Cover: *"Cyclist – Not Quite There Yet"*, two-dimensional oil on canvas, with sand and wire, by Jeremy Ballard, originally from Tiverton, who is now a glassblower, painter and sculptor in Savannah, Georgia.

Medicine & Health Rhode Island

VOLUME 86, NO. 5 MAY, 2003

PUBLICATION OF THE RHODE ISLAND MEDICAL SOCIETY

COMMENTARIES

POSITRON EMISSION TOMOGRAPHY (PET) IMAGING
Guest Editor: John J. Cronan, MD

COLUMNS

ACKNOWLEDGEMENT: **A grant from Philips has paid for the reproduction of images in this issue.**

Medicine and Health\Rhode Island *(USPS 464-820), a monthly publication, is owned and published by the Rhode Island Medical Society, 235 Promenade St., Suite 500, Providence, RI 02908, Phone: 401-331-3207. Single copies $5.00, individual subscriptions $50.00 per year, and $100 per year for institutional subscriptions. Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society, unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Periodicals postage paid at Providence, Rhode Island. ISSN 1086-5462. POSTMASTER: Send address changes to Medicine and Health\Rhode Island, 235 Promenade St., Suite 500, Providence, RI 02908. Classified Information: RI Medical Journal Marketing Department, 175 Mathewson Street, Providence, RI 02903, phone: (401) 331-4637, fax: (401) 331-3594*

COMMENTARIES

How Much Choice Does a Patient Have?

When I was a neurology resident a patient once kicked me out of her room, or rather, her husband did. I wasn't insulted. It was a small plus for me actually. As a first year resident one spent most time on the ward service, seeing patients without private attendings referred primarily from the emergency room and occasionally the clinics. The months on the private service were quite different. On the ward service we'd admit three to five patients every fourth day usually, and took charge of the cases, formulating the differential, ordering and interpreting tests and generally caring for the patients. An attending level neurologist supervised but generally kept a low profile. On the private service, we'd admit ten patients, write a history, document a detailed neurological exam and conclude, "tests per Dr. X." On non-admitting days, if interested, we'd stop by to see what was happening. But generally, if one wasn't admitting, one didn't have any in-patient work. The teaching advantage of the private service was extraordinary. Patients came from far and wide to see the famous experts. In those days patients would be admitted sight unseen. In this particular case, the patient came form Ohio to see the famous Dr. X., a true world expert. Rather then seeing him in the office she was admitted directly so that it would be easy to obtain any tests and also so that the fellows could see the patient on rounds. When I went to see the patient her husband informed me that his wife had seen a slew of neurologists in the Midwest, was here to see Dr. X., not me, and I should take a hike. I explained my need to examine all patients because I was responsible when I was the only doctor in the hospital overnight, but the man was adamant. I happily wrote up my admission note with a detailed history and, in large letters, "patient refused exam." This saved a half-hour or more. As I was leaving to go to another floor I met Dr. X. and told him what happened, expecting him to shake his head and move on. He didn't. "She can't do that." He marched me in to the room and told the patient and his spouse that I could examine her or she could leave. Although not pleased, I was impressed.

Recently a colleague was similarly thrown out of a patient's room and it brought to mind the very complex issues surrounding medical care in hospitals, particularly teaching hospitals. In this case a patient, who was a university professor, asked a young Asian-born woman not to return. Dr. Asian woman was brought in as a consultant. She was an assistant professor and attending for one particular consulting service. Private doctors may also have been available but hers was the teaching service at the university hospital. The patient told her boss that he didn't want a doctor who had trained at a foreign medical school. Her fellowship training at the Harvard hospital they were in didn't seem to overcome his jingoist inclination and her status as a Harvard assistant professor didn't either. Perhaps he didn't feel comfortable with women. What was the "proper" response? What would the response have been if the doctor was black and the patient racist? Most likely the patient's request would have been ignored. What if the patient was female, the doctor male and the problem gynecologic? Where do we draw a line between reasonable and unreasonable requests?

Should the service director have said, "Dr Asian woman has our complete confidence or we wouldn't have hired her. If you don't feel comfortable with her despite her unimpeachable conduct then she will be taken off your case and your primary doctor can find another consultant?" I think so. Medical treatment is a service that has several constraints. Patients cannot always exercise free choice. There is a TV commercial in which a plumber enters a house to find it submerged while water is gushing out of a pipe. The young owner instead of looking relieved that his disaster is about to be taken care of, instead asks for an estimate to make sure he's getting a good price. An emergency is an emergency and generally if you're in an American hospital in the 21st century it's an emergency and there's usually not time to comparison shop. When the emergency resolves you can take time to find the best and most compatible doctor. In the case of a hospitalized patient, the rejection of a service without justifiable cause puts the onus on the patient or the patient's primary doctor to provide alternate care. If the patients said, "I never heard of you but your boss is famous, I want her," the request would have died immediately (unless the patient was a donor or a VIP).

Discrimination by doctors is unacceptable and punishable. Discrimination by patients, while not punishable, is no more tolerable and should not be supported.

– JOSEPH H. FRIEDMAN, MD

A Medical Student Is Elected To the Presidency

His relatives described him as slim and of average height. His hair was said to be thin, beginning to grey at the temples and was combed carelessly over his prominent forehead. His face was of fair complexion, long and slim, with an elongated nose, strong jaw-line and thin lips. From a distance he appeared to be a forbidding and unapproachable statesman; but in truth he was plain-spoken, affable, accessible and quite unpretentious.

William Henry Harrison may have seemed unpretentious to his close friends, relatives and pastor, but to others his ancestry alone would have made him a formidable and unapproachable personage. His mother's lineage, for example, was traceable all the way back to Plantagenet England's Henry III [1207-1272]. His father's family had migrated from England to Virginia in 1632. The first of six successive William Henry Harrisons then became one of Virginia's largest landowners. His son, the second William Henry Harrison, was elected to the House of Burgesses, Virginia's legislative council. The third William Henry Harrison became Virginia's Attorney General; the fourth William Henry Harrison was a colonel in the local militia as well as a member of the House of Burgesses. And William Henry Harrison's father, the fifth bearing the name, was a member of the Continental Congress, a signatory of the Declaration of Independence and governor of Virginia.

The sixth William Henry Harrison [1773-1841] was born on February 9, 1773, at the family's ancestral home, Berkley Plantation, Virginia, the youngest of seven living children. The plantation was attacked and partially destroyed by Benedict Arnold and his troop of loyalist militia and the family, including four year-old William Henry, sought refuge elsewhere. Biographers claim that it was during this critical interval in his life that he declared his intention to become a physician.

William Henry's elementary education was in the hands of competent private tutors. At the age of 14, he was sent to Virginia's Hampden-Sydney College for premedical studies. Records indicate that he successfully completed his classes in rhetoric, mathematics, geography, history and classical languages. From early childhood William Henry was deeply religious and committed to the verity of the Bible. He left college when the institution's formerly Episcopalian spirit was supplanted by a "Methodist fervor."

In 1790, at age 18, William Henry began his medical apprenticeship with Dr. Andre Leiper of Richmond, Virginia, and in 1791 he transferred to the medical college of the University of Pennsylvania to complete his final requirements for the degree of Doctor of Medicine. His principal tutor was a political acquaintance of his father, Dr. Benjamin Rush, also a signer of the Declaration of Independence.

In August of 1791, William Henry's father unexpectedly died, leaving the family's fiscal status in disarray. William Henry, with heavy heart, then left the medical school and enlisted in the United States Army.

His military career was auspicious. He rose to the rank of captain and later to the rank of major general in the infantry, playing a leadership role in the decisive battle of Tippecanoe in 1811. William Henry participated in the Indian Wars within the Northwest Terrirtory and in the battles with the British during the War of 1812, during which time he led the American troops in the recapture of Detroit. He was appointed by President John Adams as Governor of the Indian Territories and he fashioned the treaty leading to unhindered white settlements in the states of Illinois, Indiana, and Ohio. He resigned from the Army in 1814 and in 1816 was elected to the House of Representatives in Washington. From this time onward his career was solely in politics and government posts. In 1819 he was elected to the United States Senate, representing Ohio [which had achieved statehood in 1803].

In 1836 the Whig party chose William Henry Harrison as its candidate for the Presidency. He lost to Martin van Buren, but ran again, this time successfully, in 1840, with John Tyler as his Vice President and Daniel Webster as his Secretary of State.

William Henry Harrison, sometime medical student, veteran infantryman, governor and legislator, was inaugurated on March 4, 1841, as the ninth President of the United States. The weather on that day was bitterly raw, with intermittent rain and high winds. Despite the inclement weather, Harrison chose to deliver an inaugural address lasting an hour and forty minutes. And despite his age [at 68, he was the oldest newly elected President until Ronald Reagan in 1980] he chose to deliver this closely reasoned speech with neither a coat, a hat nor even the partial protection of an umbrella.

Within a day he took to bed with a high fever and signs of pulmonary involvement. His chest infection then seemed to abate but within a few more days his fever rose precipitously, associated now with severe chest pains made worse by a hacking cough. The President's physicians diagnosed his mortal condition as "bilious pleurisy." And within a few weeks he died. John Tyler of Virginia, his vice president, assumed the Presidency.

William Henry Harrison served a total of 31 days as President, the shortest tenure in office of any American President and the first President to die in office. One of his sons had the distinction of being both the son of the ninth President of this nation and the father of the twenty-third President [Benjamin Harrison, 1833-1901]. Another son became a practicing physician in Vincennes, Indiana.

There is little in Harrison's career as military officer, legislator, governor or President that reflects his earlier training in clinical medicine. Most physicians, during their years of formal education, do learn the basic Hippocratic aphorisms, one of which is: *Primum non nocere* [first, do no harm; do not intervene, in other words, unless you are certain that your intervention has some positive value]. One can speculate that a bare hint of this aphorism emerges in one of Harrison's more memorable quotations: "The people are the best guardian of their own rights and it is the duty of their executive to abstain from interfering or thwarting the sacred exercise of the lawmaking functions of their government."

– Stanley M. Aronson, MD, MPH

Imaging in the Second Century: The Introduction of Functional Imaging

John J. Cronan, MD

A new era of imaging has arrived. Diagnostic Imaging is no longer focused on morphology-lumps, bumps, masses, etc. We are now probing metabolism and cellular function, creating an image based upon metabolic activity within the cell.

Positron Emission Tomography (PET) is our introduction to molecular imaging. The future of imaging depends upon functional imaging because it will permit "visualization in space and time of normal as well as abnormal cellular processes at a molecular or genetic level of function." [1] The radiologist will use a probe such as 18 **fluoro dioxoglucose (FDG)**, directed to specific targets within the body, permitting imaging of cellular function.

How is this image different from the CT or MRI images employing the iodinated contrast of CT or Gadolinium in MRI? These latter agents are not specific for a particular metabolic activity. Rather, the present contrast agents respond to distribution dynamics, such as extra cellular space, blood flow and the breakdown of the blood brain barrier. They do not demonstrate cellular metabolic activity.

