POSITRON EMISSION TOMOGRAPHY

The Imaging of Function
Rather Than Form

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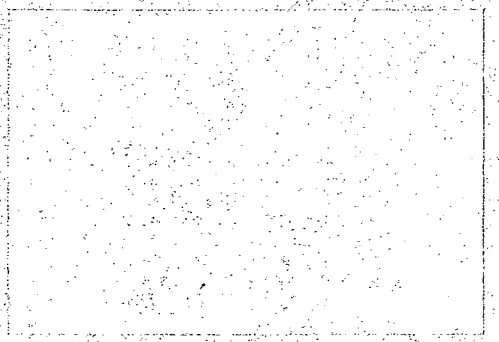

United States of America
Department of Energy
and
Mallinckrodt Institute of Radiology
at Washington University School of Medicine

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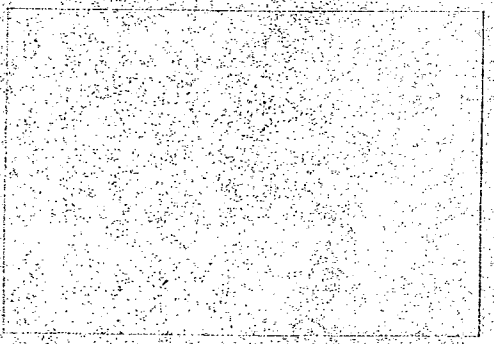

PET can distinguish tumors in the human brain from other abnormalities. The cover image represents a study using Fluorodeoxyglucose (FDG) in a patient with a malignant brain tumor. The area of the tumor shows increased glucose uptake. This technique helps physicians clinically to differentiate tumor from areas of radiation necrosis in the treatment of brain cancer. (Mallinckrodt Institute of Radiology at Washington University)

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POSITRON EMISSION TOMOGRAPHY (PET)

Final Report

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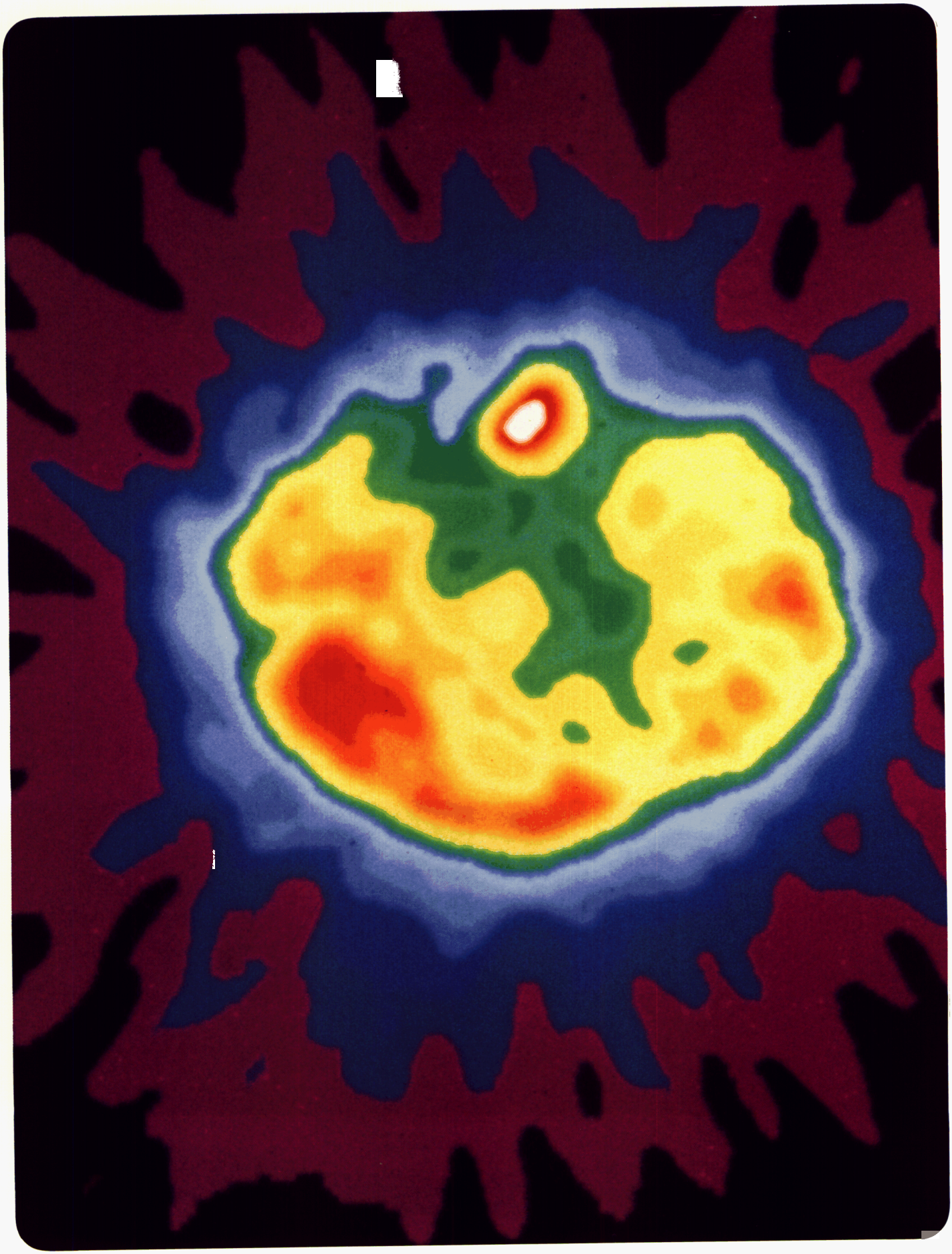
DISCLAIMER

According to the terms of the contract, a brochure was designed, produced, and printed. Four thousand copies have been sent to Dr. Paul Cho of Human Health and Assessments Division, ER-73, of the Office of Health and Environmental Research, Office of Energy Research in Germantown, MD. The remaining copies are being kept at Washington University. A copy of the brochure "Positron Emission Tomography - The Imaging of Function Rather Than Form" is attached to this report.

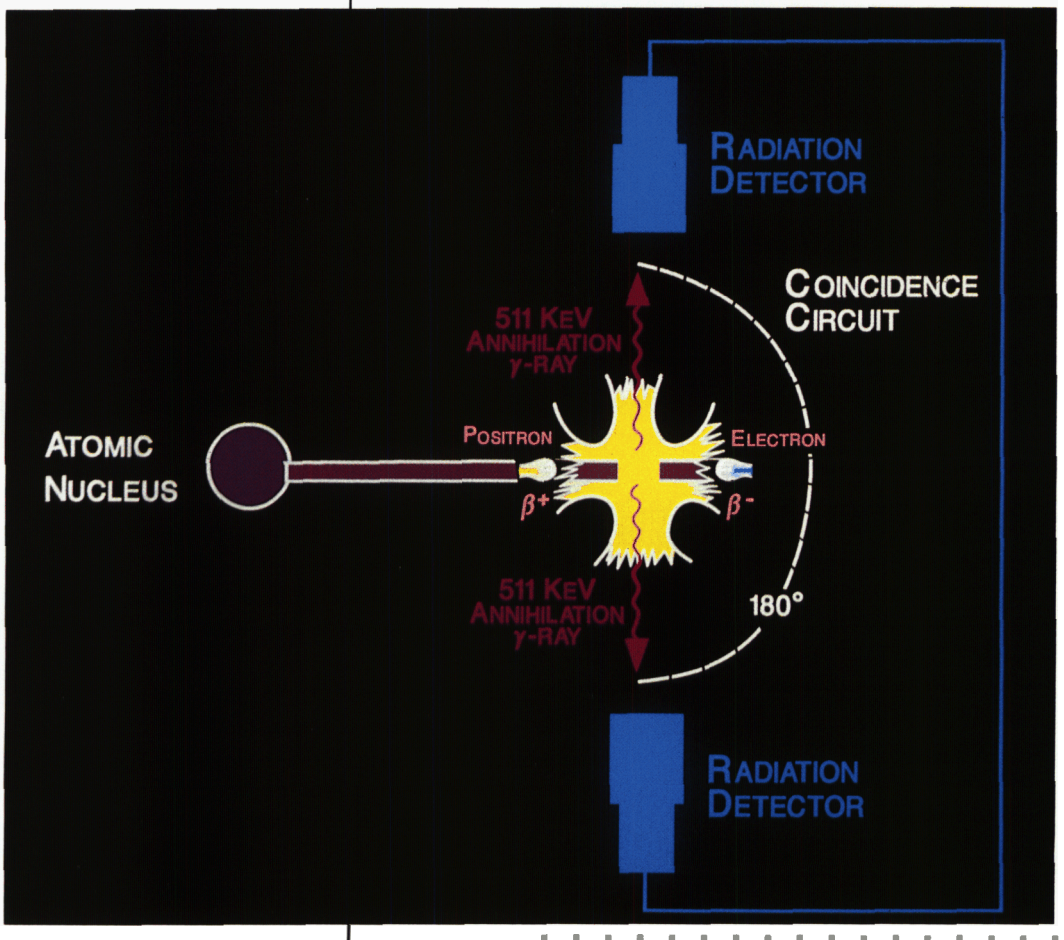


THE PRINCIPLES OF PET

Since the late 1930s, positron emitting isotopes have been used to study physiological processes. And in the ensuing years much important research has been undertaken. The first useable positron emission tomography (PET) instrument for human studies was developed in the early 1970s by a team of researchers led by Michel M. Ter-Pogossian, Ph.D., at Washington University's Mallinckrodt Institute of Radiology in St. Louis. Significant studies by many researchers continue to contribute to the ongoing development of PET.

