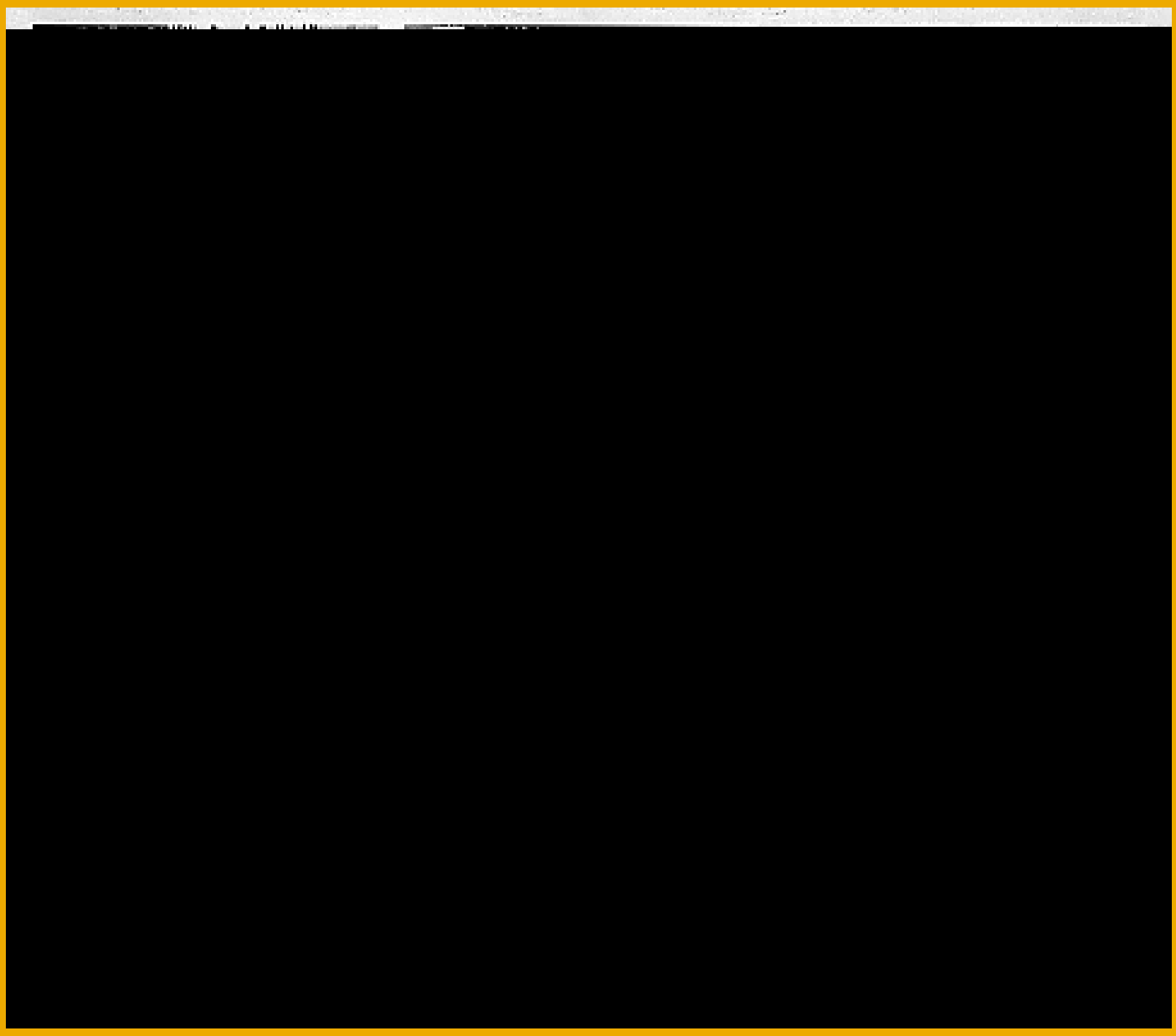
A **Brookhaven invented medical kit** is widely used for imaging blood pool in the heart and other organs. This kit is useful for diagnosing cardiovascular problems, spleen function, and internal bleeding. About a million such procedures are performed annually in the U.S.

A typical blood pool image of the heart (three different views) in a patient obtained using the red blood cell labeling kit. Note the excellent resolution of the various heart chambers. Such images provide important diagnostic information to the clinician.



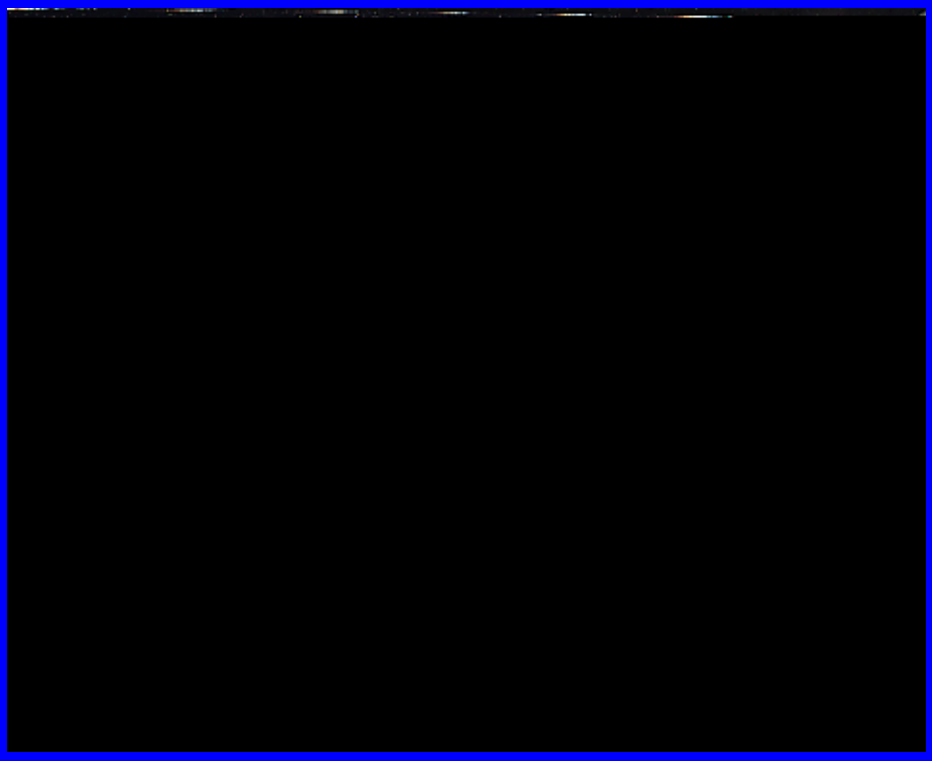


Shown here a typical whole body blood pool scan in a patient, obtained using the **Tc-99m RBC kit**.