Today we hope to identify abnormal cellular processes before they create lumps or bumps in organs. We wish to image abnormal pathophysiology when it is only a metabolic process, not a morphologic process. Futuristically, these probes will be targeted specifically to match a patient's tumor or metabolic defect. We will be freed of the evaluation of tumor size as a criteria for chemotherapy success and instead evaluate the molecules responsible for the tumor. Hitherto, we begin chemotherapy and wait months before determining if our therapeutic effort is effective. Tumor size is our barometer of success or failure of treatment. Utilizing molecular imaging, we will soon evaluate the tumor's ability to replicate and express certain proteins as soon as chemotherapy is initiated.

As we are introduced to molecular imaging, FDG is our initial probe. It is a marker of glucose, which is increased in tumors because of increased cellular metabolism. This increased cellular activity is a biomarker for the presence of tumors.

We seek more specific markers that will delineate specific molecular events, which are signatures of diseases – ovarian cancer, Alzheimer's disease, breast cancer.

We will be freed of the evaluation of tumor size as a criteria for chemotherapy success and instead evaluate the molecules which are responsible for the tumor.

Our initial focus in the use of PET will be with oncology. The brake on the development of PET, which has been available for over twenty years, has been the limited reimbursement by Medicare. Unfortunately, the penetration of PET into other disease processes will also be determined mainly on the basis of approved indications, which ultimately lead to reimbursement. An examination technique, lacking reimbursement, will not be performed in the clinical arena.

Concern is continuously raised that PET is just "another imaging tool" that will not replace any previous modality. This may well be true, but delineation of tumor extent will permit a markedly improved staging process, and hopefully avoid unnecessary and non-therapeutic surgical procedures.

We anxiously await the opportunity as radiologists to illuminate the potential of PET and introduce the concept of functional imaging. Rhode Island is probably the last state in the union to acquire this technology, so I cannot construe that it is extravagant, but rather an important service to be provided to our patients. In this issue we hope to review how PET was acquired in this state, how the Department of Health determined PET was ready for clinical introduction and the mechanism they developed to ensure quality reading when the examinations begin. In addition, we will review the physics of PET, review the present indications for PET, which although mainly oncologic, do have some limited uses in neurologic and cardiac disease. And finally, we will explore the future potential for PET.

I trust you will find this issue useful and exciting as you look at cellular activity. This is our first probe into assessing cellular function.

References

1. Ronald Blasbey, MD., Director of Neuro-Oncology PET program at Memorial-Sloan Kettering Cancer Center, New York, New York.

John J. Cronan, MD, is Professor and Chairman, Department of Diagnostic Imaging, Rhode Island Hospital and Brown Medical School.

Correspondence:
John J. Cronan, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: Jcronan@lifespan.org

Positron Emission Tomography (PET): The Basics

Richard B. Noto, MD

"**Positron Emission Tomography** (**PET**) is the most important advance in biomedical science since the invention of the microscope."[1] While this may sound like excessive praise for a modality that has only recently proven itself in the clinical arena, this quote from Henry N. Wagner, Jr., MD, Director of the Division of Radiation Health Services at the Johns Hopkins Bloomberg School of Public Health and former Chief of Nuclear Medicine at Johns Hopkins, gives a sense of the vast potential of PET in the twenty-first century. As a clinical and research tool, PET has the capability of providing the medical community physiologic and molecular information that has heretofore not been available and that may improve the management of a wide variety of diseases. Already, PET is contributing new information to our understanding of oncology, cardiology, and neurology. All who are involved with this modality would agree that we have only begun to scratch the surface of the potential of PET imaging.

PET refers to the branch of nuclear medicine where a radioactive positron emitting radiopharmaceutical is administered to a patient for the purposes of producing tomographic images of the distribution of the radiopharmaceutical. The radio-isotopes that decay by positron emission include Fluorine-18, which is readily linked to a glucose analog to produce 2-(F-18) **fluoro-2-deoxyglucose** (**FDG**), and carbon-11, nitrogen-13, and oxygen-15, which have the advantage of being the atoms that are the basic building blocks of all physiologic processes.

The history of PET dates back to the discovery of the positron by Anderson and the invention of the cyclotron by Lawrence in the 1930s. The first positron-detecting camera was produced by Ter-Pogossian in the early 1970s and this technology was refined over the subsequent decades to the modern day PET camera.[2] While research studies with PET imaging date back almost 30 years, it was not until the advent of clinical studies with FDG in the late 1980s that the clinical potential of PET started to become apparent.[3] Multiple studies in the 1990s indicated the efficacy of PET in oncology and applications in cardiology and neurology were refined for clinical use.[4,5]

While it was becoming clear that PET was potentially a formidable clinical tool, its development was severely limited until the late 1990s by issues related to the production and availability of positron emitting radiopharmaceuticals. Positron emitting radio-isotopes can only be produced in sufficient quantity for medical use by a cyclotron: the high cost of purchasing and maintaining a cyclotron limited this technology to only a few sites in the country. Because all medically useful positron emitters are short-lived (half-life of 109 minutes for F-18, 20 minutes for C-11, 10 minutes for N-13, and 2 minutes for O-15), it is necessary to have a cyclotron in close proximity to the

TABLE 1. CURRENT MEDICARE APPROVED APPLICATIONS OF PET

Clinical Condition	Coverage
Solitary Pulmonary Nodules	Characterization
Lung Cancer (Non-small cell)	Diagnosis, Staging, and Re-staging
Esophageal Cancer	Diagnosis, Staging, and Re-staging
Colorectal Cancer	Diagnosis, Staging, and Re-staging
Lymphoma	Diagnosis, Staging, and Re-staging
Melanoma	Diagnosis, Staging, and Re-staging Not covered for evaluating regional nodes
Head and Neck Cancer	Diagnosis, Staging, and Re-staging Not covered for CNS and thyroid cancers
Breast Cancer	As an adjunct to standard imaging modalities in staging (patients with distant metastasis) and re-staging (patients with locoregional recurrence or metastasis) As an adjunct to standard imaging modalitiesfor monitoring tumor response to treatment for women with locally advanced and metastatic breast cancer when a change in therapy is anticipated.
Refractory Seizures	Pre-surgical evaluation only
Myocardial Perfusion	Noninvasive imaging of heart perfusion
Myocardial Viability	Primary or initial diagnostic study, or following an inconclusive SPECT, prior to revascularization (SPECT may not be used following an inconclusive PET scan)

Specific conditions apply to some of the above coverage policies. See the Blue Cross Blue Shield of RI Policy RI-2002-100 for further details.

imaging device since the activity will rapidly decay to too low a level to be clinically useful. However, once it became apparent that FDG had potentially major applications in oncology, a variety of manufacturers set up regional cyclotrons that could produce FDG and ship it rapidly to sites in that region. Currently, FDG is readily available in all urban areas throughout the US and many more rural areas also now have FDG access as well. Unfortunately, the shorter lived isotopes like C-11, N-13, and O-15 remain available only to those locations that have an on-site cyclotron. Another positron emitting radio-isotope, rubidium-82, has been used for evaluating myocardial perfusion and has an extremely short half-life (76 seconds), but can be produced from an on-site generator for immediate use on an as-needed basis.

FDG has become such an important agent in recent years because it allows the imaging of sites of active glucose metabolism. It is transported into cells that consume glucose and then undergoes phosphorylation to FDG-6-phosphate. In this form, it is retained in the cell and can be imaged with PET scanners. Under normal circumstances, there is intense uptake in the brain, which is an obligate glucose user, and variable degrees of normal uptake in the myocardium depending on serum glucose levels. In addition, a variety of pathologic processes lead to alteration of glucose metabolism. In the brain, sites of decreased glucose metabolism may be seen in patients with Alzheimer's disease and epilepsy. In the heart, areas of decreased perfusion that show increased glucose metabolism are indicative of viable myocardium that has switched from aerobic to anaerobic metabolism because of inadequate perfusion.

Because many cancers show markedly increased glucose metabolism, FDG can be utilized to visualize sites of active tumor. This is useful in staging because the whole body is visualized and sites of malignancy show up as areas of increased activity. However, PET with FDG is often even more useful in re-staging after treatment because it can differentiate residual tumor from scar tissue, which is often not possible with anatomic imaging modalities like CT and MR. Unfortunately, the downside of this ability to image physiology is some non-specificity; non-malignant processes such as infection and inflammation may also have increased glucose metabolism and therefore can show up as increased activity on an FDG PET scan.

FDG has become such an important agent in recent years because it allows the imaging of sites of active glucose metabolism.

While FDG is an extremely useful radiopharmaceutical, it is just the first in what will be a long line of PET imaging agents.

All positron emitting radio-isotopes produce emissions that are detectable by PET cameras through a process called annihilation. The positron that is emitted by the process of nuclear decay travels a very short distance in soft tissues before encountering an electron. This distance is determined by the energy of the positron and should be as small as possible for accurate localization and image production. For F-18, the energy of the positron is relatively low and the mean positron range in water is only 1.4 mm which is ideal for imaging purposes. When a positron of appropriate energy encounters an electron, the two annihilate, meaning that there is complete conversion of the positron-electron pair into energy in the form of two gamma photons. The two gamma photons produced in annihilation each have an energy of 511 keV and travel in opposite directions, 180 degrees from each other.

PET scanners are designed to detect these annihilation photons in a highly efficient manner. Most modern PET scanners consist of a ring of detectors which encircle the patient. For an event to be recorded, 511 keV photons must strike detectors that are 180 degrees opposed to each other within a very brief time period; such an event is called a coincidence event and a line of response is drawn between the two involved detectors. PET images are produced by generation of a large number of such lines of response, which are proportional to the concentration of the radiopharmaceutical in that particular location. The line of response data is then reconstructed into transaxial, coronal, and sagittal planes as well as three dimensional volume renderings using complex iterative reconstruction algorithms.

Numerous variables in the construction of PET cameras have a major impact on the quality of images that are produced. Probably the most important variable is the choice of a full ring detector system versus a modified dual head gamma camera. As PET radiopharmaceuticals began to become readily available, manufacturers devised methods for modifying conventional dual head gamma cameras with a thicker sodium iodide (NaI) crystal and computer improvements such that one could use these modified gamma cameras to image both single photon and positron emitting radiopharmaceuticals. While these cameras served as a first step into the world of PET imaging for many institutions, the resolution and sensitivity of these modified dual head units is not comparable to that of dedicated PET scanners and **CMS** (**Centers for Medicare and Medicaid Services**, formerly HCFA) has placed severe limitations on their reimbursement of studies performed on these cameras in the future.

Modern dedicated PET systems use one of four types of crystal material for their detectors. **Bismuth germanate** (**BGO**) has been the most commonly used detector material in large part due

to its very high density which is good at stopping and registering the high energy photons produced in PET. More recently, two new detector materials have reached the market which may eventually replace BGO. Both **gadolinium oxyorthosilicate (GSO)** and **lutetium oxyorthosilicate (LSO)** have characteristics that allow faster acquisitions with no loss of resolution compared with BGO. The fourth crystal material that is currently available is NaI, which is the least expensive but also the least effective choice for PET detectors. The resolution of modern BGO, GSO, or LSO PET cameras is approximately 4 mm.

The most recent innovation in PET systems is the hybrid PET/CT scanners. These units, which include both a dedicated ring detector PET system and a multi-slice CT scanner placed back-to-back in the same or immediately adjacent gantries, may eventually become the standard for PET imaging. These units have the advantage of superior attenuation correction algorithms by using the CT acquisition to correct the PET image and also allow near perfect co-registration of the PET and CT images. This means that the anatomic information from CT and the physiologic information available from PET can be viewed on a single image which has major advantages in confirming and localizing PET findings.