PET assesses biochemical processes in the living subject, producing images of function rather than form. Using PET, physicians are able to obtain not the anatomical information provided by other medical imaging techniques (e.g., X rays, ultrasound, computed tomography, magnetic resonance imaging), but pictures of physiological activity. In metaphoric terms, traditional imaging methods supply a map of the body's roadways, its anatomy; PET shows the traffic along those paths, its biochemistry.

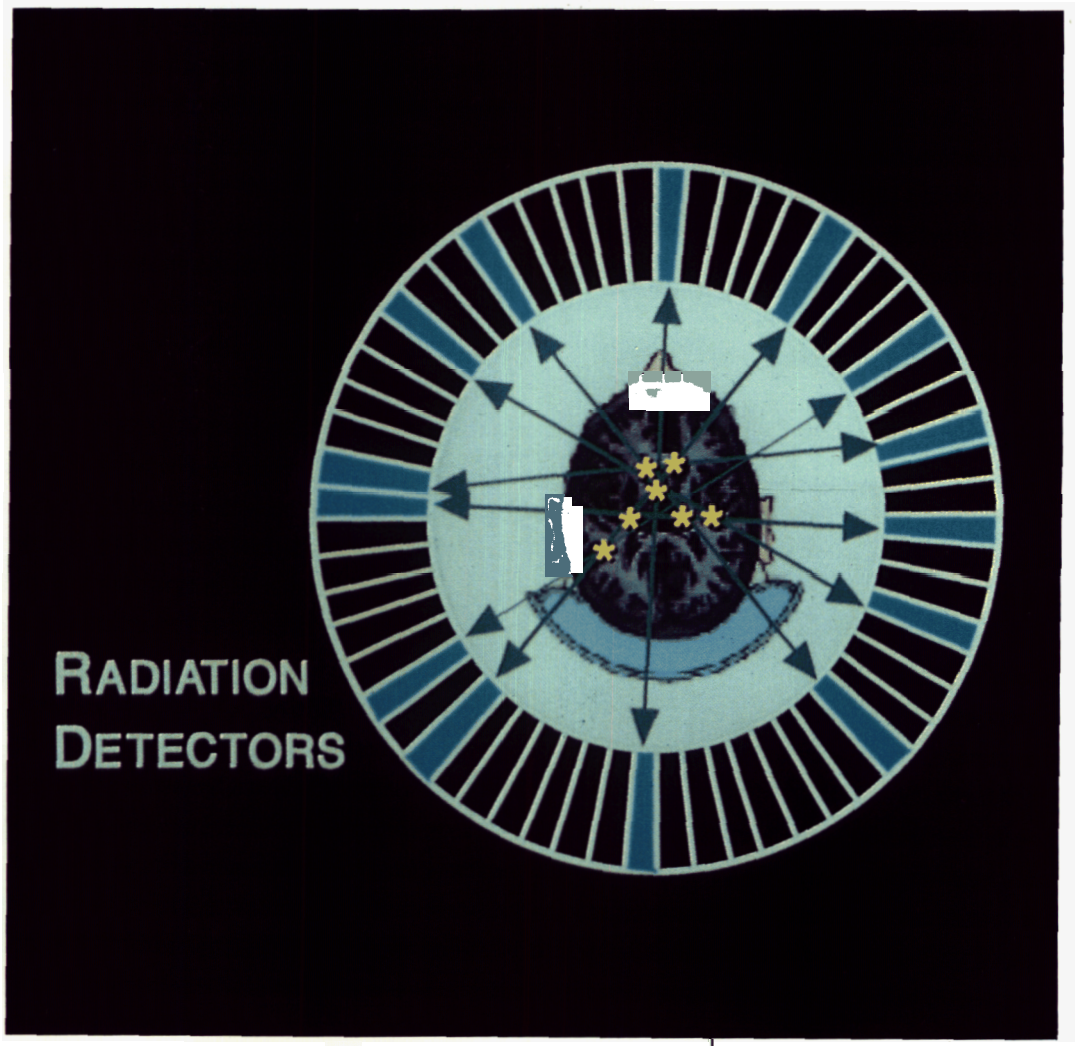
In PET studies, short-lived, cyclotron-produced radioactive nuclides of carbon, nitrogen, and oxygen are used to prepare radiolabeled compounds normally found in the body. These radiopharmaceuticals, after inhalation or infusion, travel



When a positron emitting radionuclide decays, a positron is emitted which, after losing energy, interacts with an electron and the masses of both are converted into energy. Two γ-rays of equal energy are emitted at 180 degrees to each other and are detected by two radiation detectors.

through the subject's bloodstream in routine fashion, serving as tracers of normal physiological activity. Because these tracer isotopes have a short half-life and deliver only a very low dose of radiation, no side effects result.

As the nuclides decay, they emit positively charged electrons, or positrons. The positrons in turn strike negatively charged electrons, annihilate and release energy in the form of two gamma-ray photons. These gamma rays are released at approximately 180 degrees from one another. A circular array of scanners around the subject detects the paired gamma rays as they simultaneously arrive on opposite sides. The PET scanner's coincidence circuits enable the localization of the source of each annihilation, and a computer then uses this information to reconstruct an image of the radionuclide's distribution within the body. (The more active a part of the organ being studied is, the greater the percentage of annihilations concentrated there.)



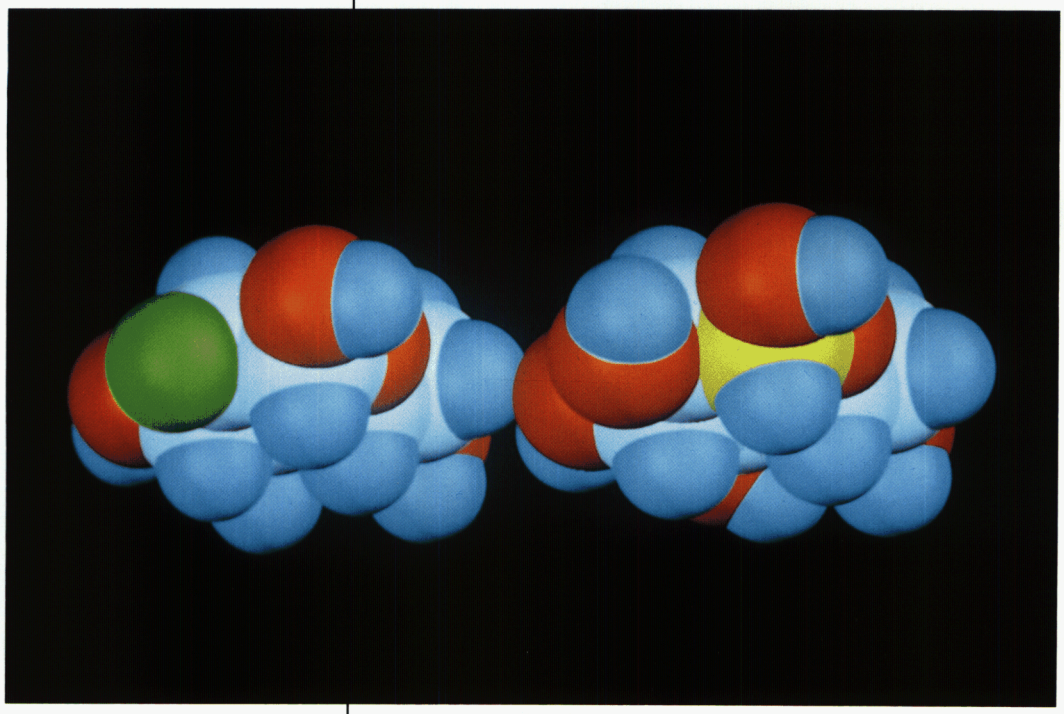
The ultimate result of the study are cross-sectional slices, akin to computed tomography (CT) images, with areas of activity clearly delineated. The PET study thus yields a picture of the organ of interest's circulation or metabolism.