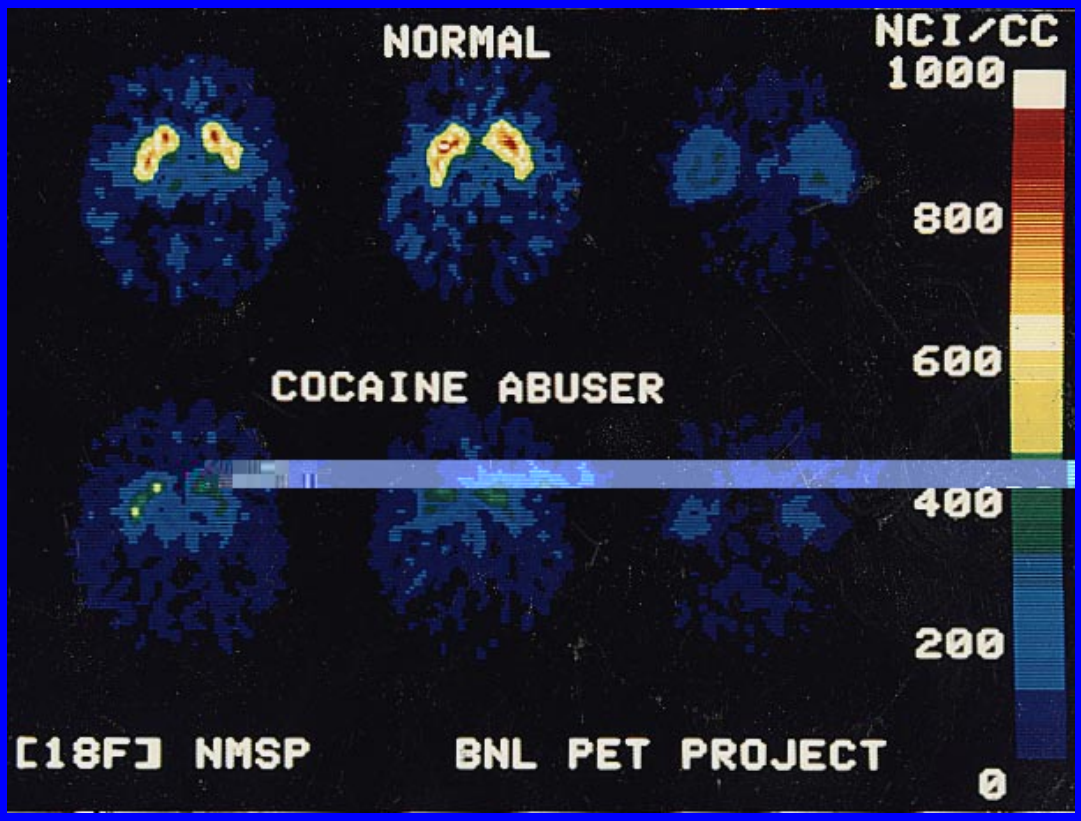


First human study at University of Pennsylvania using BNL-produced F-18 labeled Fluorodeoxyglucose (^{18}F-FDG), (late 1970's).

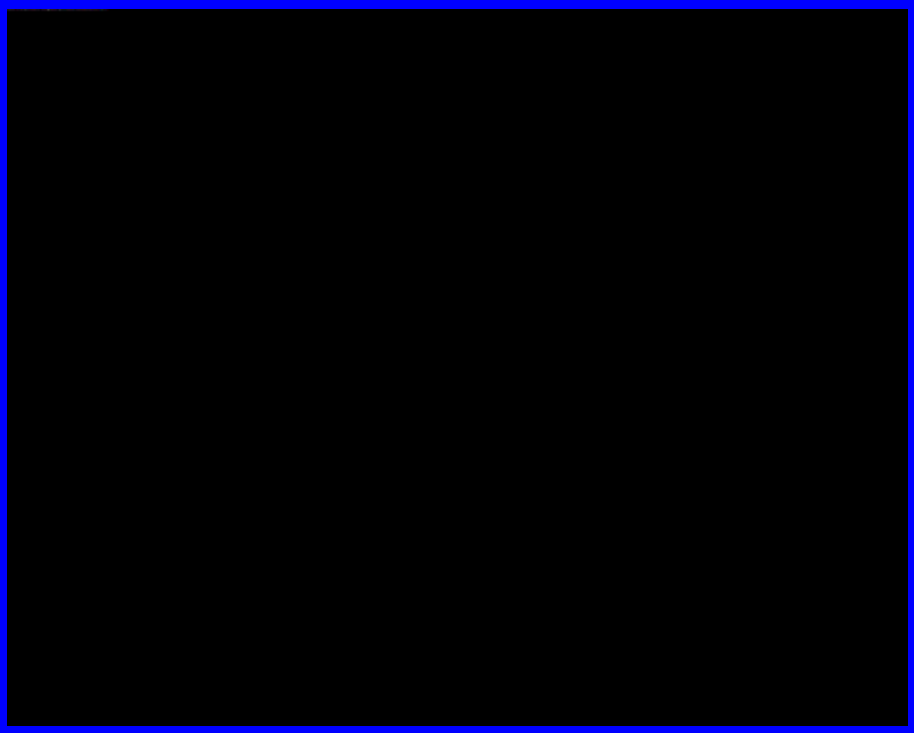
A patient at Brookhaven National Laboratory is intravenously injected with a radiotracer in preparation for being positioned in the PET scanner



[^{11}C]Cocaine bining in human brain 15 minutes after intravenous injection as measured by PET. Fifteen brain slices from the top of the brain to the base of the skull are shown (upper left to lower right). These PET images of the distribution of cocaine in the living human brain show that the highest uptake occurs in the stratium, an area of the brain important in the regulation of pleasure, drive and movement. It is also the area of the brain most rich in dopamine reuptake sites with which cocaine interacts. This PET study supports the importance of dopamine reuptake sites in the action of cocaine in the human brain. It is also an example of how PET technology can be used to investigate the molecular mechanisms of action of drugs abuse in the living human brain.



PET measurement of dopamine D_2 receptor availability using the tracer [^{18}F]N methylspiroperidol in normal human brain top) and in a chronic cocaine user (bottom). Tracer uptake occurs in the striatum, an area which is rich in dopamine D_2 receptors and which is important in the regulation of pleasure, drive and movement. This PET study shows reduced D_2 receptor availability in the cocaine abuser compared to the normal subject possibly due to down-regulation of D_2 receptors as a result of cocaine induced increases in intrasynaptic dopamine levels. This demonstrates the ability of PET to uncover molecular mechanisms which may be deranged by the chronic abuse of cocaine.