When PET was first utilized clinically, the potential applications were primarily neurologic and included evaluation of complex partial seizures prior to surgical therapy and evaluation of brain tumors, especially to differentiate recurrent tumor from radiation therapy. It was also apparent in the 1980's that PET could be useful for detection and evaluation of coronary artery disease and determination of myocardial viability. However, it has been the burgeoning oncologic applications for PET that have brought the modality to the forefront in the past few years and which continue to evolve rapidly at this time. The current list of applications for PET that are approved for reimbursement by CMS and the local Medicare carrier are listed in Table 1.[6]

The potential of PET is limitless. While FDG is an extremely useful radiopharmaceutical, it is just the first in what will be a long line of PET imaging agents. Because of the possibility of distribution through regional pharmacies as with FDG, a variety of F-18 labeled agents are under development, primarily for oncologic applications. Potentially even more intriguing are the C-11 agents which can be used to image various receptor and transporter systems in the brain as well as fatty acid metabolism in the heart. Further in the future, it is within the capabilities of PET to image DNA synthesis mechanisms and cellular proliferation as well as enzymes that may be important tumor targets.

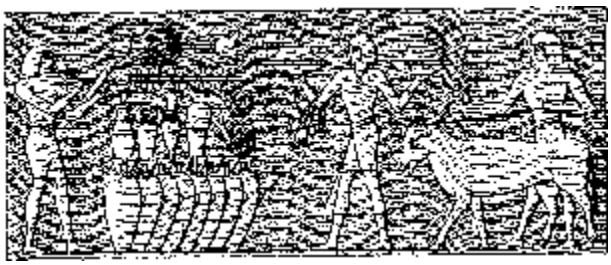
In summary, the PET applications that we are seeing in 2003 are just a small sampling of the future directions of this technology which will be an essential tool in the imaging armamentarium available to clinicians and researchers now and in the future.

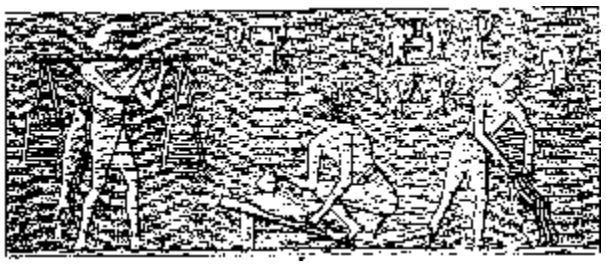
References

1. Wagner HN. Historical Outline. In: Wahl, RL, ed. *Principles and Practice of Positron Emission Tomography.* Philadelphia: Lippincott, Williams & Wilkins, 2002: xiii.
2. Ter-Pogossian MM. The origins of positron emission tomography. *Semin Nucl Med* 1992; 22:140-9.
3. Kessler RM, Partain CL, Price RR, James, AE. Positron emission tomography: prospects for clinical utility. *Invest Radiol* 1987; 22:529-37.
4. Coleman RE. Clinical PET in oncology. *Clinical Positron Imaging* 1998; 1:15-30.
5. Bar-Shalom R, Valdivia AY, Blaufox MD. PET imaging in oncology. *Semin Nucl Med* 2000; 30:150-85.
6. www.rimedicare.org/files/RI-2002-100.htm.

Richard B. Noto, MD, is Director of Nuclear Medicine, Department of Diagnostic Imaging, Rhode Island Hospital, and Clinical Assistant Professor of Radioloty, Brown Medical School.

Correspondence:
Richard B. Noto, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: RNoto@lifespan.org





PET: Oncological Applications

Jac D. Scheiner, MD

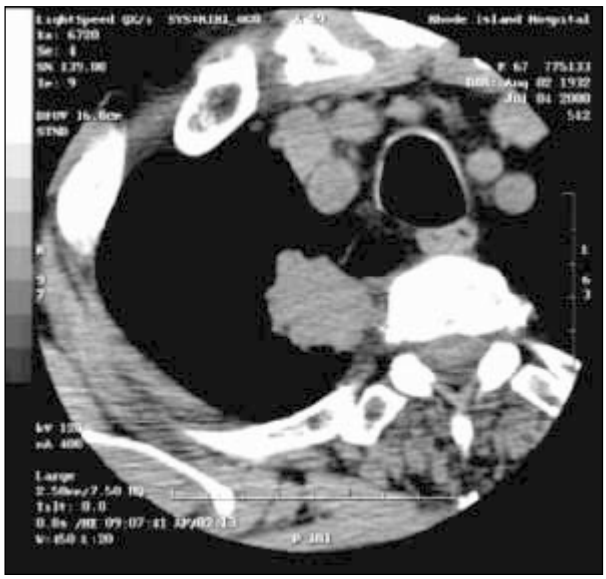
Positron Emission Tomography (PET) has many clinical applications. Most are in the oncologic arena. There are currently seven Medicare-reimbursable oncologic indications for performing PET scans; i.e., staging and restaging for cancer of the colon, head and neck (excluding CNS and thyroid), esophagus, lung, lymphoma, breast (distant to the axilla) and melanoma. PET has also been approved for evaluating the response of breast cancer to therapy, as well as to evaluate for the presence of malignancy in a pulmonary nodule.

PET is effective in cancer imaging because it is able to image radiolabelled glucose. Many types of cancers elaborate an increased amount of glucose receptors to obtain sufficient glucose to maintain their high metabolic rates. 18-**Fluoro-deoxyglucose [FDG]** is thus taken up by cancer cells in high amounts. FDG is then phosphorolated, which results in it staying in the cell without undergoing glycolysis. A PET camera images this phosphorylated version of FDG.

Intracellular FDG provides several advantages in oncologic imaging over 'morphologic' imaging modalities such as **computed tomography (CT)**. With CT, the possibility of a lymph node being involved with malignancy is typically not suggested unless it is enlarged (i.e. greater than 1 cm). Of course, there can be malignant involvement with smaller lymph nodes. However, to raise suspicion for malignancy in these smaller nodes would result in significantly decreased specificity, because these nodes are common even in normal patients. Freed of morphologic criteria, small nodes involved with malignancy can be detected on FDG PET scans.

PET is effective in cancer imaging because it is able to image radio-labelled glucose.

There are other advantages of FDG PET over CT or MRI. FDG PET can detect malignancy in tumor sites that have the same appearance as adjacent normal structures on CT. FDG PET also has the ability to differentiate post-therapeutic/surgical changes (such as scar, which is not metabolically active) from residual/recurrent neoplasm (which is metabolically active).



Case 1a - Patient with known right upper lobe lung cancer. CT demonstrates patients known lung cancer. No enlarged lymph nodes were noted on CT.

Limitations of PET in Oncology

Despite the widespread oncologic applications of FDG PET, several cautions should be noted.

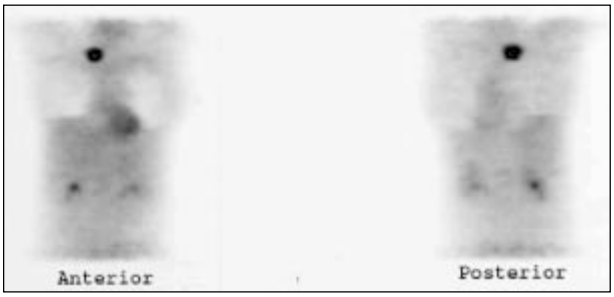
1. Some common cancers which are either not as metabolically active, do not elaborate significant amounts of glucose receptors, or are unable to retain FDG - Prostate cancer, BronchoAlveolar Lung Cancer, and Hepatocellular Carcinoma - are not well seen on FDG PET scans. In addition, small amounts of tumor [such as malignancy in <5 mm lung nodules or nodes] are not so easily detectable on FDG PET.

2. FDG PET scans tend to have decreased sensitivity in patients with diabetes. FDG PET scans can be performed in diabetic patients, although it more active tumors may need to be present before imaging is abnormal.

3. The brain typically takes up a significant amount of FDG on PET scans. This increased background makes it difficult to discern a focus of metastatic disease. MRI of the brain with i.v. contrast is thus superior to PET for detecting brain metastases.

4. CT of the chest is more sensitive for detecting very small lung metastases (especially those less than 5 mm) than FDG PET.

5. In addition to being taken up by sites of malignancy, FDG is also taken up by active granulomatous disease such as sarcoidosis and tuberculosis, as well as pneumonia. Thus, FDG



Case 1b - PET scan demonstrates increased metabolic activity in the right upper lobe, consistent with known lung cancer. No other areas of abnormal activity are seen. There is normal activity in the urinary tract and heart. The findings are consistent with a resectable lung cancer.

PET should not be used to distinguish malignancy from inflammatory disease.

6. As is true with all imaging studies, FDG PET scans should not be performed unless they can potentially change patient management. For example, if a patient with lung cancer has known diffuse metastatic disease to the bone, finding a few more sites of tumor on FDG PET will not change patient management. However, if a patient has potentially resectable lung cancer by CT and other modalities, FDG PET should be performed to ensure correct staging.

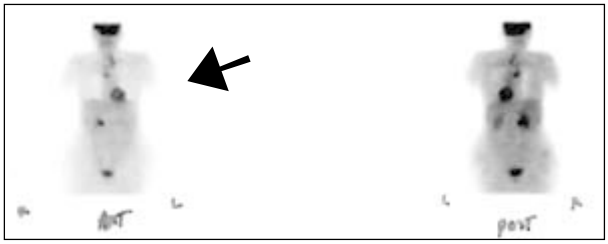
PET AND PUBLISHED ONCOLOGIC STUDIES

1. Lung Cancer

a. Lung Nodules – Approximately 80% of lung nodules will be benign granulomas or malignancies. The standard work-up of a nodule seen on a chest radiograph is to identify central calcification within the nodule indicating with benignity. If this finding can not be ascertained, the next step is to compare the chest radiograph to prior radiographs to document approximately 2-3 years of stability, consistent with benignity. If the possibility of malignancy persists, the next step is CT of the chest, which can detect benign central calcification within the nodule with a higher sensitivity than conventional radiographs.

If the possibility of malignancy persists after CT evaluation, the next step is to decide whether to biopsy the nodule or perform short term follow-up imaging with CT. FDG PET is a powerful triage tool. A nodule which demonstrates FDG uptake on PET typically warrants a biopsy. Alternately, a nodule without PET activity is *evaluated with short term follow-up imaging with CT*.

FDG PET is not recommended to evaluate nodules less than 5mm or a tumor that is not very metabolically active, such as bronchoalveolar cell carcinoma.[1] Thus, a negative PET scan should not stop the work-up of lung nodule. However, it provides greater confidence for triaging the patient to the 'follow-up imaging' arm of the lung nodule work-up, as opposed to biopsy.



Case 2 - PET scan demonstrates increased metabolic activity in the right paratracheal region, consistent with known lung cancer seen on CT. PET scan also demonstrates activity in the left cervical region, corresponding to normal sized lymph nodes on CT. Thus, this is now a non-resectable lung cancer.