In a PET scanner the penetrating radiation originating within the subject is carried out of the patient and is counted with two radiation detectors. The detectors are arranged in a circle around the patient so that only simultaneous events occuring at 180 degrees are recorded. A computer program then reconstructs the distribution of the decaying positron emitting radionuclide.

RADIOPHARMACEUTICALS IN PET

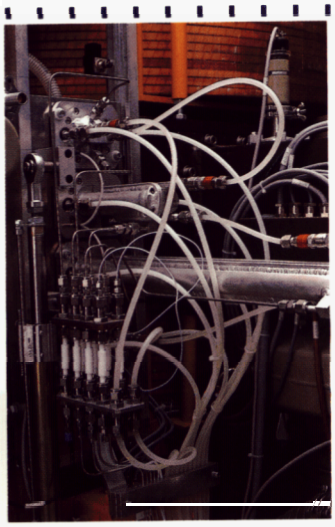
The four major nuclides employed in PET studies are oxygen-15, nitrogen-13, carbon-11, and fluorine-18. These radioactive tracers are used to synthesize radiopharmaceuticals designed to measure specific biochemical or physiological pathways in the body. For example, glucose can be tagged with fluorine-18—producing the compound fluorodeoxyglucose (FDG)—to trace glucose metabolism in the brain, the heart, or tumors. Alternatively, glucose can be labeled with carbon-11 to produce carbon-11 labeled glucose.

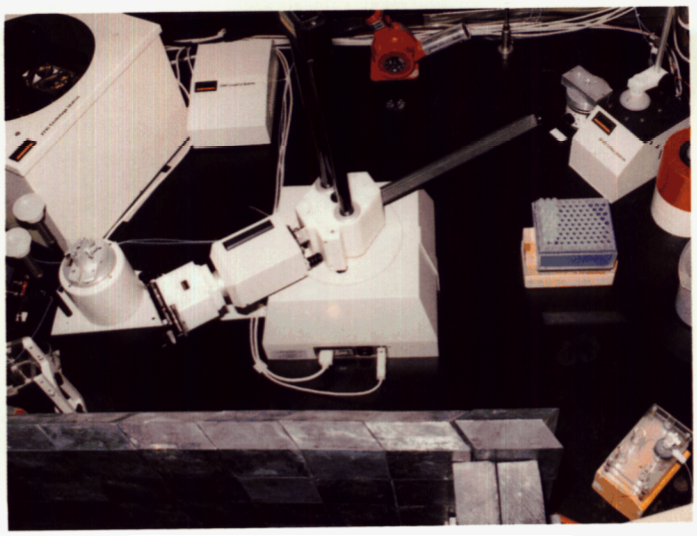
Because of their short half-lives, which range from one minute to two hours, the radiopharmaceuticals most used in PET are generally produced in on-site medical cyclotrons, although the longer-lived fluorine-18 can also be obtained from a regional distribution center. At sites remote from an available cyclotron, a radioactive generator system can be used to derive shorter-lived isotopes from longer-lived radioactive nuclides as they decay. The shorter-lived radionuclide—examples include gallium-68 (from germanium-68) and rubidium-82 (from strontium-82)—is then used to label compounds.



The most common PET radiopharmaceutical at the present time is fluorodeoxyglucose (FDG) which is chemically similar to glucose except that a hydroxyl group has been replaced by a radioactive fluorine atom (green). Glucose has also been labeled with carbon-11 (yellow). Both structures are shown with fluoroglucose on the left.

The most common method of producing radiopharmaceuticals is with a cyclotron installed in the medical center basement. Shown are a typical cyclotron and the targets utilized to produce the short-lived positron emitting radionuclides.



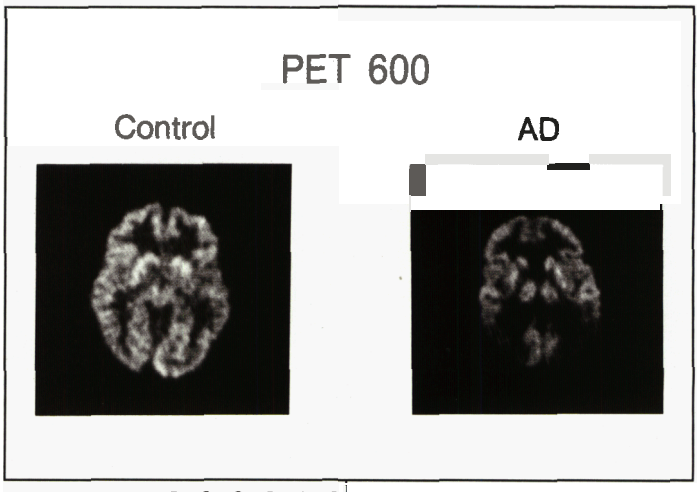


Automated systems have been developed to prepare complex labeled radioactive compounds with no radiation dose to the operator. One approach is to use laboratory robotics. A robotic synthesis of PET radio tracers has been developed to measure blood flow, glucose metabolism, dopamine receptor density, estrogen receptor density as well as various parameters of lung function. (Mallinckrodt Institute of Radiology at Washington University)

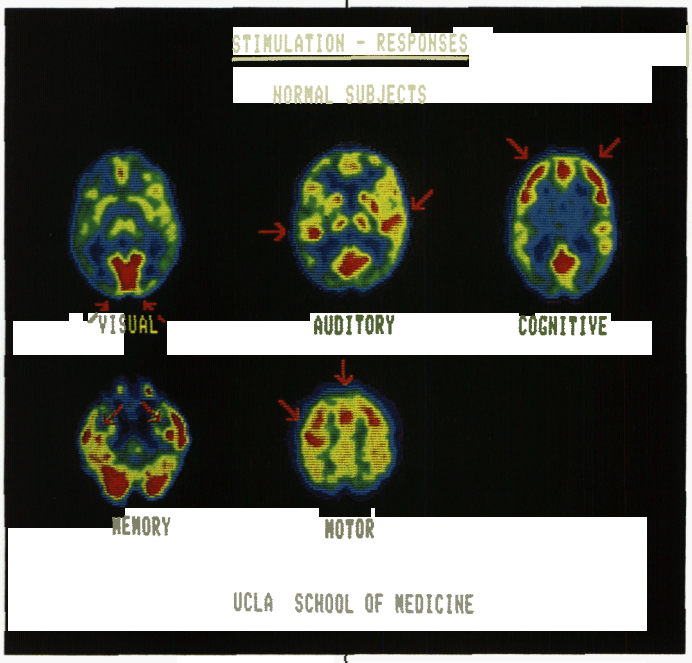
PET RESEARCH

Since its introduction in the '70s, PET has been used for a wide variety of research. PET data have particularly enhanced our understanding of the brain. Using PET, researchers have explored the basic physiological changes associated with such abnormalities as Alzheimer's disease, epilepsy, stroke, schizophrenia, panic attack, and Parkinson's and Huntington's diseases. The heart has also been extensively studied, especially the damaging effects of myocardial infarctions. PET studies of aging, depression, multiple sclerosis, substance abuse, lung function, and tumors have also been undertaken.

PET is being used to broaden our knowledge not only of disease states but also normal physiological processes. The pathways the brain follows to perform tasks, from the simple (seeing and hearing) to the complex (processing words and expressing emotion), are now being mapped.



Shown here are images of a control patient and those of a patient with Alzheimer's disease. In the Alzheimer's patient, glucose metabolism is reduced, particularly in the posterial parietal temporal region of the brain. (Donner Laboratory, University of California, Berkeley)



This study demonstrates the stimulus response characteristics of the human brain to visual, auditory, cognitive, memory and motor behavioral paradigms.