Technology transfer to the pharmaceutical industry (collaboration between BNL and Hoffmann LaRoche). PET was used to determine the minimum effective dose for clinical trials of a new reversible inhibitor of brain monoamine oxidase B for the treatment of Parkinson's disease. This drug is now undergoing clinical trials to determine its effectiveness in halting the progression of Parkinson's disease. The PET image on the top left shows brain monoamine oxidase B activity of a patient under baseline conditions. The top right image shows a patient after receiving the new MAO B inhibitor for 1 week. The image on the bottom shows that monoamine oxidase B activity returns to control values 1 day after the last dose of drug demonstrating the rapid reversibility of the effects of the drug. With PET, it has been possible for the first time to monitor the effects of a drug directly on a brain enzyme in the patient and to use this information in planning clinical trials in Parkinson's disease. This exemplifies the applicability of medical imaging techniques like PET to study the effects of drugs directly in the human subject. This example of technology transfer has enormous potential in streamlining the development of new drugs and in understanding their mechanism of action.

nature

INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

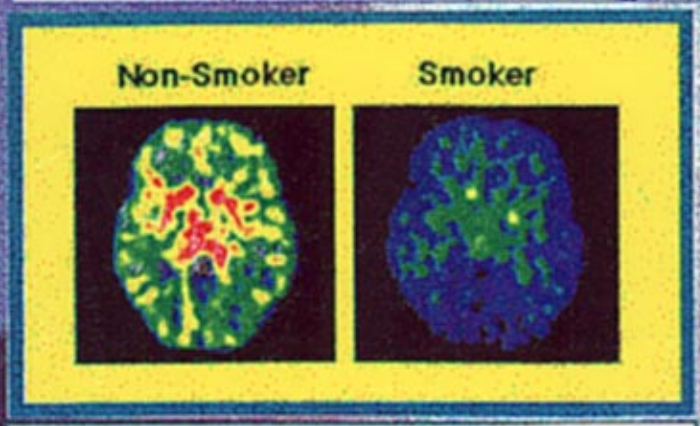
Volume 379 No. 6567 22 February 1996 $10.00

NEWS AND VIEWS

Psychoactive smoke

Inhibition of monoamine oxidase B in the brains of smokers

J. S. Fowler*‡, N. D. Volkow*†, G.-J. Wang*,



Comparison of monoamine oxidase B activity in the brain of a smoker and a non-smoker. Smokers have decreased levels of the enzyme which may account for their decreased risk of Parkinson's disease and may also enhance the effects of nicotine.

Smoking gun: among other issues, the study of Fowler et al. raises the question of whether cigarettes are a 'gateway' drug leading to addiction to other drugs of abuse.