When lung cancer is treated via radiation therapy and/or chemotherapy, post-treatment CT often cannot distinguish scar tissue from persistent cancer in residual masses.

A meta-analysis of PET studies of 1474 lung nodules/masses published from 1966-2000 showed that PET had an impressive 97% sensitivity for malignancy. [2] The specificity was 78%, thus emphasizing the importance of utilizing PET in the appropriate clinical context, such as not using this modality to distinguish malignancy from pneumonia.

b. Staging/Restaging of **Non-Small Cell Lung Cancer (NSCLC)** – A recent study of 102 patients who underwent invasive surgical staging of the mediastinal lymph nodes, chest CT and FDG PET, showed that the sensitivity/specificity for malignant lymph nodes was 95%/86% for FDG PET, vs. 75%/66% for CT.[3] Often, the FDG PET scan reveals previously unknown sites of metastatic disease that will obviate the need for a thoracotomy. A recent randomized controlled trial of 188 patients with NSCLC demonstrated that the futile thoracotomy rate (ie. those patients that underwent lung cancer resection and then demonstrated recurrence within 1 year) was 41% in patients who underwent non-PET staging vs. 21% for those staged with PET.[4]

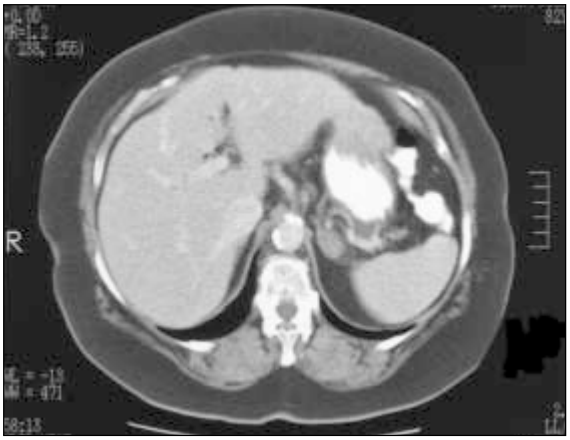
When lung cancer is treated via radiation therapy and/or chemotherapy, post-treatment CT often cannot distinguish scar tissue from persistent cancer in residual masses. PET is an ideal solution in this situation becauses live cancer cells usually take up FDG, whereas scar tissue does not. In a study of 126 patients with stage I – IIIb NSCLC, of whom 60 had persistent or recurrent tumor, the sensitivity/specificity for persistent or recurrent tumor was 100%/92% for FDG PET vs. 71%/95% for CT.[5] In addition, PET correctly predicted response to therapy in 96% of these 126 patients.

2. Esophageal Cancer

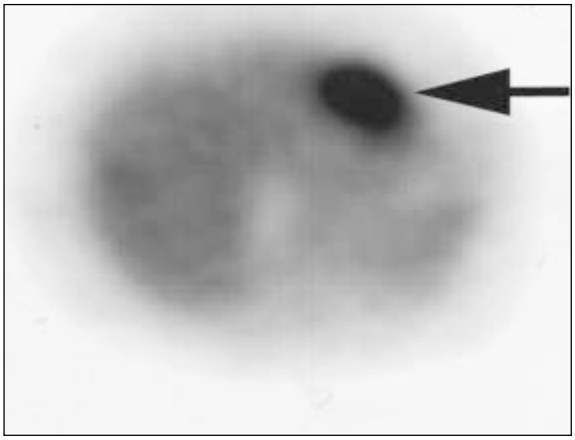
The main advantage of PET in staging esophageal cancer is its ability to accurately detect malignancy in non-regional lymph nodes which are not enlarged on CT or **endoscopic ultra-**

Approved Oncologic Indications – PET

- Staging and restaging of
  - colon cancer
  - head and neck
  - esophagus
  - lung
  - lymphoma
  - breast (distal and axial)
  - melanoma
- Evaluating response to therapy of beast CA



Case 3a - CT scan performed on patient with history of resected colon cancer and rising CEA was originaly read as negative.



Case 3b - PET scan demonstrates increased activity in the region of the gastrohepatic ligament, consistent with a site of recurrent tumor [arrow]. In retrospect, this mass was present on CT, although its appearance was similar to a non-distended gastric fundus.

sound (EUS). A recent prospective study was performed in which 42 patients all underwent PET, CT and EUS before surgical staging of espophageal cancer.[6] PET was less accurate for detecting malignancy in local regional lymph nodes (N1, N2) compared to combined CT and EUS, 48% vs. 69%. This was likely due to the higher sensitivity of EUS for detecting small regional nodes. However, the accuracy for distant nodal metastatic disease was greater for PET, 86% vs. 62%. This was mostly due to greater specificity of PET uptake, 90% vs. 69%.

3. Colorectal Cancer

A prospective, blinded study was performed on 115 patients with a history of colon cancer.[7] All had a clinical suspicion for persistent/recurrent colon cancer and underwent CT and PET. Compared to a gold standard of follow-up imaging and/or findings at surgery, the sensitivity/specificity of PET was 93%/98% vs. 69%/96% for CT. Impressively, PET scans were true positive in 12 (67%) of 18 patients with elevated serum carcinoembryonic antigen levels and negative CT findings.

4. Head and Neck Cancer

When a patient presents with malignant cervical lymph nodes, conventional forms of diagnostic imaging such as CT often fail to identify the primary tumor. As a result, patients may need to undergo neck dissection or radiation of both sides of the neck with random biopsies. PET scanning can reveal the site of the primary tumor preventing the adverse effects of random biopsies or unneeded radiation. In pooled data from 4 studies, which included 76 patients with malignant cervical lymph nodes and unknown primary despite CT, FDG PET correctly demonstrated the primary site in 30% of these patients.[8] [The review paper did not cite the percentage of false positives.]

In patients with malignant cervical lymph nodes, FDG PET allows for more accurate staging, which is essential for determining whether to perform dissection or radiation. A prospective, blinded study of 19 patients with malignant cervical lymph nodes was performed. [9] CT alone correctly staged 69% of patients, whereas CT and FDG PET combined correctly staged 92%.

5. Melanoma

FDG PET is useful in detecting sites of melanoma, but not in defining regional draining lymph nodes. Sentinel node biopsy is superior in these cases. A prospective, blinded study of 74 patients with melanoma (70 of whom had melanoma > 1mm in depth) was performed.[10] All had FDG PET scans followed by sentinel node biopsy as the gold standard. The sensitivity/specificity of FDG PET for malignancy in regional lymph nodes was 17%/96%.

For assessing sites of melanoma elsewhere, however, FDG PET has been shown to be superior to conventional imaging such as CT. A prospective study of 100 patients with high risk (>1.5 mm depth) melanoma was performed.[10] All underwent conventional imaging (which included CT) along with FDG PET. For sites of malignancy in the 52 patients who presented for initial staging, the sensitivity/specificity for FDG PET was 100%/94%, whereas conventional imaging did not detect any of the 9 sites of lymph nodes metastases. Among the 48 patients assessed for melanoma recurrence, the sensitivity/specificity for patients with recurrence was 100%/96% for FDG PET vs. 85%/68% for conventional imaging. For sites of recurrence, FDG PET was more sensitive to conventional imaging for detecting melanoma in the neck and abdomen (100% vs. 67% and 100% vs. 27% respectively), although CT was more sensitive for detecting small lung metastases (87% vs. 70%).

6. Lymphoma

Traditionally, patients with lymphoma underwent both CT and **Gallium Scintigraphy [GS]** at initial staging. The purpose of GS was twofold. GS allows true whole body imaging, from head to toe, and thus a larger field of view for detecting sites of active lymphoma than on CT. More importantly, most post-therapy lymphoma patients will have residual masses at original lymphoma sites on CT. The initial follow-up CT is unable to differentiate residual masses due to scar tissue vs. active lymphoma. However, if the initial GS demonstrated that the lymphoma is of a type that takes up Gallium, the GS can be repeated, with a lack of uptake indi-

cating scar tissue.

A number of studies have recently been published showing that not only can FDG PET be used for the same purposes that GS had been used in lymphoma patients, but also that FDG PET was more accurate than GS. A study was performed on 51 patients with lymphoma (38 non-Hodgkins, 13 Hodgkins).[11] All had FDG PET and GS (including single photo emission computed tomography), and the significance of discordant sites were determined via correlation with CT and other clinical exams (including follow-up imaging). FDG PET detected all 51 patients with active lymphoma, as well as all 158 known sites of disease in these patients. GS detected 72% of sites and 80% of patients with active lymphoma.

7. Breast

FDG PET at the current time does not play a role in differentiating benign from malignant breast lesions. There are no significant studies on FDG PET playing a discriminating role in populations with a < 50% prevalence of breast cancer who have lesions referred for biopsy. However, a meta-analysis of pooled data of 13 studies (n=606) with a >50% prevalence of breast cancer showed the sensitivity/specificity of FDG PET to be 89%/80% for primary breast malignancy.[12] Given the high costs of FDG PET compared to the less expensive, more accurate results of biopsy, FDG PET does not play a role in this realm.

Sentinel node biopsy is superior to FDG PET for staging the axilla. A meta-analysis was performed on 4 studies with a pooled patient population of 203 patients with breast cancer and non-palpable axillary lymph nodes.[12] All underwent FDG PET and sentinel node biopsy (as the gold standard). The sensitivity/specificity of FDG PET for detecting malignancy in the axilla was 80%/89%.

FDG PET has been approved for the staging/restaging of distant spread of breast cancer (beyond the axilla). A study was performed in which 48 breast cancer patients underwent both FDG PET and Tc-99m Bone Scans.[13] The accuracy of FDG PET for detecting metastatic lesions to bone was 95% vs. 79% for Bone Scans. This was likely related to the greater specificity of FDG PET for malignancy.

In another study, 57 breast cancer patients with suspicion of recurrence underwent whole body FDG PET.[14] Results were compared to a gold standard of biopsy, follow-up imaging of up to 2 years, and other diagnostic tests. The sensitivity/specificity for detecting patients with recurrence was 93%/79%.

FDG PET has also been approved for evaluating tumor response to treatment. A prospective study was performed on 40 patients with estrogen receptor positive breast cancer that was at least locally advanced.[15] Comparing the pre-therapy FDG PET to one obtained 7-10 days after the start of therapy, the sensitivity/specificity of FDG PET for predicting responders to therapy was 95%/89%.