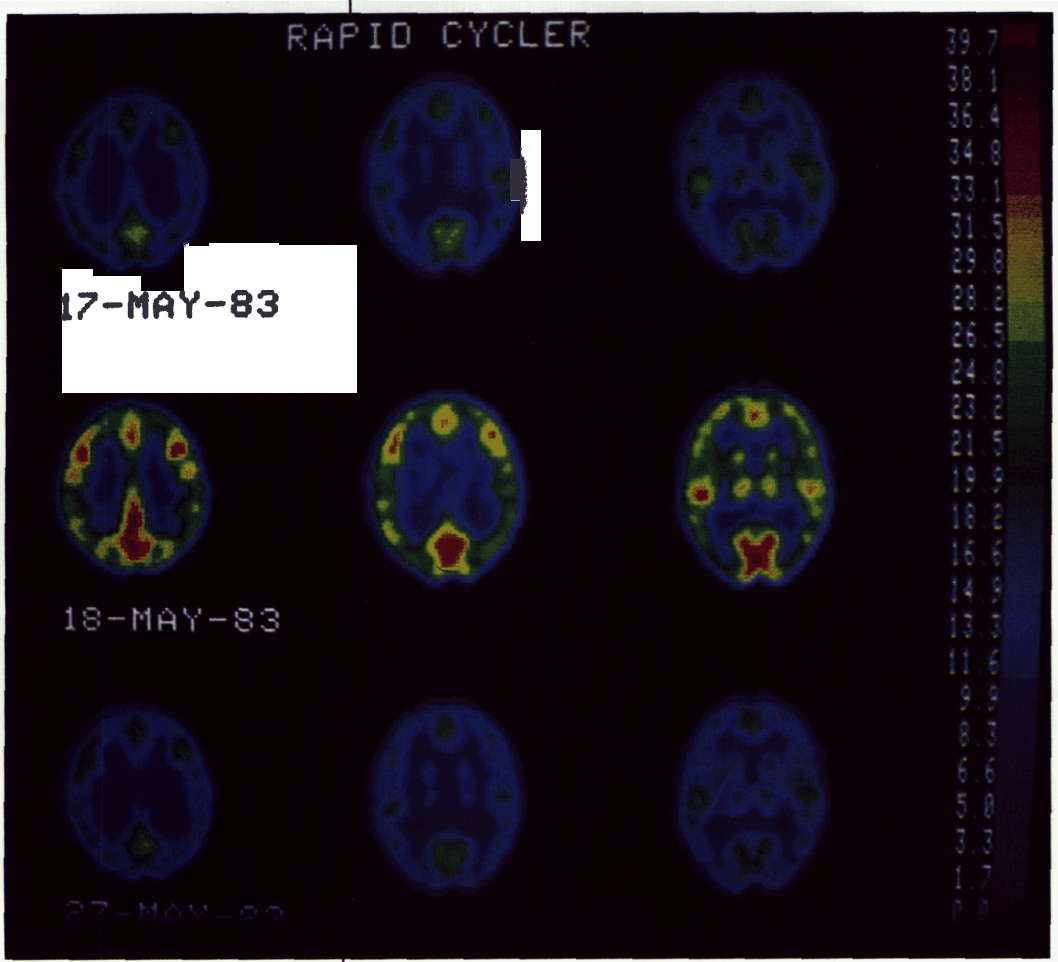
The areas of high metabolic rate are indicated in red and are emphasized with arrows. These are glucose metabolism studies using FDG. (UCLA School of Medicine)

CLINICAL APPLICATIONS OF PET

Assessing the Brain

PET studies offer significant clinical potential in a large number of important brain-related areas:

- Diagnosing and differentiating between different forms of dementia
- Locating epileptic foci
- Characterizing degenerativ diseases
- Identifying tumors and their extent
- Managing strokes
- Evaluating the effects of psychoactive and other drug
- Targeting pharmacologica therapy

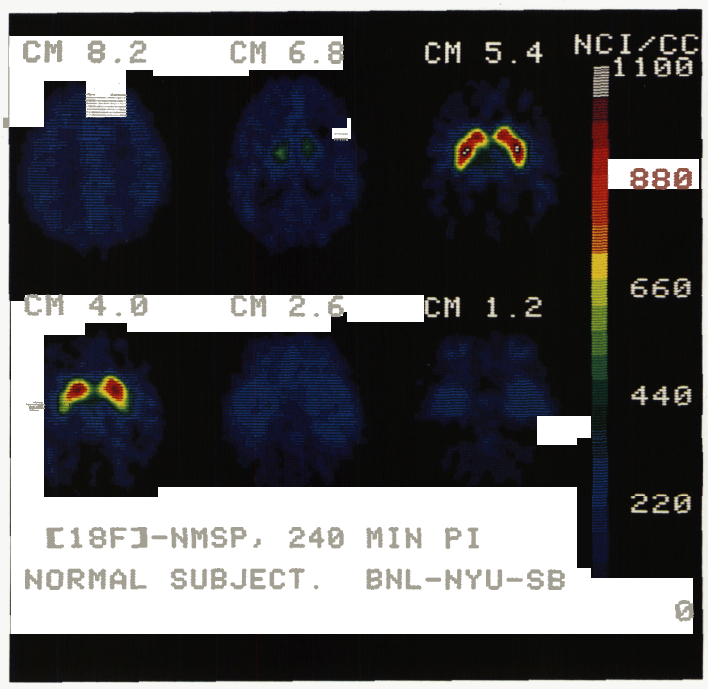


These are three PET studies of the same individual with manic depressive bipolar illness. The top and bottom rows are studies obtained during episodes of depression while the middle study represents a period of relative normality. The middle study is no different from age matched controls. The study demonstrates that in depressed patients the metabolic rate can fluctuate dramatically. (UCLA School of Medicine)

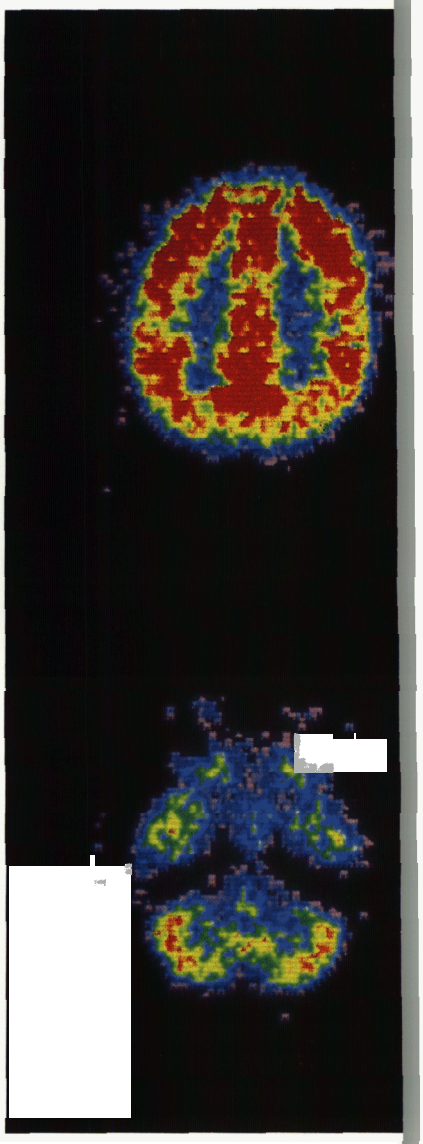
Because of its relatively non-invasive nature, PET promises to supplant other more dangerous and often less exact neurological examinations. At Washington University's Mallinckrodt Institute, for example, PET studies are being evaluated as a substitute for the Wada test, an invasive preoperative exam in which a barbiturate is injected through a catheter in the internal carotid artery to determine language laterality. (Before operating to remove an injured portion of the brain for control of epilepsy, the surgeon must ascertain which hemisphere controls language to avoid damaging it.) The PET examination not only carries far less risk than the Wada test, but also provides much more specific information about the discrete areas relating to language. In the future, PET may even be able to supply detailed functional brain maps to guide neurosurgeons before operations.