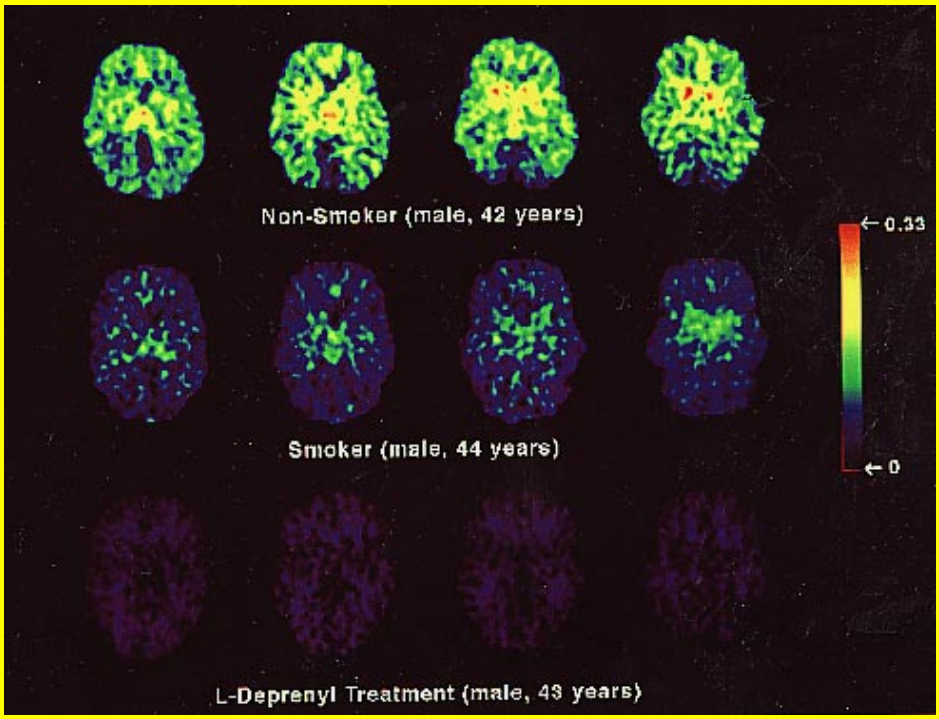
Harmonic tremor at Old Faithful

Early water in primitive meteorites

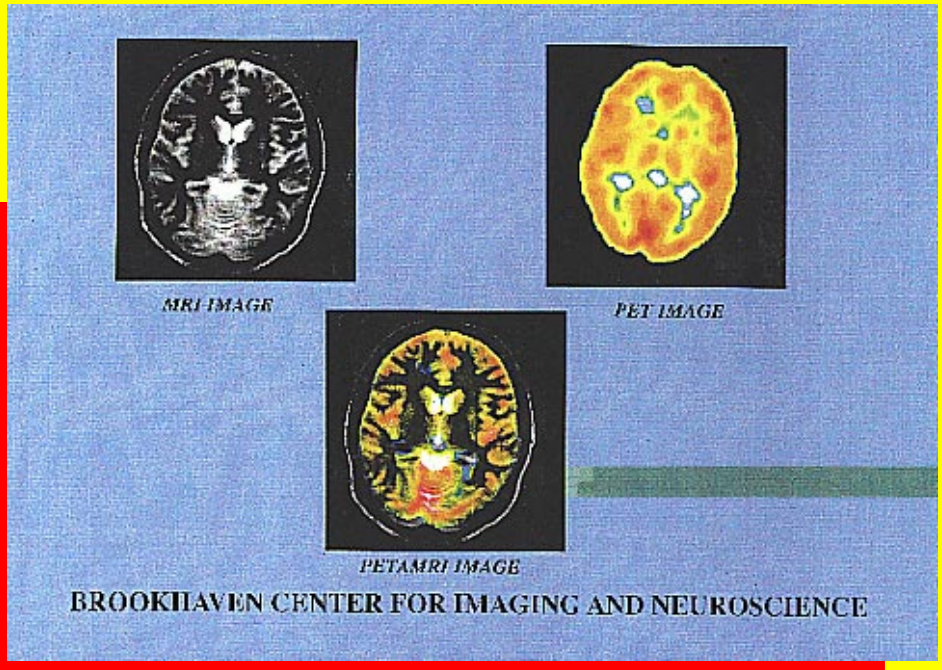
RNA and homeodomains

The smoker's brain

Software PRODUCT REVIEW



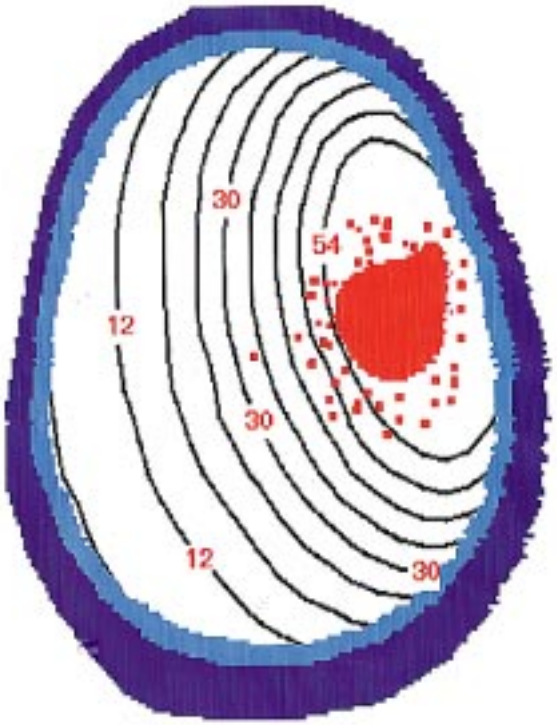
The images on the top row are quantitative images of 4 levels of the brain of a non-smoker (male, 42 years) with deuterium substituted [^{11}C]L-deprenyl, a tracer which maps monoamine oxidase B (MAO B), an enzyme which breaks down neurotransmitters like dopamine. The four images in the middle row are quantitative images of MAO B in an age-matched smoker. The four images on the bottom row are quantitative images of a person who was treated for 1 week with L-deprenyl, a MAO B inhibitor drug used to treat Parkinson's disease. **Note the profound reduction of brain MAO B in the smoker.** The inhibition of MAO B in some smokers is similar to that observed in the person being treated with pharmacological doses of drugs that inhibit MAO B. MAO B inhibition by cigarette smoke may account for the decreased risk of Parkinson's disease in smokers and some of the epidemiological features of smoking which include a high rate of smoking in depression and in addictions to other substances.



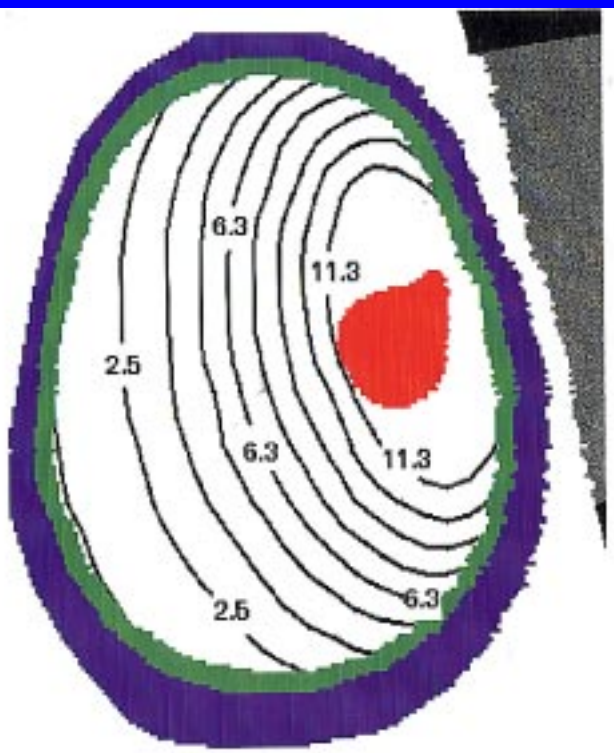
These **MRI** and **PET** human brain images depict the same slice of the same individual, and were obtained with the respective BNL instruments. They have been mathematically co-registered.
The **MRI** image was produced with a contrast to emphasize the grey matter (as well as CSF). The **PET** image was made with 18F-labeled flourodeoxyglucose (**FDG**). Since it is known that **FDG** is concentrated mostly in grey matter, these images can be superimposed to advantage. One sees essentially a **PET** image with the high spatial resolution of **MRI**. In effect, the **PET** color intensity scale is used to color the **MRI** pixels.

Boron neutron capture therapy (**BNCT**) is an experimental radiation treatment that consists of two components: 1) a tumor-selective drug containing ^{10}B, a stable isotope of boron and 2) irradiation by low energy (thermal) neutrons. The interaction of the ^{10}B with a thermal neutron (neutron capture) causes the ^{10}B nucleus to split, releasing an alpha particle and a lithium nucleus. These products of the $^{10}B(n,a)^{7}Li$ reaction are very damaging to cells but have a combined path length in tissue of approximately 14 **m**m, or roughly the diameter of one or two cells. Thus, most of the ionizing energy imparted to tissue is localized to ^{10}B-loaded cells.

A clinical trial of **BNCT** for malignant brain tumors (**glioblastoma multiforme**) is underway at Brookhaven National Laboratory using the epithermal neutron beam of the Brookhaven Medical Research Reactor. Since September 1994, 30 patients have been treated in this FDA-approved study.