The oncologic indications for PET continue to evolve. This is an area in evolution and formal indications are constantly changing

References:

1. Kim BT, Kim Y, Lee KS, et al. Localized form of bronchioloalveolar carcinoma: FDG PET findings. *AJR* 1998; 170:935-9.
2. Gould MK, Maclean CC, Kuschner WG , et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001; 285:914-24.
3. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *NEJM* 2000; 343:254-61.
4. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002; 359:1388-93.
5. Bury T, Corhay JL, Duysinx B, et al. Value of FDG-PET in detecting residual or recurrent nonsmall cell lung cancer. *Eur Respir J* 1999; 14:1376-80.
6. Lerut T, Flamen P, Ectors N, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: A prospective study based on primary surgery with extensive lymphadenectomy. *Ann Surg* 2000; 232:743-52.
7. Valk PE, Abella-Columna E, Haseman MK, et al. Whole-body PET imaging with [18F]fluorodeoxyglucose in management of recurrent colorectal cancer. *Arch Surg* 1999; 134:503-11.
8. http://cms.hhs.gov/coverage/8b3-hh2.asp
9. Myers LL, Wax MK. Positron emission tomography in the evaluation of the negative neck in patients with oral cavity cancer. *J Otolaryngol* 1998; 27:342-7.
10. Rinne D, Baum RP, Hor G, et al. Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. *Cancer* 1998; 82:1664-71.
11. Kostakoglu L, Leonard JP, Kuji I, et al. Comparison of fluorine-18 fluorodeoxyglucose positron emission tomography and Ga-67 scintigraphy in evaluation of lymphoma. *Cancer* 2002; 94:879-88.
12. http://www.cms.hhs.gov/coverage/download/8b1-g1.pdf
13. Yang SN, Liang JA, Lin FJ, et al. Comparing whole body (18)F-2-deoxyglucose positron emission tomography and technetium-99m methylene diphosphonate bone scan to detect bone metastases in patients with breast cancer. *J Cancer Res Clin Oncol* 2002; 128:325-8.
14. Moon DH, Maddahi J, Silverman DH, et al. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. *J Nucl Med* 1998; 39:431-5.
15. Mortimer JE, Dehdashti F, Siegel BA, et al. Metabolic flare: indicator of hormone responsiveness in advanced breast cancer. *J Clin Oncol* 2001; 19:2797-803.

Correspondence:

Jac D. Scheiner, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: Jscheiner@lifespan.org

Neurologic PET

Anthony F. Posteraro, MD, and Richard B. Noto, MD

Since the 1960s, functional brain imaging, using a variety of radiopharmaceuticals, has been utilized to non-invasively study neurological diseases in vivo. The initial pharmaceuticals used were labeled with various isotopes of radioiodine and technetium, allowing the pharmaceutical distribution to be localized using **single photon emission computed tomography (SPECT).**

Positron emission tomography (PET) has become a clinical reality with recent advances in instrumentation and radiopharmaceutical development. PET imaging offers markedly improved spatial resolution compared to standard SPECT imaging of the brain (4-5mm compared with 8-10mm) as well as the ability to directly image metabolism.[1] Positron-emitting radionuclides (^{18}F, ^{15}O, ^{13}N, ^{11}C) can be used to synthesize a variety of biologically important radiotracers because the elements used for labeling occur naturally in such compounds. The most widely used radiotracer, ^{18}F-**Fluorodeoxyglucose (FDG),** is a glucose analogue that images metabolism, providing a direct evaluation of the cerebral metabolic rate for glucose. In comparison to SPECT imaging, metabolic imaging combined with better inherent spatial resolution compared to conventional SPECT perfusion scans has revealed some extraordinary findings which may influence the management of patients with seizures, brain tumors, dementia, movement disorders, and other neuropsychiatric diseases. In the following discussion, various applications of PET will be reviewed with an emphasis on applications useful in clinical practice.

Technique

Neurologic PET requires some special preparation and attention to detail compared to imaging other areas of the body. For the majority of applications, ^{18}F-FDG is the primary radiopharmaceutical used. FDG is taken up in proportion to the regional cerebral metabolic rate for glucose, thus providing a map of cerebral metabolic activity. Following intravenous administration of FDG, the patient is allowed to rest quietly in a dimly lit room for 30 minutes during the uptake phase. External stimulation and cognitive processes will result in patterns of uptake corresponding to areas of neural activity. By minimizing external stimulation, the "background noise" of various areas of cortical activation can be eliminated, providing a uniform baseline for comparison. Typically an 'eyes and ears' open technique is used as uptake values are less variable under such circumstances.[2]

Neurologic PET imaging, used for a variety of research applications over the last two decades, is now emerging as a powerful clinical tool.

Other techniques used for cerebral PET imaging include perfusion imaging with ^{15}O-H_2O and imaging with radiolabeled neurotransmitters and receptor ligands. ^{15}O-H_2O is a freely diffusible radiotracer and can provide imaging of cerebral perfusion. In addition, ^{15}O has a half-life of 2 minutes, so the tracer is rapidly cleared from the patient by positron decay, allowing multiple scans to be obtained in a short period of time. While beneficial for research purposes, the short half life requires an on site cyclotron and limits clinical applications.[3] Radiolabeled neurotransmitters are mostly used for research applications, though ^{18}F Fluorodopa has shown great clinical promise in its ability to image the dopaminergic neurotransmitter system.

Dementia

Dementia is usually defined as a decline in multiple cognitive functions such as memory, language and visuospatial ability sufficiently severe to interfere with daily life. There are several distinct clinical dementia and dementia like syndromes; the most common is Alzheimer disease. PET can be used to help distinguish different types of dementias, which may be particularly helpful early in the course.

Alzheimer's disease has become a major problem as our population ages. About 8% of the population over 65 will have Alzheimer disease; this rises to over 30% for people older than 85.[4] Therapy tends to work best and prolong independent living the longest when started early in the course of the disease, when the clinical diagnosis is most challenging. PET offers an accurate means of evaluating patients for Alzheimer disease. A recent report by the members of

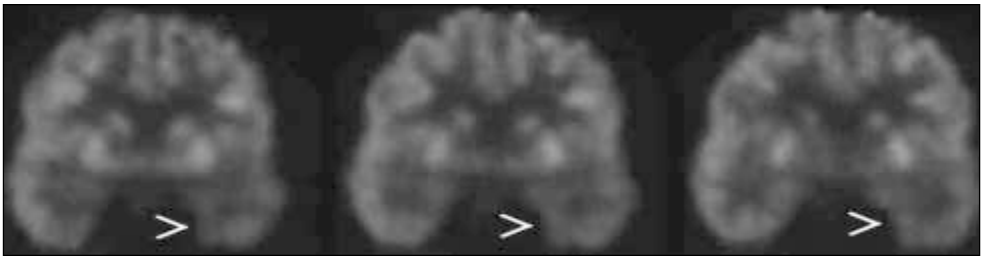


Fig. 1. There is decreased interictal FDG uptake within the left temporal lobe of this patient with medically refractory epilepsy (arrows). No other foci of abnormal cortical activity were localized. The patient subsequently underwent successful left temporal lobectomy for treatment.

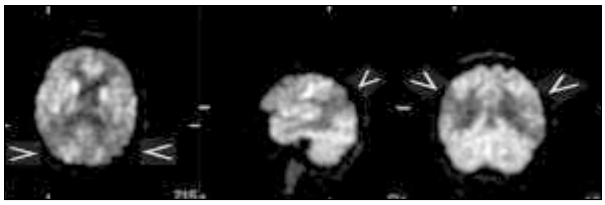


Fig. 2. Transaxial, sagittal and coronal FDG PET images in a patient with Alzheimer's Disease showing bilateral temporo-parietal defects (arrows). Images courtesy of Abass Alavi, MD, Hospital of the University of Pennsylvania.

the Quality Standards Subcommittee of the American Academy of Neurology concluded that "PET scanning appears to have promise for use as an adjunct to clinical diagnosis of Alzheimer disease." Their review of published studies showed diagnostic specificity of 86%-100% for F18 FDG PET.[6]

PET imaging in Alzheimer disease demonstrates decreased metabolic activity in the mesial temporal lobes as well as the posterior temporal and parietal lobes. With time this progressively worsens and also involves the frontal lobes. This contrasts with the "frontal lobe dementias" such as Pick disease, which presents with decreased metabolic activity in the frontal lobes, followed by decreased metabolic activity in the temporal and parietal lobes. End stage Alzheimer disease and frontal lobe dementias have overlapping findings, which is why brain PET is most sensitive and specific for evaluating dementia early in the disease.

Brain Tumors

Primary malignant brain tumors are mostly gliomas, with histologic grade ranging from low grade astrocytomas to high grade tumors such as glioblastoma multiforme. In general, patients with lower grade tumors live longer while patients with higher grade tumors have a dismal prognosis (2% 5 year survival for glioblastoma multiforme).[7] Gliomas tend to be infiltrating heterogeneous tumors with areas of varying grade spread within the tumor mass. In addition, the distribution of the tumor does not always correspond to the area of enhancement or T2 abnormality seen on MRI. FDG PET, in conjunction with conventional MRI, can accurately image the spatial distribution of the tumor as well as determine areas of higher and lower grade tumor for better localization at the time of biopsy.[8]

The degree of FDG uptake within brain tumors is directly related to tumor grade as described by the **World Health Organization (WHO)** grades I-IV. Measurements of **tumor to white matter (T:WM)** and **tumor to grey matter activity (T:GM)** can distinguish low grade (WHO grade I and II) from high grade tumors (WHO grade III and IV). High grade tumors are detected by a T:WM ratio greater than 1.5 and T:GM ratio greater than 0.6 with a sensitivity of 94% and specificity of 77%.[9] In addition, FDG PET has proven useful for differentiating recurrent tumor from radiation necrosis in patients with treated gliomas.

In general, high grade tumors tend to mimic the intensity of grey matter uptake while low grade tumors mimic the intensity of white matter uptake, making co registration of images with MRI for anatomic localization necessary for accurate staging of brain tumors with FDG PET. Because of the high background activity within the brain observed with FDG PET, detection of metastatic disease to the brain is difficult with recent literature giving brain PET a sensitivity of 61% for detecting cerebral metastatic disease.[10] The only exceptions include lymphoma and melanoma. These tumors have greater specific uptake than grey matter and can be readily discerned from background brain activity.[11] PET can be used to stage primary brain lymphoma and has been used to differentiate cerebral toxoplasmosis from lymphoma in patients with AIDS. For most applications, contrast enhanced MRI remains a more sensitive screen of the CNS for metastatic lesions in patients with a primary neoplasm elsewhere.

Epilepsy

Epilepsy has a prevalence of 0.5% to 1.0% with rare patients having frequent seizures unresponsive to medications. In patients with focal EEG abnormalities, a single hypometabolic region can be identified in 55% to 80% of patients interictally using FDG PET.[12] During a seizure these regions are hyperactive. In those patients who have medically refractory focal onset seizures, surgical removal of the epileptic focus can be effective in controlling the seizure disorder. Interictal PET and ictal perfusion SPECT imaging have similar sensitivity and specificity for localizing seizure foci; however, interictal imaging is easier to perform and eliminates the need for hospitalization and monitoring while waiting for a seizure to occur.[13] Because of the short-half life of FDG, ictal PET imaging is logistically impractical.

Pre-surgical ealuation for epilepsy surgery is the only neurologic application approved by the **Centers for Medicare and Medicaid Servces (CMS)** (formerly the HCFA, the Health Care Financing Administration).

Movement Disorders

Recently, ^{18}F-Fluorodopa has become clinically available for evaluating Parkinson disease. Fluorodopa images the dopaminergic neurons in the striatum allowing accurate objective quantification of nigrostriatal function. With time there is progressive loss of dopaminergic activity within the striatum as Parkinson disease progresses. Findings on Fluorodopa PET imaging have been shown to correlate with disease progression as well as the likelihood of treatment response.[14] Fluorodopa PET will likely find clinical utility in differentiating Parkinson-like disorders from Parkinson's disease, as well as monitoring progression.