CLINICAL APPLICATIONS OF PET

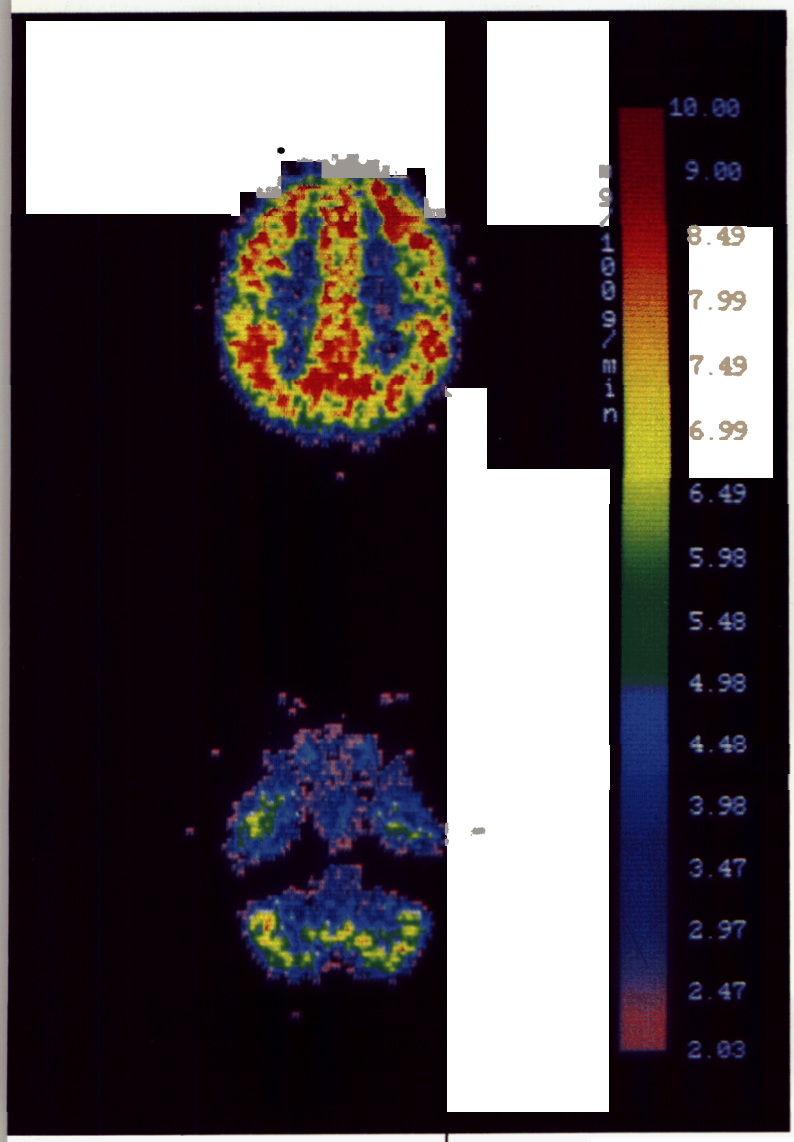
Continued

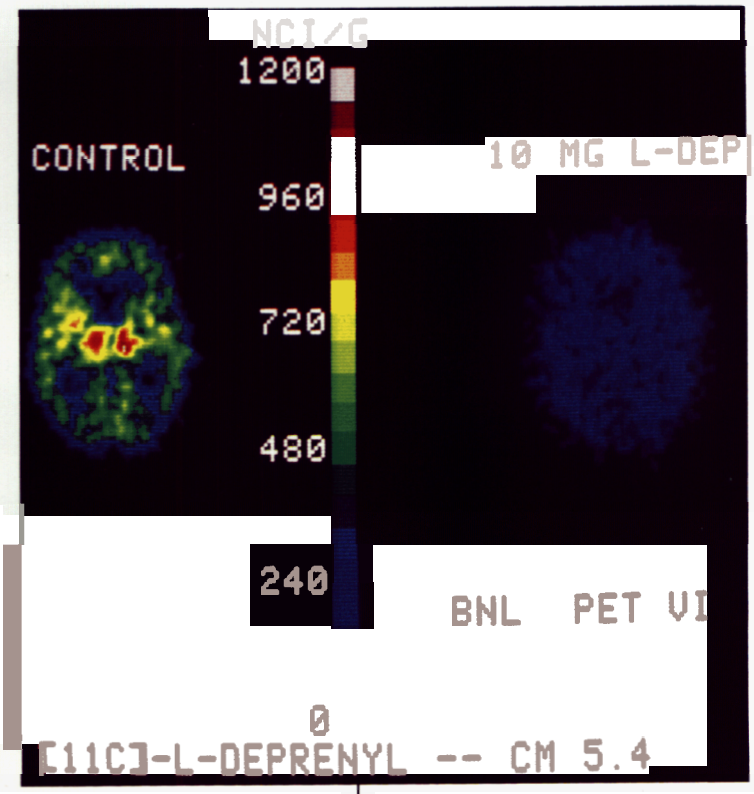


Pictured above:
Neurons in the brain are activated when neurotransmitter molecules bind to specific receptor sites. N-Methylspiroperidol (NMS) is a ligand that binds to the dopamine neuronal receptors, which are presumed to be the sites of action of many anti-psychotic drugs. Fluorine-18 labeled NMS and PET have been used to map the distribution of dopamine receptors in the living human brain in normal and disease states. This series of six PET scans shows uptake in the basal ganglia, the receptor-rich region of the brain. (Brookhaven National Laboratory)



Pictured at right:
This figure shows the effects of abused drugs on brain metabolism using PET. These scans show glucose utilization in a human volunteer with a history of opium and cocaine abuse. One study was performed under placebo conditions (left) and the other study (right) while the individual received morphine. Regional glucose utilization is indicated according to the scale on the right with the highest rate indicated as red. Morphine produced a feeling of a euphoria simultaneously selected to reduced activity in the cerebral cortex. The findings suggest a relationship between euphoria and the reduced functional activity in the cortex. (Johns Hopkins University and the National Institute of Drug Abuse)





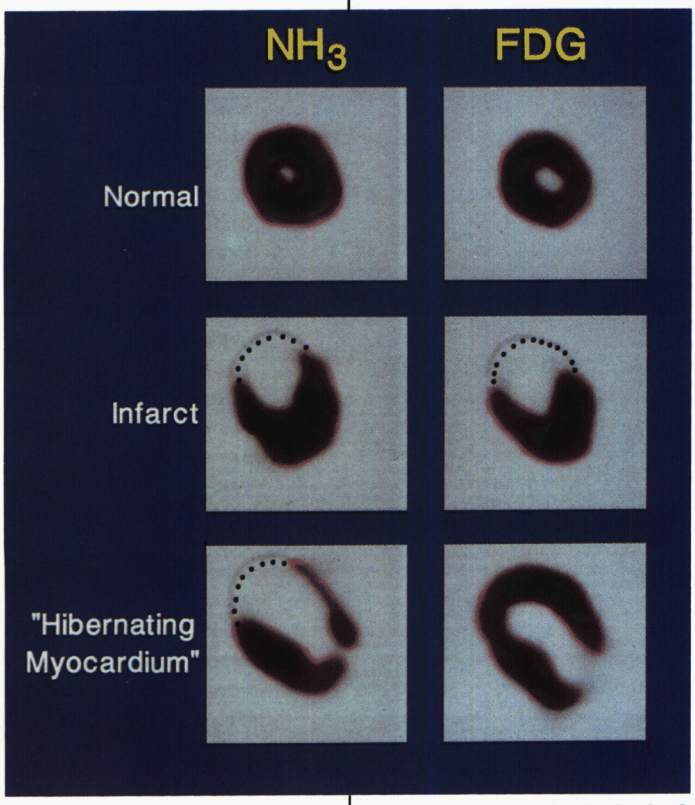
Pictured above:
L-Deprenyl is a new drug used to treat Parkinson's disease. It works by inhibiting monoamine oxidase (MAO), an enzyme responsible for regulating the concentration of neurotransmitters in the brain. Since Parkinson's disease patients have too little of the neurotransmitter dopamine, L-deprenyl helps to maintain the concentration of dopamine by preventing its degradation by MAO. Two different PET studies of the same human subject are shown on this figure. In the image on the left, a tracer dose of carbon-11 labeled L-deprenyl is used to label MAO in the brain. High uptake is seen in the thalamus and the basal ganglia which are known to have high concentrations of the enzyme. The image on the right was taken on the same patient after he had received a single 10 milligram dose of L-deprenyl. It is interesting that a single dose of L-deprenyl reduces the activity of the enzyme below detectable levels showing that L-deprenyl is remarkably effective at inhibiting MAO. Furthermore, recovery of enzyme activity takes several weeks, information that may be important in defining the frequency of treatment. (Brookhaven National Laboratory)