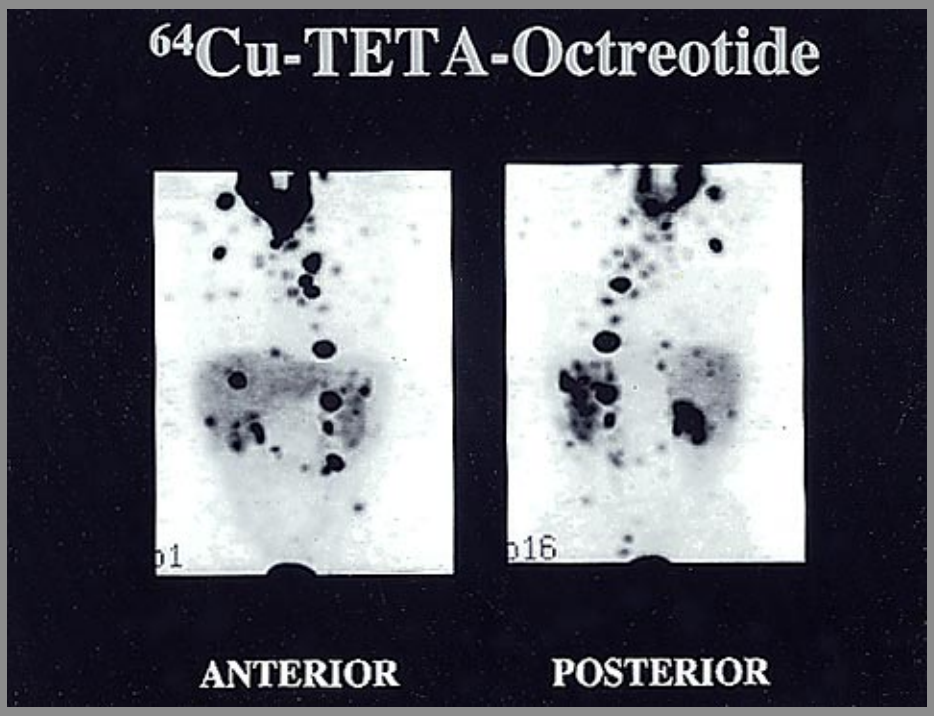


Tumor Doses (Gy-Eq)



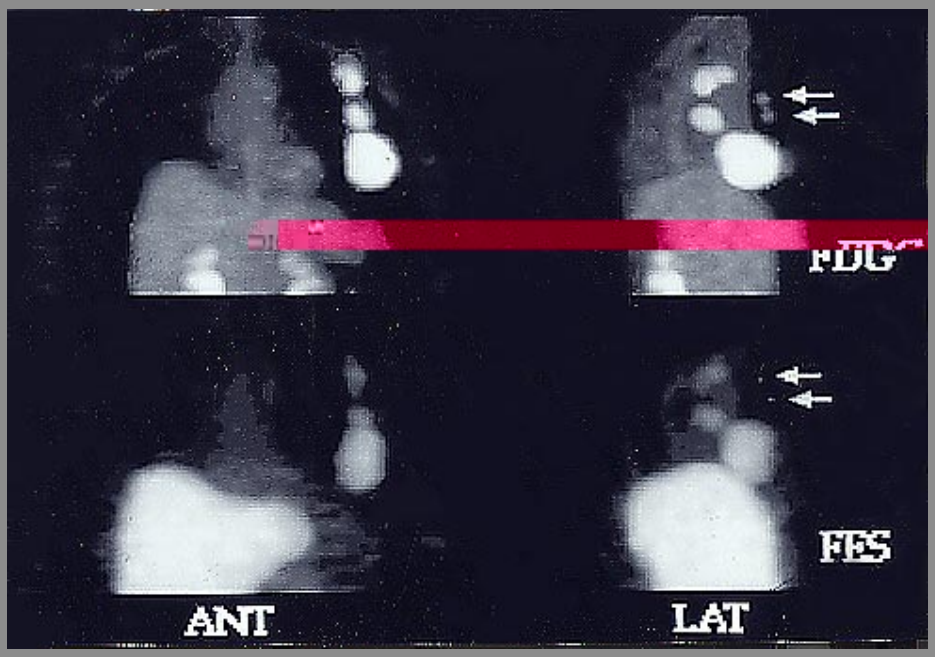
Brain Doses (Gy-Eq)

Capala, 1997



This figure shows a series of carcinoid tumors imaged using copper-64 labeled octreotide. This peptide binds to somatostatin-receptor-positive tumors.

Washington University, St. Louis

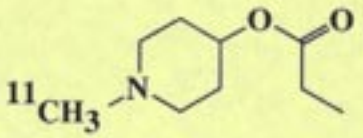


This PET image compares the uptake of flourinated estradiol (FES) with the uptake of a glucose analog, flouro-deoxyglucose (FDG), labeled with flourine-18.

Washington University, St. Louis

NEW RADIOPHARMACEUTICALS: FROM MOLECULES TO MAN

In Alzheimer's disease, neurons in the cortex lose their ability to function and eventually die. To measure such losses of neuronal function, a unique new radiopharmaceutical [^{11}C]PMP has been developed. This radiopharmaceutical, used with Positron Emission Tomography, will allow physicians to measure the brain activity of acetylcholinesterase, an enzyme important in neurotransmission. This enzyme is the target of current drug therapies for Alzheimer's, such as tacrine (Cognex). Using PET and [^{11}C]PMP, we can now evaluate changes in brain function, and benefits of such therapies, directly in Alzheimer's disease patients.



[^{11}C]PMP

MR Kilbourn, SE Snyder, RA Koeppe and DE Kuhl
University of Michigan Medical School

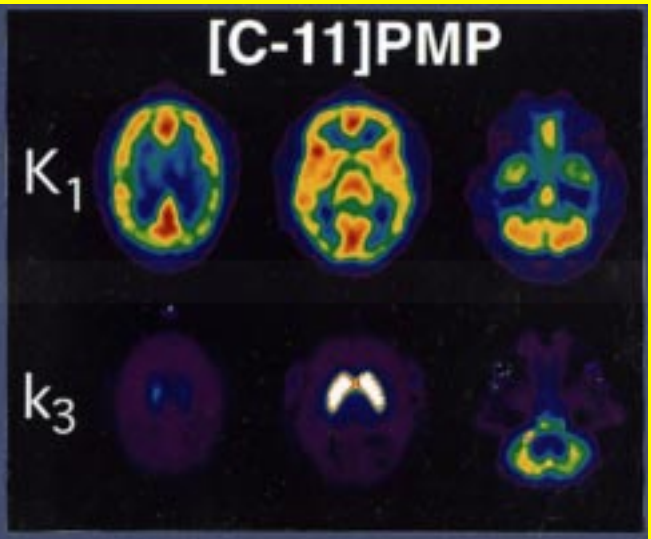
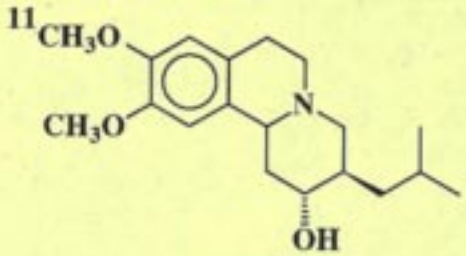


Figure Legend. PET images of the enzymatic activity of acetylcholinesterase in the normal human brain, measured using [^{11}C]PMP. The upper row of images show the early uptake of the radiopharmaceutical into many brain regions. The lower row of images show the high enzymatic rate of acetylcholinesterase found in the striatum (center) and cerebellum (right), and low enzyme activity throughout the remainder of the brain including the cortex.