PET has a role only in research on Huntington's Disease at this time.[15]

Conclusions

Neurologic PET imaging, used for a variety of research applications over the last two decades, is now emerging as a powerful clinical tool. Currently the only CMS approved indication for PET imaging of the brain is pre-surgical seizure evaluation. There is, however, a body of evidence demonstrating PET's utility in accurately evaluating early dementia and Parkinson disease,

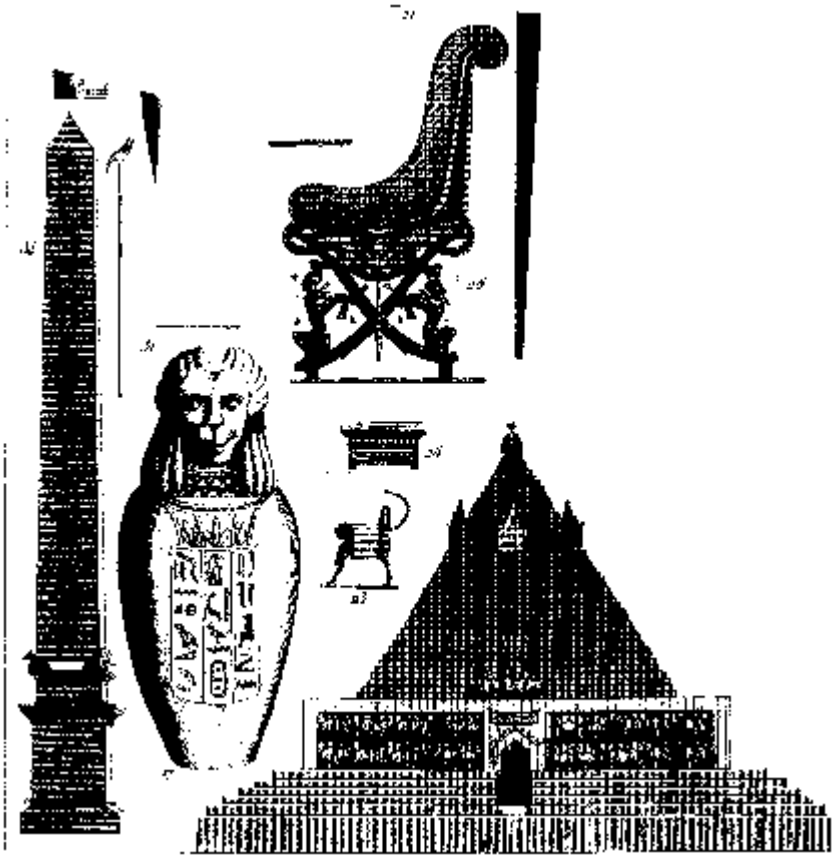
as well as staging and restaging brain tumors. Acceptance of PET by CMS for reimbursement has revolved not about PET's accuracy but whether PET diagnosis is cost-effective and improves clinical management compared with clinical diagnosis alone. Recent decision analysis supports such a role for neurologic PET imaging and as therapies for dementia and other neurologic diseases improve, PET's role will likely increase as an accurate, non-invasive means of evaluating various neurologic disorders.[16]

Anthony F. Posteraro, MD, is Senior Resident, Department of Diagnostic Imaging, Rhode Island Hospital.

Richard B. Noto, MD, is Director of Nuclear Medicine, Department of Diagnostic Imaging, Rhode Island Hospital, and Clinical Assistant Professor of Radiology, Brown Medical School.

References

1. Budinger TF. Future developments in poitron emission tomography for incorporation into the clinical sphere. *Invest Radiol* 1993; 28 (suppl 3): S142-3.
2. Mazziotta JC, Phelps ME, Carson RE, Kuhl DE. Tomographic mapping of human cerebral metabolism: sensory deprivation. *Arch Neurol* 1976; 33: 523-6.
3. Van Heertum RL, Tikofsky RS. *Functional cerebral SPECT and PET imaging, 3rd ed.* Philedelphia PA: Lippincott Willims & Wilkins, 2000.
4. Bachman DL, Wolf PA, Linn RT. Incidence of dementia and probable alzheimer's disease in a general populace: the Framingham study. *Neurol* 1993; 43: 515-9.
5. Knopman DS, DeKosky ST, Cummings JL. Practice parameter: diagnosis of dementia (an evidence-based review) – report of the quality standards subcommittee of the American academy of neurology. *Neurol* 2001; 56: 1143-53.
6. Hagge RJ, Wong TZ, Coleman, RE. Positron emission tomography brain tumors and lung cancer. *Radiol Clin N Amer* 2001; 39: 871-81.
7. Pirotte B, Goleman S, Bidaut LM. Use of positron emission tomography (PET) in stereotactic conditions for brain biopsy. *Acta Neurochir* 1995;134: 79-82.
8. Delbeke D, Meyerowitz C, Lapidus RL. Optimal cutoff levels of F-18 fluorodeoxyglucose uptake in the differentiation of low-grade from high grade brain tumors with PET. *Radiol* 1995; 195: 47-52.
9. Rohren EM, Provenzale JM, Barboriak DP, Coleman RE. Screening for cerebral metastases with FDG PET in patients undergoning whole-body staging of non-central nervous system malignancy. *Radiol* 2003; 226: 181-7.
10. Roelcke U, Leenders KL. Positron emission tomography in patients with primary CNS lymphomas. *J Neuro-Oncol* 1999; 43: 231-6.
11. Henry TR, Sutherling WW, Engel J Jr. Interictal cerebral metabolism in partial epilepsies of neocortical origin. *Epilepsy Res* 1991; 10: 174-82.
12. Ho SS, Berkovic SF, Berlangieri SU, et al. Comparison of ictal SPECT and interictal PET in the presurgical evaluation of temporal lobe epilepsy. *Ann Neurol* 1995; 37: 738-45.
13. Brooks DJ. PET studies and motor complications in Parkinson's. *Trends Neurosci* 2000; 23(10 Suppl): S101-8.
14. Hayden MR, HewittK, Stoessl AJ. The combined use of positron emission tomography and DNA polymorphisms for preclinical detection of Huntington's disease. *NEJM* 1987; 317: 3823.
15. Silverman DHS, Gambhir SS, Huang HW. Evaluating early dementia with and without assessment of regional cerebral metabolism by PET: A comparison of predicted costs and benefits. *J Nuc Med* 2002; 43: 253-66.



Correspondence:
Anthony F. Posteraro, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: Aposteraro@lifespan.org

Cardiac Applications of Positron Emission Tomography (PET)

Richard B. Noto, MD

One of the first clear clinical indications for **Positron Emission Tomography (PET)** imaging was in the evaluation of cardiac disease. PET techniques to evaluate both myocardial perfusion and myocardial viability have been available for several years and have been proven to be accurate and reliable. While cardiac PET has not seen the growth in volume that has occurred in oncologic PET, there is tremendous potential for future applications of cardiac PET and it is likely that PET will play a role in the evaluation of a variety of cardiac disease processes in the future.

Coronary blood flow can be evaluated by PET with a variety of tracers. In research applications, both O-15 water and N-13 ammonia have been used for many years to evaluate myocardial perfusion. O-15 water is probably the most accurate tracer available for quantifying myocardial perfusion. This radiopharmaceutical freely diffuses across cell membranes in the myocardium giving a highly accurate reflection of myocardial blood flow. However, because of rapid equilibration of the tracer between tissue and vascular spaces, sophisticated techniques to separate myocardial from blood pool activity are necessary.[1]

N-13 ammonia is an excellent tracer for imaging myocardial blood flow and, after passively diffusing into the myocardium in proportion to perfusion, is incorporated in myocardial cells in the form of glutamine. Because of its high extraction and target to background ratio, N-13 ammonia yields the best imaging quality of the agents available for PET myocardial perfusion imaging and can also be used to quantify myocardial blood flow.[1] However, both O-15 water and N-13 ammonia are rarely utilized in the clinical setting because of their short half-life and need for cyclotron production. The half-life of O-15 is only 110 seconds and the half-life of N-13 is 10 minutes, meaning that they decay very quickly to levels that are too low for imaging purposes. These very short half-lives limit the utilization of these tracers to facilities that have on-site cyclotrons immediately adjacent to their PET scanners.

Because of the logistical issues related to the short half-lives, the most commonly used tracer for PET myocardial perfusion imaging is neither O-15 water nor N-13 ammonia. Instead, rubidium-82 is the agent that has proven most practical in some centers. While rubidium-82 also has a very short half-life of 76 seconds, it is produced from strontium-82 via a commercially available generator which can be purchased and kept on site. Each generator can produce adequate doses of rubidium-82 for about a month. Therefore, there is no need for an on-site cyclotron. Rubidium-82 is approved by the FDA. While the generators are expensive, they may prove cost-effective for sites that are performing high volumes of myocardial perfusion studies.[2]

Like thallium-201, rubidium-82 is an analogue of potassium. It is rapidly and efficiently extracted from the blood pool by the myocardium and localizes in the myocardium in proportion to regional coronary blood flow. Because of its extremely short half-life, it is possible to give large doses (50-60 mCi) of rubidium-82 for each portion of the study. Combining this with the high imaging quality of PET cameras, excellent myocardial perfusion images can be obtained in very short acquisition times.[2] Because of the rapid acquisition time and the fact that the rubidium-82 activity decays so rapidly, it is possible to perform a routine rest/stress myocardial perfusion scan in less than one hour (Figure 1).

In most studies, PET myocardial perfusion imaging has demonstrated a high sensitivity for coronary artery disease in the range of 85-95% as well as specificity in the range of 80-90%.[3,4] In studies that have compared PET and SPECT myocardial perfusion imaging, PET has usually been shown to be more accurate, especially with regard to specificity, although the differences are not great.[5] Advantages of PET imaging over SPECT include higher count rates and better image quality, superior attenuation correction algorithms, and greater ability to quantify myocardial blood flow and flow reserve. Studies have also shown more accurate localization of coronary artery disease and greater interpreter confidence with PET.

While PET has some advantages over SPECT for myocardial perfusion imaging and is probably the best non-invasive study to evaluate myocardial perfusion, the use of PET for this purpose has not been widespread. This has clearly been because of cost considerations; in addition to the cost of the PET camera, the radiopharmaceutical costs are significant even if one uses a rubidium generator. However, recent studies have indicated that PET, with its high specificity for coronary artery disease, can be cost-effective, especially in those with an intermediate pre-test probability. For those with high pre-test likelihood of coronary artery disease, coronary angiography remains the most cost-effective choice.[6]

The other primary application of PET in cardiac disease is the evaluation of myocardial viability. In patients with coronary artery disease leading to left ventricular dysfunction and heart failure, the decision as to whether to attempt revascularization can be a difficult one. Patients with severe left ventricular dysfunction have increased morbidity and mortality, but these patients are also at higher risk of complication from surgical revascularization procedures. Therefore, it is important to have a non-invasive study that can accurately predict which patients will have significant improvement in left ventricular function after revascularization. At the present time, PET is the most accurate non-invasive procedure available for this purpose.