CLINICAL APPLICATIONS OF PET

Continued

Studying the Heart

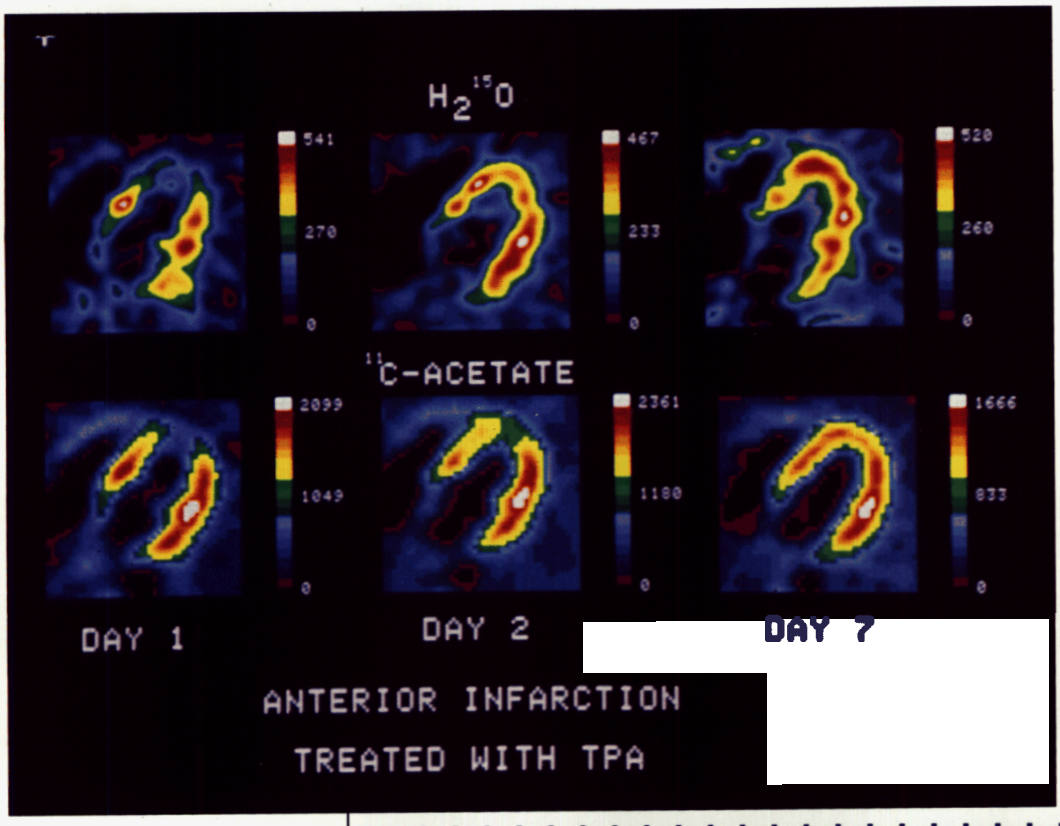
PET studies of metabolism and blood flow in the heart supply valuable data on the viability of myocardial tissue. Techniques developed at University of California, Los Angeles, help the physician in determining the extent of damage after a heart attack and provides an excellent method for determining if bypass surgery would be beneficial for a patient. Because of its ability to detect changes in metabolism, PET may also allow for the early diagnosis of coronary artery disease, thereby affecting the treatment approach and improving prognosis.



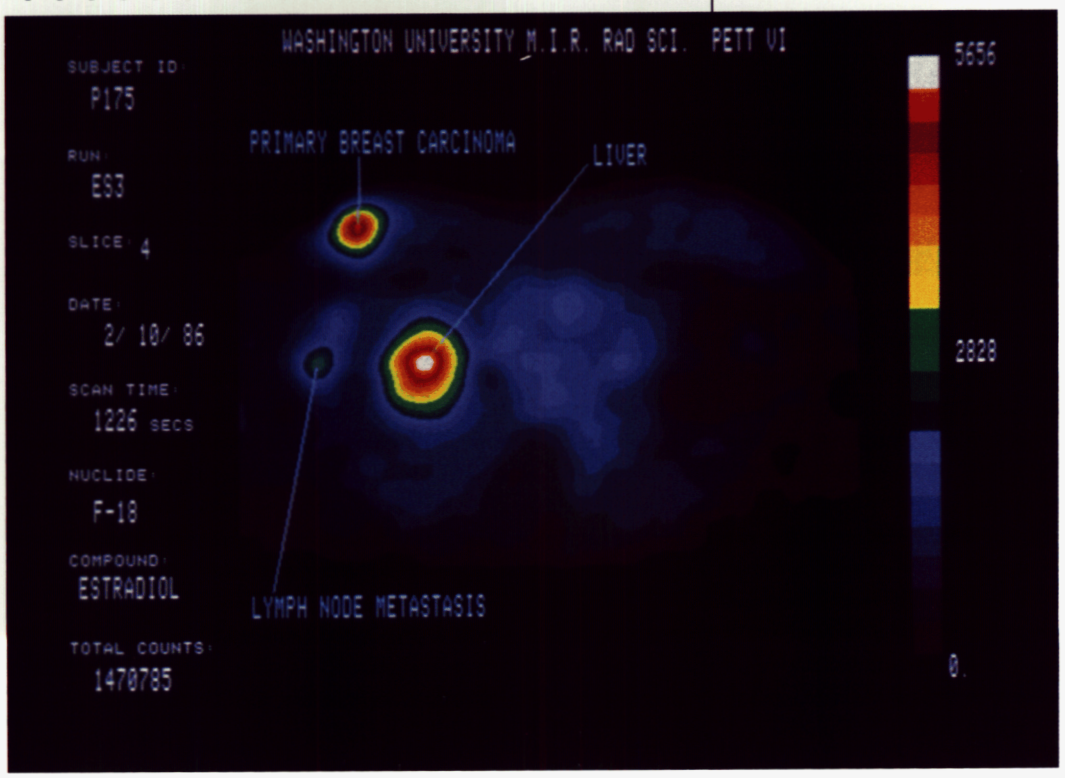
This figure compares the distribution of N-13 ammonia as a tracer of blood flow to the distribution of FDG in transaxial images in three patients with coronary artery disease. In Panel A, (normal) blood flow and glucose utilization are homogenous. In Panel B, both blood flow and glucose utilization are concordantly decreased, indicating the presence of scar tissue in the anterior wall. This shows an irreversible condition that would not benefit from coronary by-pass surgery. In Panel C, blood flow is decreased in the anterior wall and anterior septum, while glucose utilization is preserved or even enhanced. Panel C is an example of a reversible ischemic injury or "hibernating myocardium." This represents a condition that would be helped by by-pass surgery or other interventions. (UCLA School of Medicine)

Planning Cancer Treatment

PET's ability to detect the presence or absence of hormone receptors in breast tumors may provide key information to physicians in determining the most effective option—hormone therapy or chemotherapy—in the treatment of the cancer. Clinical trials are now underway using PET and fluorine-labeled progestin and estradiol to measure estrogen, progestin and androgen receptor levels in breast cancer patients. In the brain, PET is able both to differentiate tumors from other abnormalities, such as radiation necrosis, and to help determine the extent of a tumor before surgery.



This study measures blood flow and metabolism with oxygen-15 labeled water and carbon-11-labeled acetate in a heart attack patient treated with tissue plasminogen activator (TPA), a drug that dissolves blood clots. Flow and metabolism increase in the affected area with time, although the recovery of metabolism is slower than that of flow. (Mallinckrodt Institute of Radiology at Washington University)



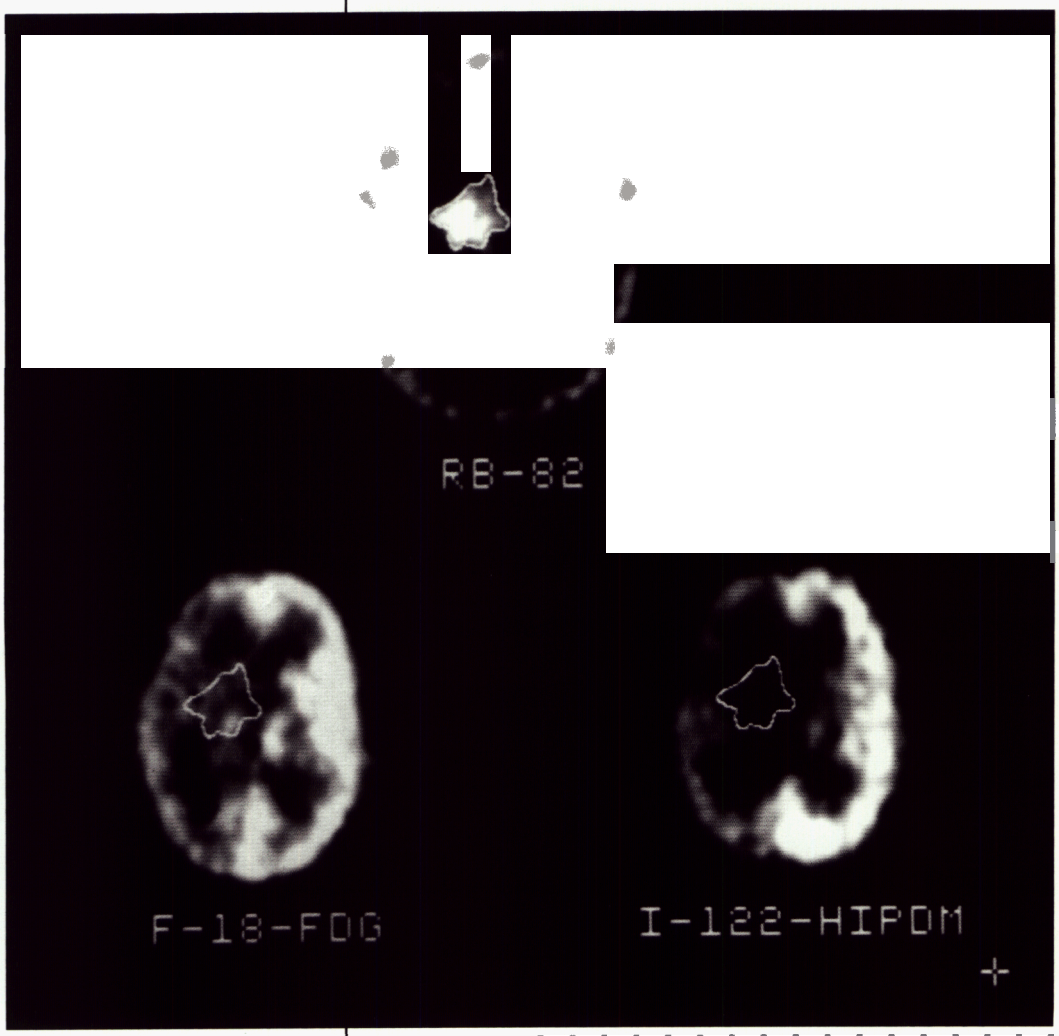
In the past, successfully imaging estrogen receptors in primary and metastatic breast tumors was only possible in excised tissue. This PET scan shows a transverse slice taken at the level of the diaphram of a 62-year-old female with breast cancer. The red-centered pattern (top) is the primary cancer. The white-centered pattern is the liver, where the fluorine-18 estrogen analogue collects before being cleared from the body. The small green spot is a metastatic tumor in a lymph node. (Mallinckrodt Institute of Radiology at Washington University)