NEW RADIOPHARMACEUTICALS: FROM MOLECULES TO MAN

Losses of specific brain neurons is a hallmark of Parkinson's disease. A unique new radiopharmaceutical, [^{11}C]DTBZ, has been developed and implemented for human studies. This radiopharmaceutical, used in Psoitron Emission Tomography (PET), will allow physicians to measure and monitor the losses of these brain neurons in Parkinson's disease. Even more exciting, this provides a means to evaluate new therapeutic approaches to the prevention or reversal of Parkinson's and related neurodegenerative diseases.



[^{11}C]DTBZ

MR Kilbourn, RA Koeppe, KA Frey and DE Kuhl
University of Michigan Medical School

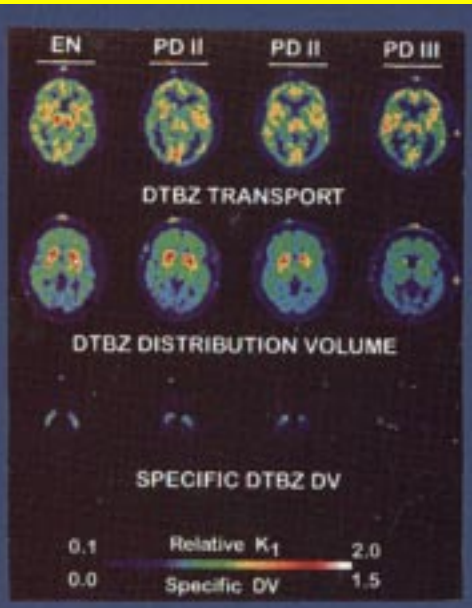
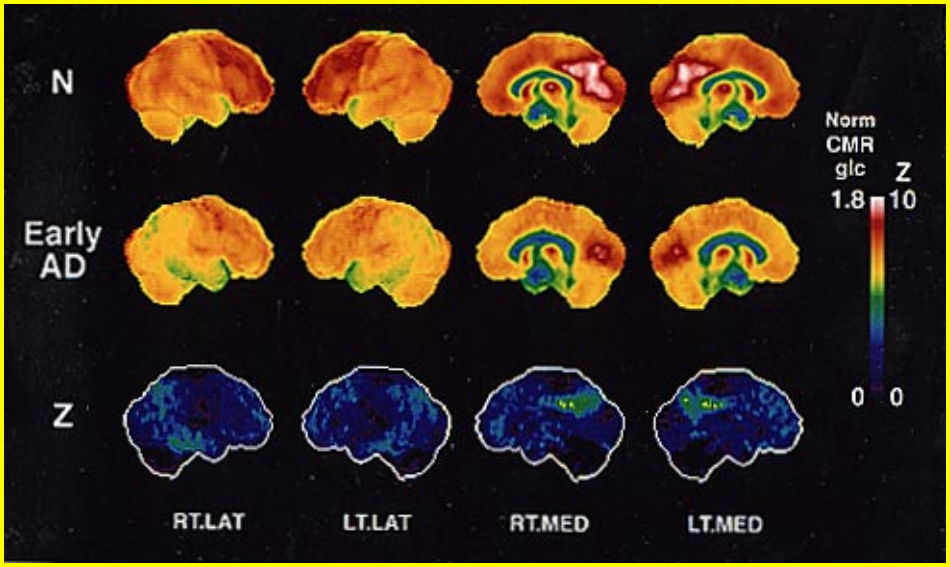


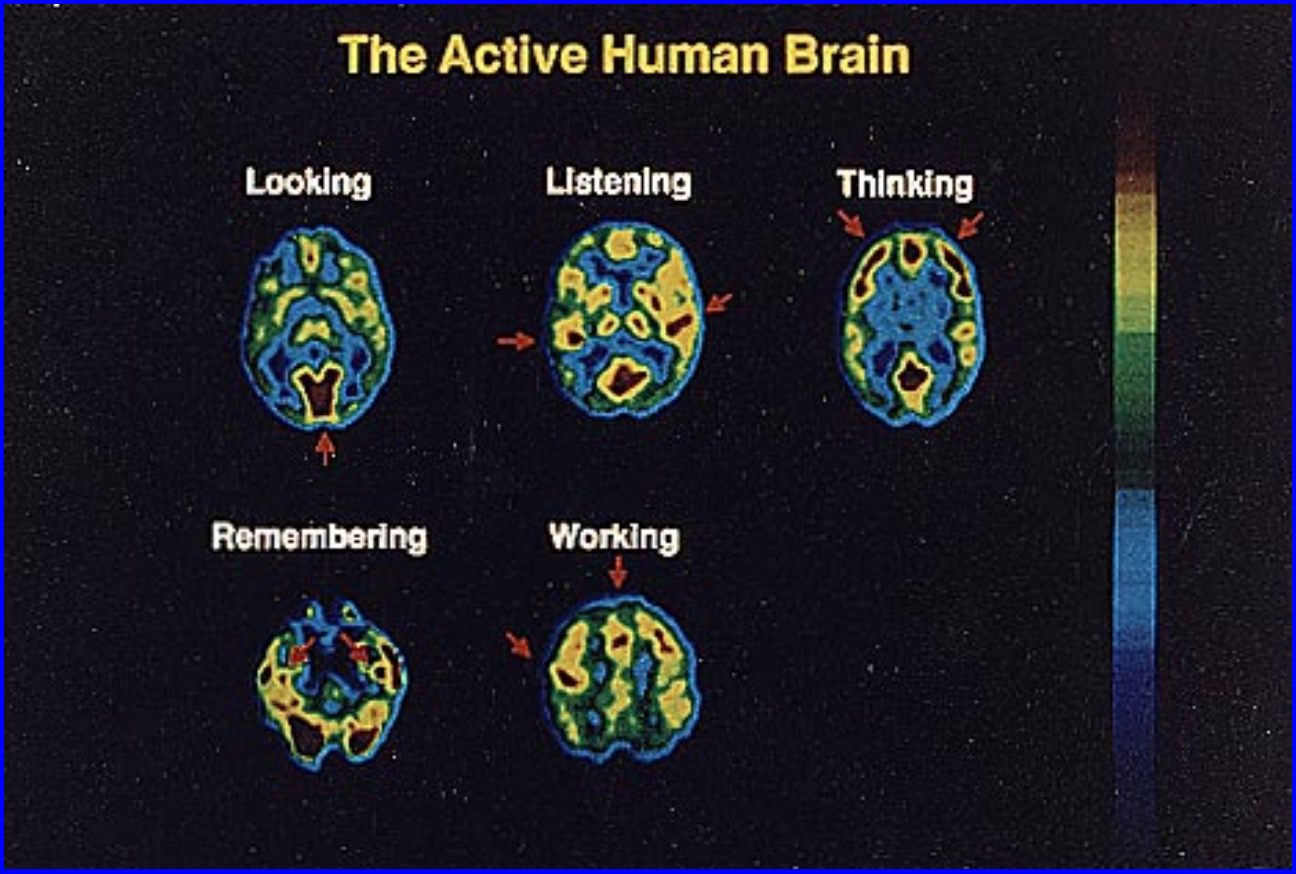
Figure Legend. PET images of the binding of [^{11}C]DTBZ in the human brain of an elderly normal (EN) and Parkinson's disease patients (PD). Note the increasing loss of specific binding with disease severity (highest in PDIII, representing stage III PD), representing continued loss of dopaminergic neurons in the basal ganglia of these patients.