The PET evaluation of myocardial viability is dependent on the varying

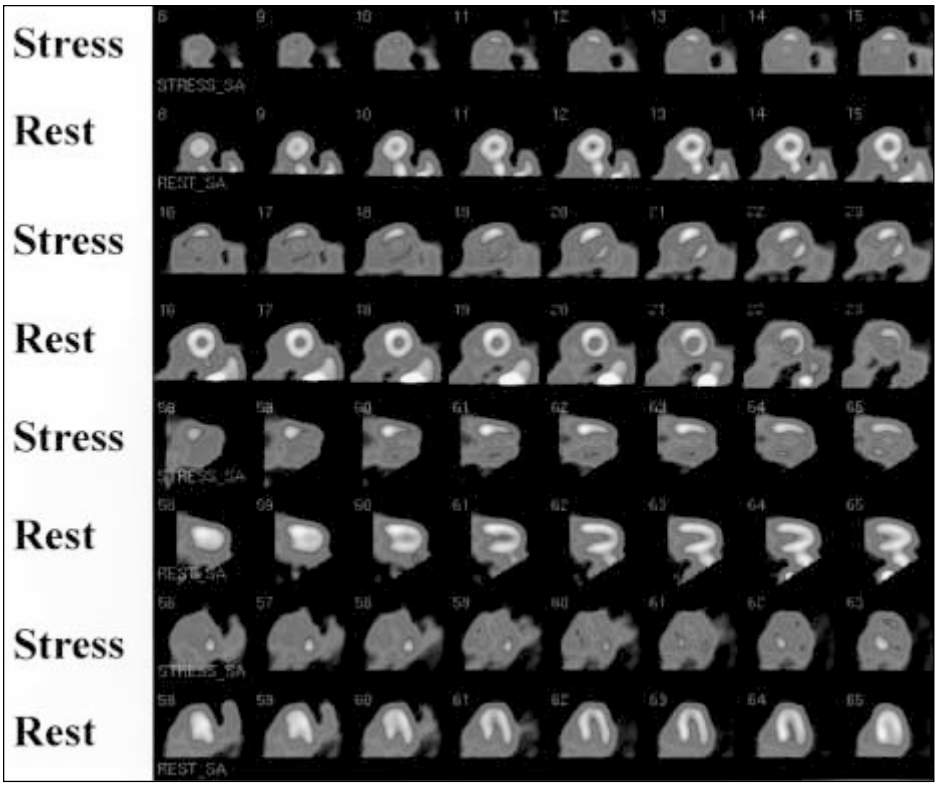


Figure 1. Stress-Rest rubidium-82 perfusion images in a 69 year old male with known CAD and chest pain. Images reveal reversible perfusion defects in the apex, inferior wall, septum and lateral wall indicative of ischemia.

methods of energy metabolism in the heart in different circumstances. In normally perfused myocardium, oxidative metabolism of fatty acids is the predominant means of energy production in the fasting state. In patients recently fed, glucose becomes the predominant metabolic substrate. If myocardial ischemia is present, oxidative metabolism is reduced and anaerobic glycolysis of glucose is the primary means of energy production.

The positron emitting radiopharmaceutical F-18 **fluorodeoxyglucose (FDG)** is ideal for evaluating glucose metabolism in the myocardium. FDG is transported into myocytes by glucose transporters, GLUT-4 and GLUT-1. In the myocyte, FDG undergoes phosphorylation by hexokinase to FDG-6-phosphate. The FDG-6-phosphate undergoes little further metabolism and effectively becomes trapped in the myocyte in proportion to glucose uptake.[7]

The main purpose of FDG imaging in the heart is to identify dysfunctional but viable myocardium. The term "hibernating myocardium" applies to areas of the myocardium that have chronically reduced blood flow at rest and impaired contractile function, but maintain viability. The term "myocardial stunning" refers to episodes of acute decreased myocardial blood flow and ischemia that may lead to myocardial dysfunction due to reperfusion injury. Repeated episodes of myocardial stunning may also cause abnormalities of contractile function despite the presence of viable myocardium and may represent a continuum with "hibernating myocardium." These viable areas will often return to normal functional status if a revascularization procedure is performed and therefore it is very important to differentiate patients with dysfunctional but viable myocardium from those with scar that will not improve despite revascularization.

*The positron emitting radiopharmaceutical F-18 **fluorodeoxyglucose (FDG)** is ideal for evaluating glucose metabolism in the myocardium.*

While cardiac PET with FDG is probably the most useful non-invasive tool for making this distinction, logistical issues make performance and interpretation of cardiac FDG studies difficult. In particular, the myocardial uptake of FDG is very dependent on the serum glucose level. In the fasting state, there is little overall uptake of FDG in the myocardium because of the predominant fatty acid metabolism and the uptake that is present is often heterogeneous with relatively less normal uptake in the septum than in the lateral wall. To combat this problem, an oral load of glucose can be administered to the patient before the FDG to increase insulin levels; insulin stimulates the myocardial uptake of FDG which usually improves image quality. However, excessive levels of serum glucose may compete with FDG for myocardial uptake and thereby decrease myocardial FDG uptake. In an ideal case, the serum glucose should be maintained below 140 mg/dL and it may be necessary to administer insulin intravenously to titrate the glucose to the correct level. Even with these measures, it is often difficult to achieve maximal cardiac FDG uptake and image quality in diabetic patients. Other approaches to maximizing myocardial FDG uptake include the use of the hyperinsulinemic-euglycemic clamp and, more recently, the use of nicotinic acid derivatives.[8]

Imaging techniques for myocardial viability PET usually include a scan to evaluate myocardial perfusion as well as a myocardial FDG scan. The perfusion scan is usually a resting study performed either with SPECT agents like Tc-99m sestamibi or Thallium-201 chloride or a perfusion PET scan performed with one of the

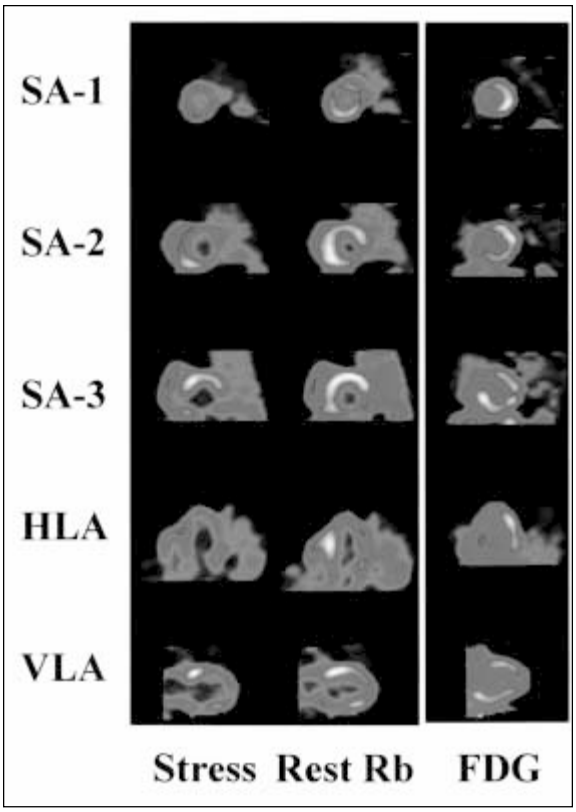


Figure 2 - Stress and rest rubidium-82 PET myocardial perfusion images and FDG PET images in the same patient. The perfusion images show extensive partially reversible perfusion defects in the septal, inferior, lateral, and antero-apical regions. The FDG images show areas of perfusion-metabolism mismatch in the lateral and infero-basal regions (arrows) indicating hibernating but viable myocardium

radiopharmaceuticals described above like rubidium-82. The perfusion images are then compared with the FDG images to evaluate the amount of glucose uptake in regions of decreased myocardial perfusion.

The classic pattern described in the case of viable, but hibernating myocardium is the "perfusion-metabolism mismatch" (Figure 2). In this circumstance, the resting perfusion to a segment of the myocardium is reduced, but there is preserved FDG uptake. The FDG uptake in this segment may be equal to the rest of the myocardium or greater than the myocardial uptake elsewhere in the heart, but in either case is indicative of viable myocardium. The relatively increased FDG uptake is felt to be due to greater glucose metabolism in the hibernating segment. Areas of "perfusion-metabolism mismatch" usually show improvement in contractility after revascularization procedures.

In the case of scarring, the perfusion and the FDG are both reduced, resulting in a "perfusion-metabolism match". The reduction in uptake of these tracers may either be severe in the case of transmural infarctions or mild in the case of non-transmural MIs. In general, segments that showed a "perfusion-metabolism match" do not show significant improvement in function after revascularization. It is also possible to have a "partial mismatch" where FDG uptake is decreased but not as much as perfusion and this likely represents a combination of scar and hibernating myocardium .[7,9]

Many studies have looked at the accuracy of PET in predicting functional improvement after revascularization procedures. Overall, the positive predictive value for significant functional recovery with a "mismatch" pattern is about 75%, the negative predictive value of a "match" pattern is about 85%, and the accuracy of PET in predicting functional recovery is about 80% .[9-14] Improvement after revascularization sometimes take months to occur. In comparison to resting thallium-201 scintigraphy, which is also used to determine viable myocardium, PET shows viability in approximately 30-45% of segments that show fixed thallium defects.[1]

In addition, PET evidence of viability has been shown in several studies to be an excellent indicator of event rate post-revascularization.[7,10,14] In those with PET evidence of significant viable, but dysfunctional myocardium, the rate of serious cardiac events was much lower in patients who were subsequently treated with revascularization rather than medical therapy. In those without viable, but dysfunctional myocardium by PET, there was no significant difference between the cardiac event rate between the revascularization and the medical therapy groups. This suggests that PET can be accurately used to suggest which patients would be amenable to revascularization therapy.

In summary, PET has tremendous potential for cardiac applications in the near future. While it has already been shown to be very useful as a perfusion tracer, costs associated with the study have limited the use of PET in myocardial perfusion imaging. In determining myocardial viability, FDG PET appears to be an accurate, non-invasive predictor of improvement after revascularization and should play an increasingly important role in deciding which patients undergo revascularization procedures in the future.

Acknowledgement: Figures 1 and 2 were provided by Dr. Josef Machac, New York University–Mt. Sinai Medical Center.