THE COSTS OF PET

It has been estimated that the typical clinical PET facility of the future will perform six to twelve procedures per day. The technical charges are estimated to range from $600 to $1500 per patient depending upon the type of study, patient volume and whether or not a cyclotron is used. These charges do not differ significantly from those of other technologically advanced diagnostic tests. Costs from which these charges are derived were reported by the Task Force on Clinical PET in the March 9, 1988 issue of the *Journal of Nuclear Medicine*. Following is a list of cost considerations:

- PET scanner—$1.0 to $1.8 million
- Cyclotron—$1.0 to $2.0 million
- Facility renovations—$50,000 to $1.0 million
- Annual operating costs—$400,000 to $1.0 million

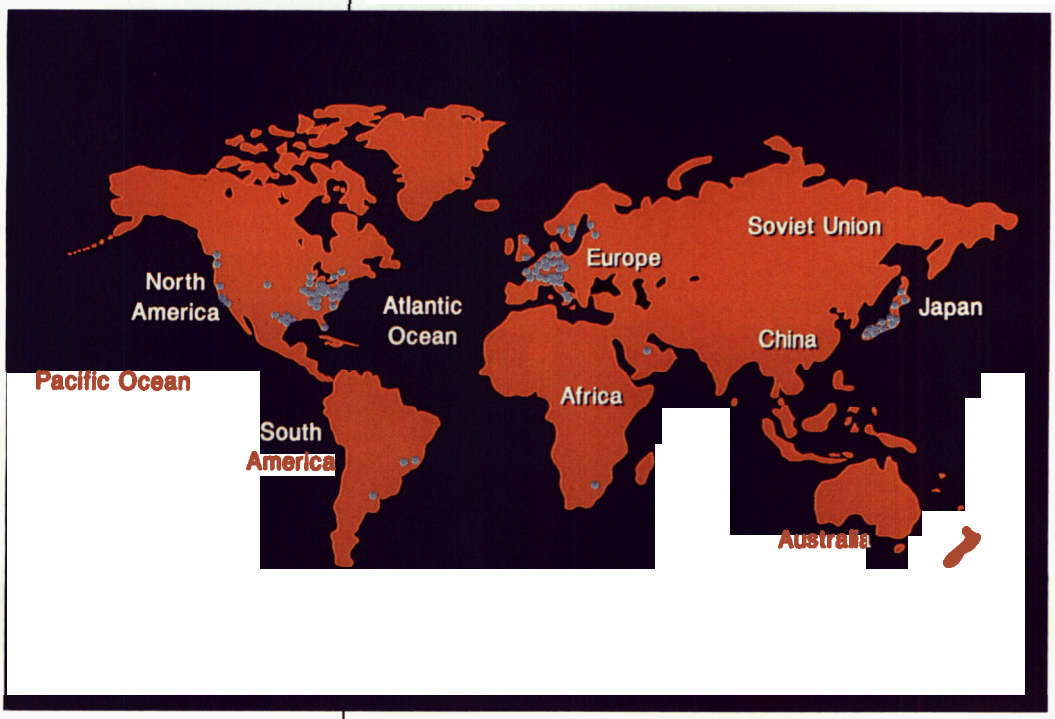
It should be noted that mass production, the sharing of cyclotrons, the use of generator-derived radiopharmaceuticals, and the conversion from research to simpler clinical environments could contribute to reducing overall costs.



PET studies can be carried out at centers without their own accelerators. These images of a patient with a brain tumor show studies with fluorine-18 that was delivered from a site 70 miles from the PET center as well as with rubidium-82 and iodine-122 which are generator produced. This type of study is possible with the introduction of regional delivery systems and new radioisotope generators. (Donner Laboratory, University of California, Berkeley)

TRAINING OF INDIVIDUALS FOR PET

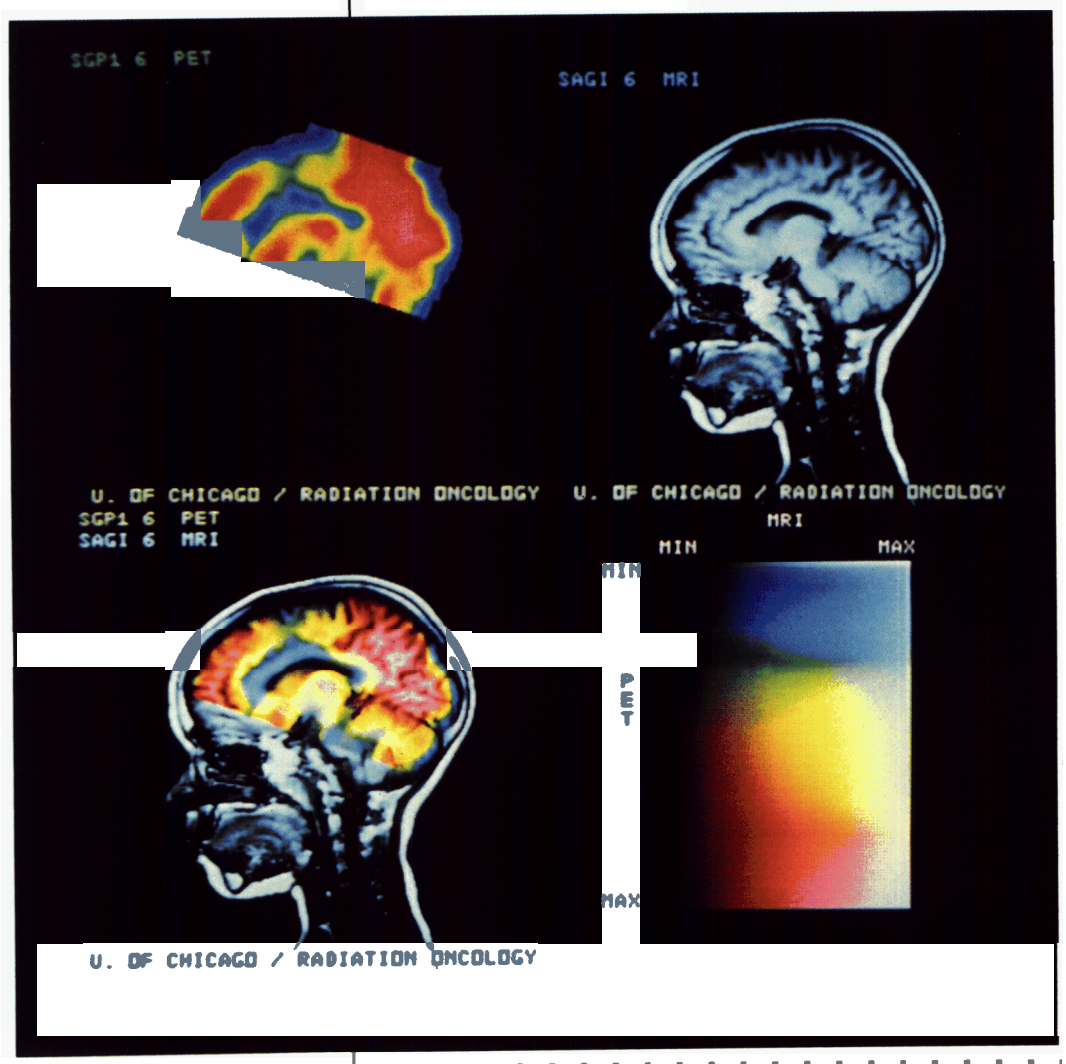
With the development and expansion of many PET centers, there is a need for chemists, physicists and physicians with training in positron emission tomography. At a workshop, organized by the National Academy of Sciences, 120 scientists from around the nation gathered in Washington, D.C. in February of 1988 to address the need for chemists in this field. Emphasized at the symposium was the current and future dearth of trained radiochemists. The panel on Nuclear Medicine applications identified 120 positions requiring knowledge of radiochemistry open at that time for chemists and pharmacists with advanced degrees. It was estimated that by 1993 over 200 positions would need to be filled. The National Academy Report that resulted from the workshop stressed the importance of PET radiopharmaceutical training programs within the disciplines of organic synthesis, analytic chemistry, and biochemistry.