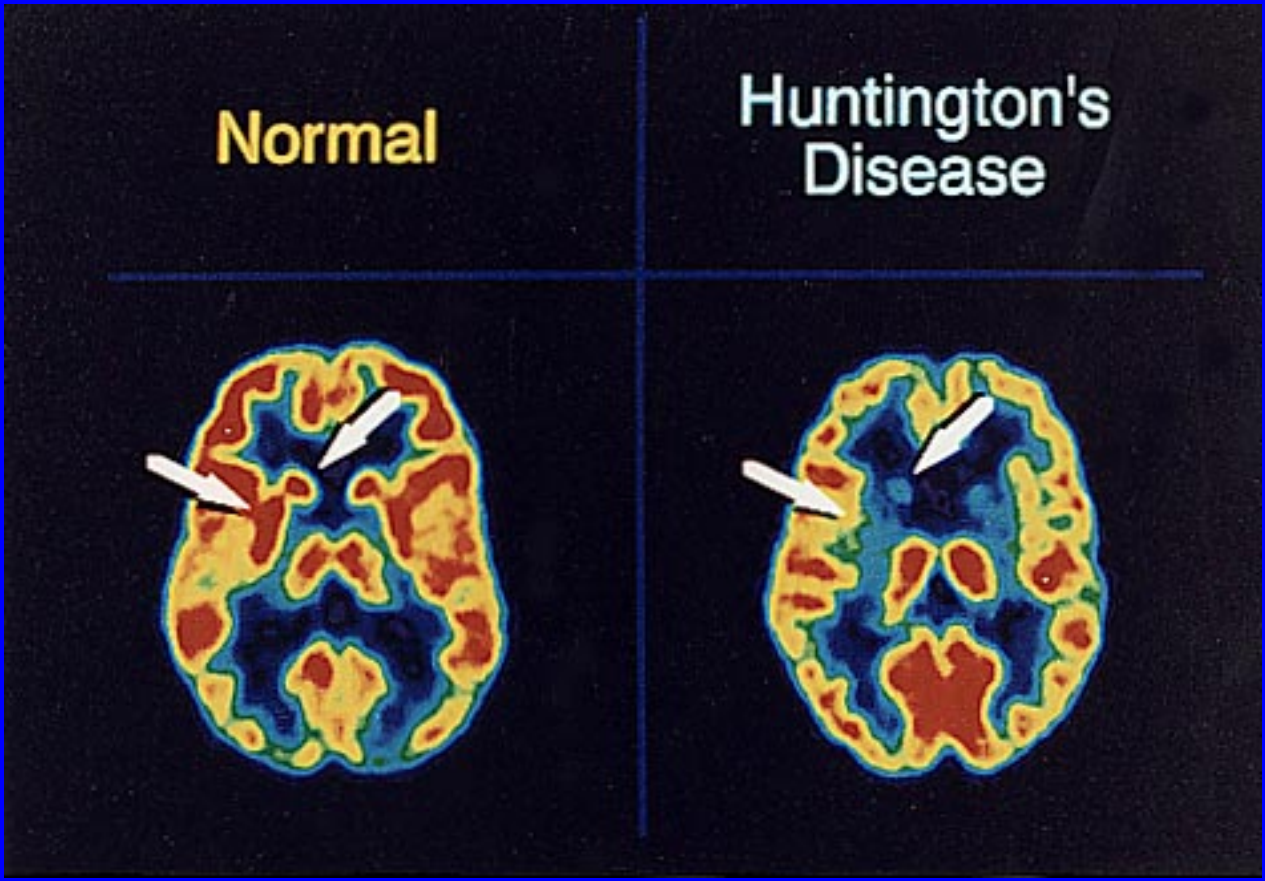
Cerebral metabolic activity, measured using [^{18}F]FDG and Positron Emission Tomography (PET), in patients with very early Alzheimer's disease (early AD) and normal controls (N). Differences between groups are represented by the Z-values (bottom row). Shown are images of the right and left surfaces of the brain (RT.LAT and LT.LAT), and along the right and left midline (RT.MED and LT.MED). This method of PET image analysis, developed under Department of Energy funding, allows clear demonstration of mild but significant losses of brain metabolic activity in cortical regions of the Alzheimer's disease brain, even at very early stages of the disease. Such methods of analysis will be important in the evaluation of new therapies designed to slow down or reverse the neuronal degeneration occurring in such as Alzheimer's disease.