The number of PET centers worldwide has increased significantly over the past decade from a handful to nearly 100.

THE ROLE OF THE UNITED STATES DEPARTMENT OF ENERGY IN PET

The Department of Energy has been involved in supporting many of the major developments in positron emission tomography. A prototype PET unit was built at Brookhaven National Laboratory many years before the initial development at Washington University's Mallinckrodt Institute. The PET Centers at Memorial Sloan Kettering Institute, University of California, Los Angeles, and Massachusetts General Hospital were initially supported by the Department of Energy. The National Laboratories have been instrumental in providing many PET radionuclides including the parents of rubidium-82, gallium-68 and copper-62. At present the majority of active PET research centers receive at least some of their research support from the Department of Energy.



As PET measures function it is easy to correlate function with anatomy. This can be accomplished by superimposition of a functional PET image with an anatomical MRI image. (University of Chicago)

THE FUTURE OF PET

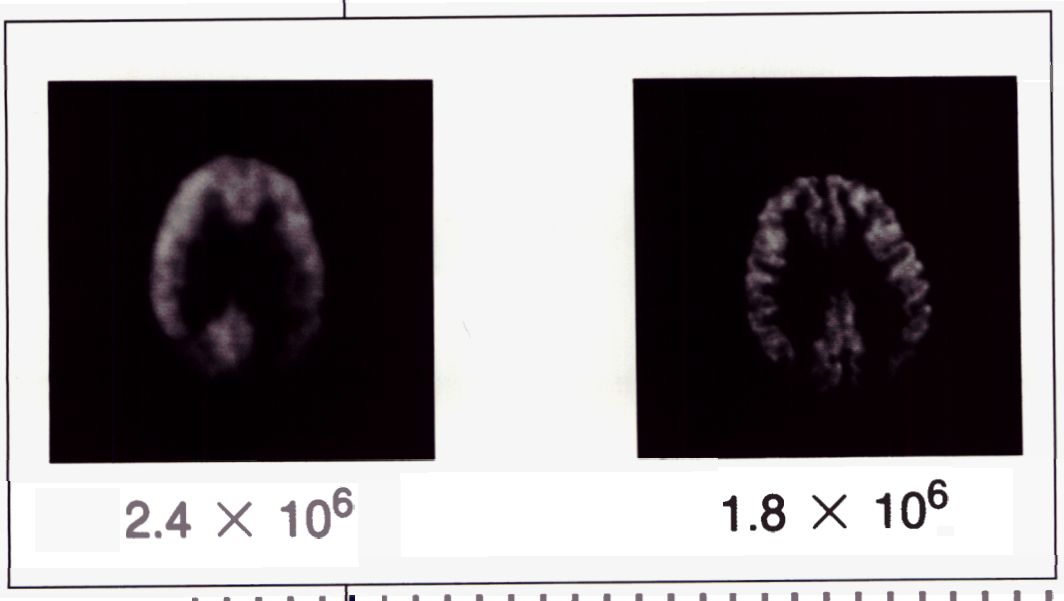
Currently, the majority of PET centers worldwide are involved in basic research, but use of the imaging device for clinical applications is increasing. Advances continue on a number of fronts, enabling further dissemination of PET in the near future.

Developments include:

- Simpler, easier-to-operate accelerators
- New radiopharmaceuticals
- Techniques for labeling molecules automatically, e.g., robotics
- Radioisotope generators (for medical centers without access to a cyclotron)
- Regional delivery systems (for distribution of longer-lived isotopes)

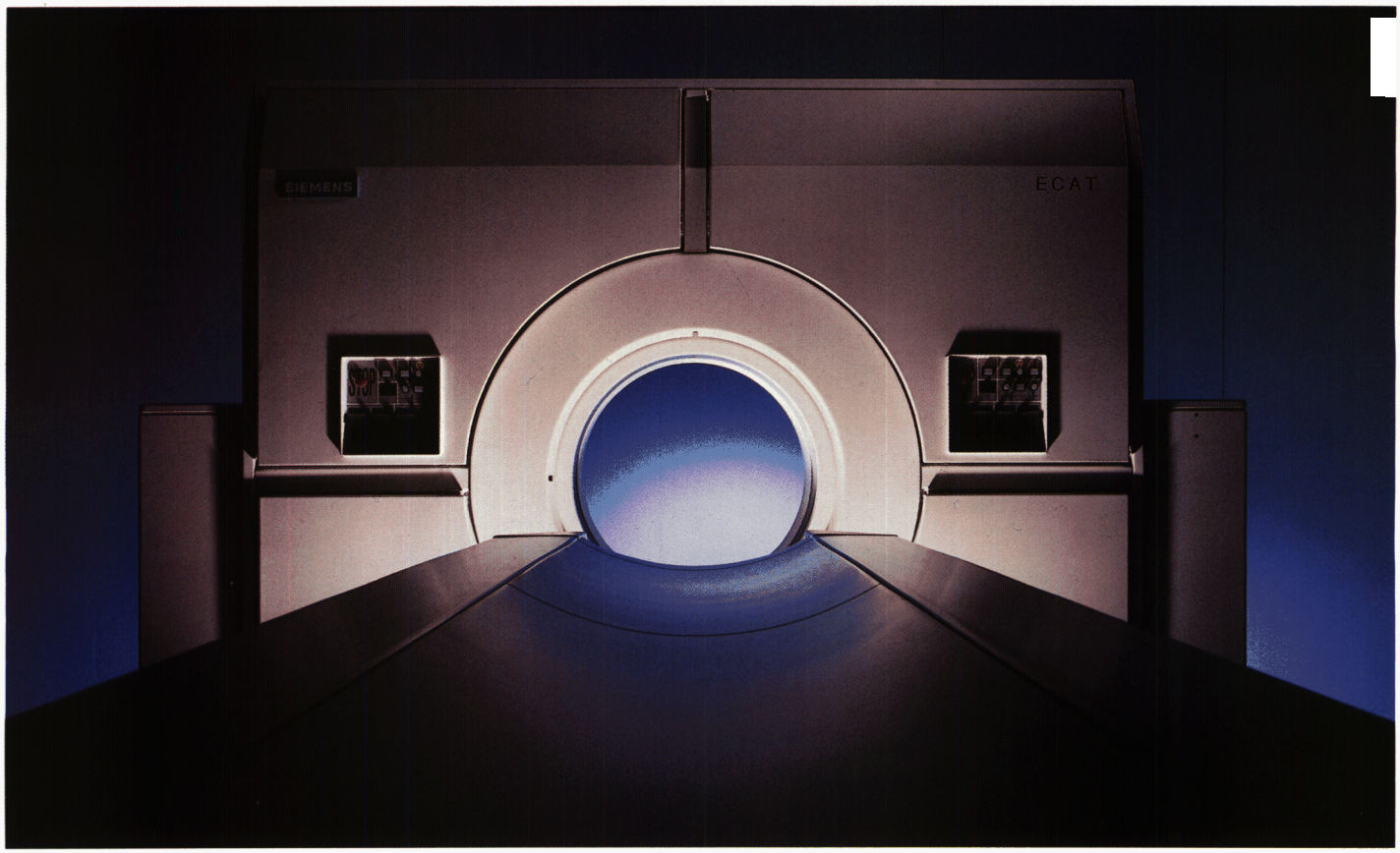
Refinements in PET scanner design have also significantly improved picture resolution and response localization. Image manipulation methods have further enhanced researchers' ability to accurately assess the degree of a physiological change and pinpoint the anatomical location of that change. These methods include subtraction (i.e., subtracting an image during stimulation from one at rest to produce a picture solely of the difference) and signal averaging (i.e., taking measurements across several subjects and averaging them), as well as the superimposition of the functional PET image with anatomical CT or MR images.

Indicating the intense interest in PET's clinical possibilities, the number of PET centers in the United States has increased from four in 1976 to 37 (operating or being installed) in 1989. And estimates indicate that the number will double in the next five years.



An area of continued development is in improved instrumentation. This image shows the comparison of a low resolution and a high resolution image of the same individual. Much greater resolution and distinguishing of brain areas is seen in the new high resolution instrument at right. With the advent of new instrumentation, the applications of PET would be greatly increased. (University of California, Berkeley)

PET



Prepared by Michael J. Welch, Ph.D and Michaele R. Gold for the U.S. Department of Energy under Grant Number DE-FG02-89 ER 60763

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