S Minoshima, RA Koeppe, and DE Kuhl, University of Michigan Medical School

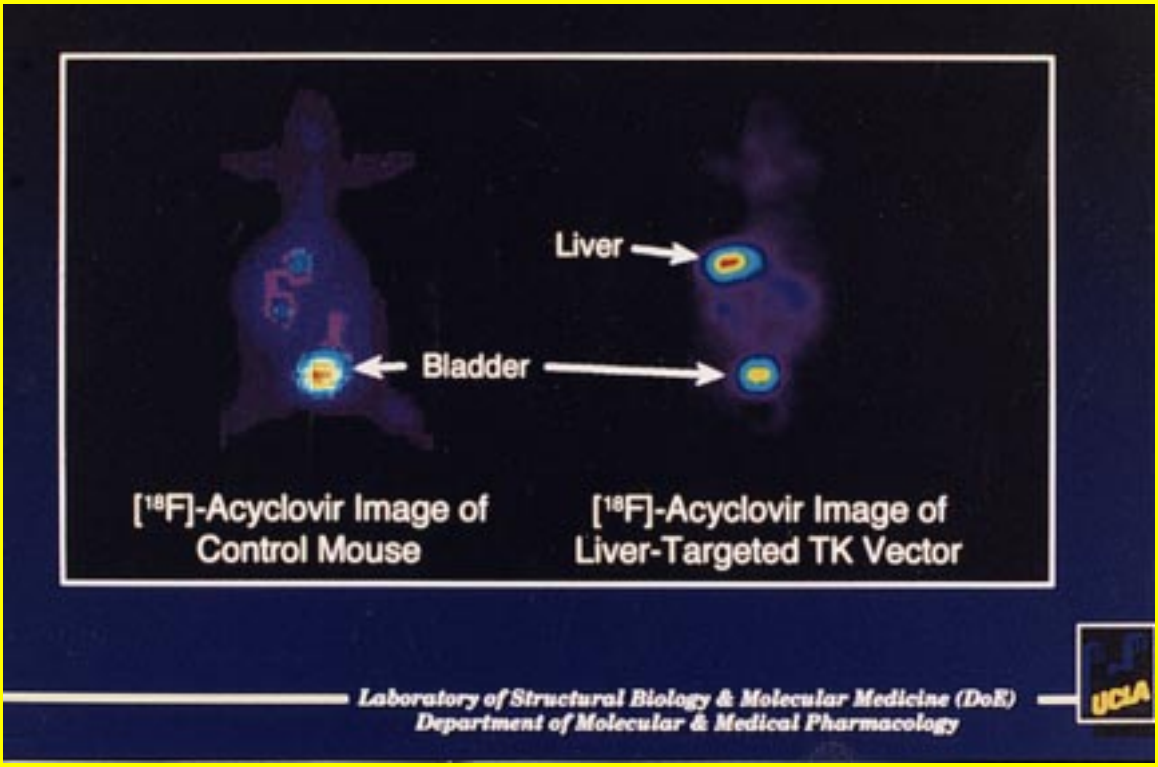
The first **PETT** scanners. The PETT II, PETT II I/2, and PETT III were developed by Drs. Michael Phelps, Edward Hoffman, Michel Ter Pogossian. The first commercial scanner was developed from Drs. Phelps and Hoffman by transferring the rights of PET to, and working with, a commercial partner, ORTEC, Inc. These systems were called the “ECAT scanners.” The first commercial ECAT scanner was delivered to the UCLA/DOE Lab in December, 1976, and is shown in the lower right hand image.



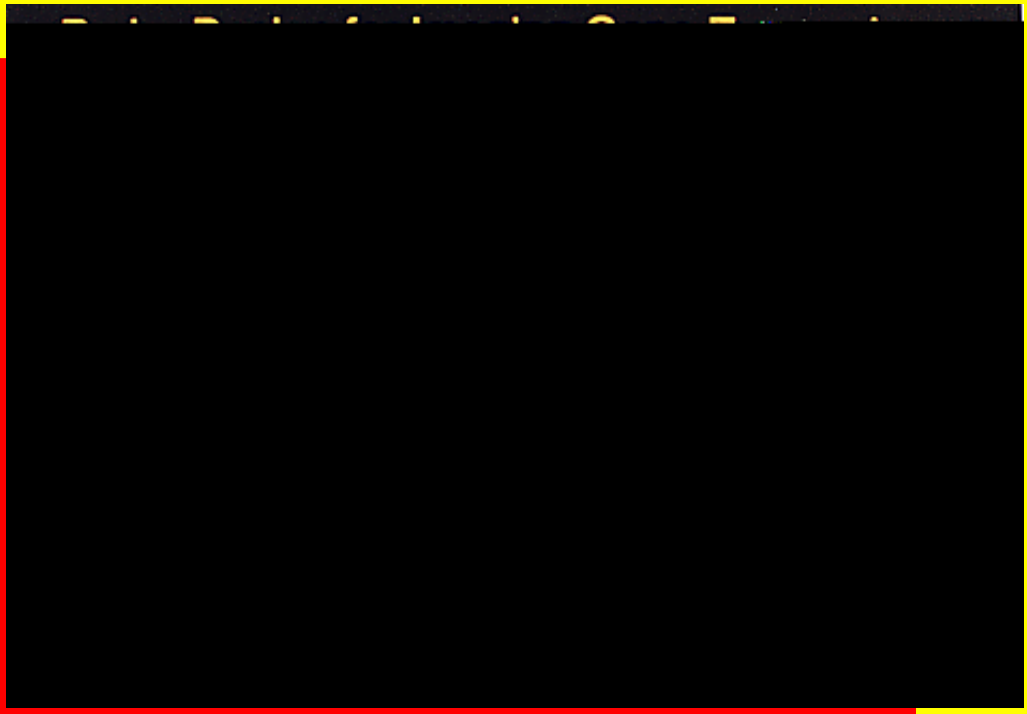
PET studies of glucose metabolism in the brain of normal volunteers while performing the task shown above each image. In the first image, the volunteer opens his eyes and looks at a visual scene. This activates the visual cortex in the back of the brain (vertical arrow). Listening: The volunteer listens to music that activates the right side of the auditory cortex (slanted arrow), and-words which activates the left side of the auditory cortex (horizontal arrow). The actual stimulus was a mystery story “The Shadow” with background music from the Brandenburg Concertos. Thinking: The volunteer is asked to count backwards from 100 by sevens which activates the frontal cortex (arrows). Remembering: The subject performs a memory recall task that activates the left and right hippocampus in the temporal cortex (arrows). Working: The subject is asked to touch their thumb to their fingers in a forward and reverse direction of their right hand. This activates the motor cortex (slanted arrow) and the supplementary motor cortex (vertical arrow). The metabolic activity of the brain is displayed in proportion to the color scale with red being the highest. These studies were performed by doctors Phelps and Mazziotta at UCLA. This slide illustrates the first mapping of the human brain.



Example of identifying a genetic disease in the brain with PET prior to any structural changes and in fact prior to even symptoms. The metabolic deficiency of Huntington's Disease is in the caudate (arrow slanting to the right) and putamen (arrow slanting to the left). Study from Mazziotta, Kuhl and Phelps at UCLA.



A PET imaging study in the living mouse using the PET reporter gene/PET reporter probe approach to measure and image gene expression using an adenovirus carrier for gene therapy. The PET reporter gene is the herpes simplex virus thymidine kinase gene and the PET reporter probe is fluorine-18 labeled acyclovir. The adenovirus was injected intravenously in the living mouse with the promoter region of the gene shut off in the control study to the left. In the mouse to the right, the PET image shows the image when the adenovirus was injected with the therapy gene and the PET reporter gene with an active promoter so that gene expression could take place. This particular adenovirus localizes with 99% specificity to the liver. Thus, this image shows that gene expression of a therapeutic gene delivered to the liver with a therapeutic adenovirus can be monitored and imaged in vivo with PET. This is the first example of in vivo imaging of gene expression.



For more information contact:

Dorry Tooker
Outreach Coordinator

Building 475-D
Upton, LI, NY 11973
Telephone: 516-344-2078
Fax: 516-344-3729

e-mail: Dorryt@bnl.gov