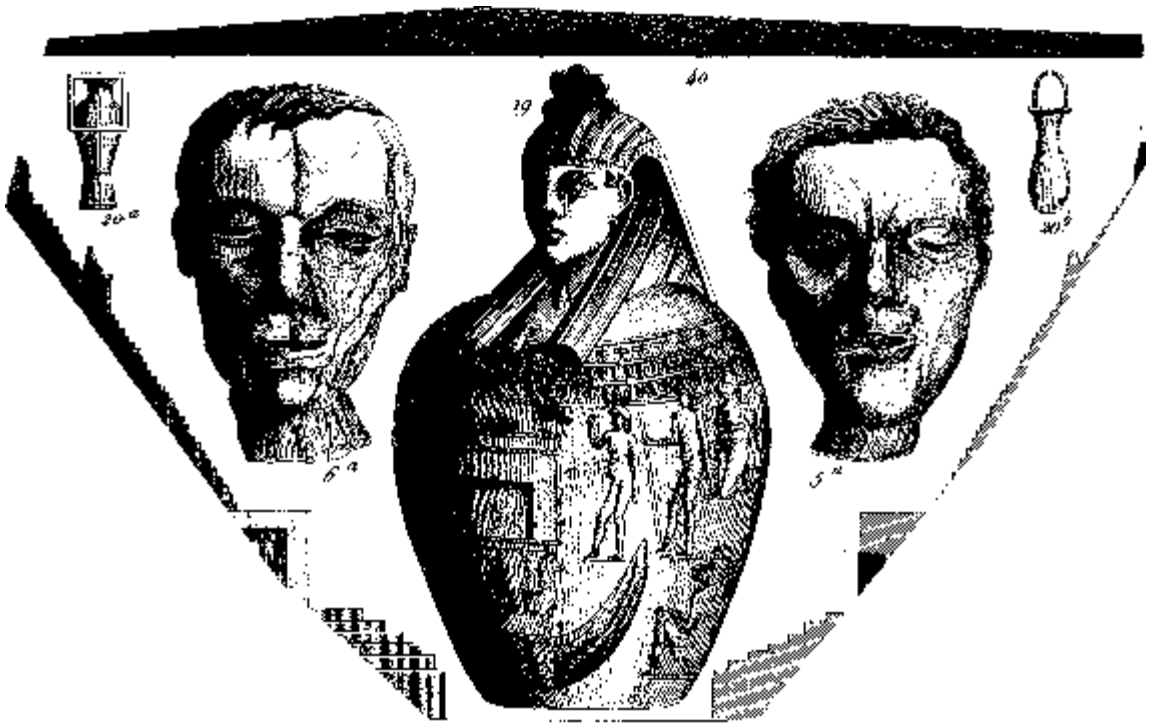
References

1. Schwaiger, M, Hutchins, GD. Evaluation of coronary artery disease with positron emission tomography. *Semin Nucl Med* 1992; 22:210-23.
2. Tamaki, N, Ruddy, TD, deKamp, R, Beanlands, RSB. Myocardial perfusion. In: Wahl, RL, ed. *Principles and Practice of Positron Emission Tomography*. Philadelphia: Lippincott, Williams & Wilkins, 2002: 320-33.
3. Schelbert H, Wisenberg G, Phelps M, et al. Noninvasive assessment of coronary stenoses by myocardial imaging during pharmacologic coronary vasodilation. VI: Detection of coronary artery disease in man with intravenous 13-NH3 and positron computed tomography. *Am J Cardiol* 1982; 49:1197-207.
4. Williams BR, Mullani NA, Jansen DE, Anderson BA. A retrospective study of the diagnostic accuracy of a community hospital-based PET center for the detection of coronary artery disease using rubidium-82. *J Nucl Med* 1994; 35:1586-92.
5. Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging

utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990; 31:1899-905.
6. Patterson RP, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. *Circulation* 1995; 91:54-65.
7. Beanlands RSB, Ruddy TD, Maddahi J. Myocardial viability. In: Wahl, RL, ed. *Principles and Practice of Positron Emission Tomography*. Philadelphia: Lippincott, Williams & Wilkins, 2002:334-50.
8. Parker JA. Cardiac nuclear medicine in monitoring patients with coronary heart disease. *Semin Nucl Med* 2001; 31: 223-37.
9. Bax JJ, Visser FC, Elhendy A, et al. Prediction of improvement of regional left ventricular function after revascularization using different perfusion-metabolic criteria. *J Nucl Med* 1999; 40:1866-73.
10. Di Carli MF, Asgarzadie F, Schelbert HR, et al. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. *Circulation* 1995; 92:3436-44.
11. Shivalkar B, Maes A, Borgers M, et al. Only hibernating myocardium invariably shows early recovery after coronary revascularization. *Circulation* 1996; 94:308-15.
12. Vom Dahl J, Altehoefer C, Sheehan FH, et al. Effect of myocardial viability assessed by technetium-99m-sestamibi SPECT and fluorine-18-FDG PET on clinical outcome in coronary artery disease. *J Nucl Med* 1997; 38:742-8.
13. Gambhir SS, Czernin J, Schwimmer J, et al. A tabulated summary of the FDG PET literature. Cardiac applications: Myocardial viability. *J Nucl Med* 2001; 42:70S-1S.
14. Schelbert HR. 18-F-Deoxyglucose and the assessment of myocardial viability. *Semin Nucl Med* 2002; 32:60-9.

Richard B. Noto, MD, is Director of Nuclear Medicine, Department of Diagnostic Imaging, Rhode Island Hospital, and Clinical Assistant Professor, Brown Medical School.

CORRESPONDENCE:
Richard B. Noto, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: Rnoto@lifespan.org



Future Advances and Applications in Positron Emission Tomography

Don Yoo, MD, and Richard B. Noto, MD

While **positron emission tomography** (**PET**) is already a useful clinical tool in a variety of areas, many advances are on the horizon which will further improve this technology, including **PET/CT** (**positron emission tomography/computed tomography**) technology, better imaging, and new radiotracer agents.

PET/CT is one of the most exciting technologic advances in radiology. PET alone gives physiologic information but is limited by spatial resolution and anatomic landmarks. CT alone gives anatomic information but cannot give functional or metabolic information. PET/CT is often described as fusion or hybrid imaging because it combines the advantages of these two different imaging modalities and incorporates their features into a new composite imaging modality. The composite image, containing overlayed voxels of data, produces an image reflecting both biologic and anatomic processes occurring at the molecular level in internal structures .[1,2]

A whole-body PET/CT scan takes about thirty minutes to perform. The data are integrated to produce a composite image. The quality of the images is higher than a conventional PET scan alone because the incorporation of CT improves attenuation correction resulting in a more accurate image. The study is also performed faster because the use of CT algorithms allows for faster attenuation correction.[1]

Because this is a new technology, research directly comparing the sensitivity and specificity of PET/CT with PET and CT performed separately (interpretation performed with both PET and CT images) is not yet available. The costs of a combined scanner cost more than each purchased separately.

New crystal technology has been crucial to the advancement of PET imaging. Crystals convert high-energy photons into flashes of light that are recorded, transmitted, and assembled into images. In order for a PET scan image to be produced, an incident photon has to interact with a detector causing a light flash detected by a photomultiplier tube behind the crystal. Smaller crystals allow a greater number of detectors, increasing the resolution. The most commonly used crystals have been NaI (sodium iodide) or **bismuth germinate oxide** (**BGO**). BGO crystal based PET scanners are currently the most common. The advantage of the BGO crystal is that it has the best efficiency in stopping the incident photon (stopping power) but it suffers from poor light output, long photoflourescent decay times and poor energy resolution. New LSO (lutetium oxyorthosilicate) and GSO (gadolinium oxyorthosilicate) crystals have been developed which, while having slightly poorer stopping power, more than compensate with better light output, markedly shorter photoflourescent decay times, and superior energy resolution, producing a better image in less time.[3-5]

New radiotracers have emerged that will increase the use of PET. ^{11}C-methionine has shown encouraging results in a variety of tumors because amino acid metabolism is increased due to an increased protein synthesis rate. ^{11}Carbon labeled tracers have shown some promise. The limitation is the half-life of 20 minutes, requiring an on-site cyclotron. Another ^{11}C labeled agent, ^{11}C-choline has shown promise in prostate and bladder cancer. ^{11}C-choline is a component of phosphatidylcholine, one of the essential phospholipids in the cell membrane. The advantage of ^{11}C–choline is that it is taken up by cancer cells by active transport, retained by phosphorylation and has minimal urinary excretion.

Until on-site cyclotrons become more economically feasible, tracers based on ^{18}fluorine are the ligands of choice dues to the relatively long half-life of 110 minutes. Recently a new fluorinated choline derivative, ^{18}F-**fluorocholine** (**FCH**), should be very useful in oncology applications. FCH has been shown to mimic ^{11}C-choline in cultured human prostate cells. FCH also has potential for imaging brain tumors. FCH may be more useful than FDG in the brain because FCH has much less uptake in normal brain cortex. FCH will have the potential to evaluate many other tumors such as lung, colon, and esophageal cancers in which ^{11}C-methionine has been shown to be effective. Other new promising tracers such as **fluoroethyl tyrosine** (**FET**) and **fluorodeoxythymidine** (**FLT**) have been studied. FLT has been shown in studies to accumulate more specifically in tumor cells than FDG.[6-9]

Medicare reimburses PET for seven types of cancers: lung, lymphoma, head and neck (excluding thyroid), colorectal, melanoma, esophageal and breast. It also reimburses PET for two non-oncologic uses: myocardial viability and seizure focus. However, the use of PET is being studied for many more tumors and non-oncologic applications. Future applications include oncologic imaging applications in urology, endocrinology, and gynecology. Future non-oncologic applications include **Alzheimer's disease** (**AD**), psychiatric disorders, inflammatory diseases, infections, and, finally, gene expression.

GU Cancer

The genitourinary system will be one of the new frontiers for PET. In terms of metastatic prostate cancer, PET has shown great promise in the preoperative evaluation of distant lymph node involvement. FCH has shown about twice the sensitivity of FDG, 70% vs. 34%.[10] In a recent study, in which 10 patients were undergoing androgen ablation for metastatic prostate cancer, the

decrease in size of tumor on CT and PSA levels corresponded to a decrease in PET uptake in the primary tumor and metastatic sites.[11] In the future, PET may be most helpful in evaluating the tumor response to treatment and determining the prognosis of the patient early in treatment, especially with new tracers .[10-14]

For patients with renal cell carcinoma, in a few recent studies, FDG-PET has been shown to be as accurate as CT (the current gold standard) in the primary diagnosis and better than CT in monitoring the response of treated renal cell carcinoma. In the primary diagnosis of renal cell carcinoma in two different studies, FDG-PET had a sensitivity of 77% (20/26 patients) and 94% (15/16 patients) in histologically proven renal cell carcinomas .[15] In 21 patients with renal cell carcinoma who were treated with interleukin-2 based therapy, PET was able to identify progression in 100% (10/10 patients) while CT only correctly identified progression in 70% (7/10 patients).[16] One of the main advantages of PET was its ability to differentiate between recurrent tumor in the renal fossa and radiation necrosis. In the future, PET especially with PET/CT fusion will have an expanding role in the diagnosis and management of renal cell carcinoma.

FDG-PET has also been shown to be useful in the diagnosis and management of testicular cancer. PET has been shown to be more sensitive than CT in diagnosing retroperitoneal disease in patients initially diagnosed with testicular cancers. In a study of 37 patients initially diagnosed with stage I or II seminomas and nonseminomas, PET was more accurate in staging than CT, 92% vs. 78% respectively.[17] PET can have an important role in monitoring the response to treatment. PET allows the differentiation between involuting tissue and residual or recurrent tumor.

Thyroid

In endocrinology, the largest emphasis has been on the use of PET for thyroid cancer. PET has shown to be effective in imaging patients with differentiated thyroid cancer who present with elevated thyroglobulin levels and a negative ^{131}Iodine scan. Progression in differentiated thyroid cancer occurs slowly with relatively good prognosis even after metastatic disease has been discovered provided that appropriate treatment is rendered. Patients with metastatic disease and negative ^{131}I scan are usually not treated with high-dose radioiodine. Usually thyroid cancer metastases that are not iodine avid have to be removed surgically if they can be localized. That is where PET can prove valuable for detection of both local recurrence and distant metastases. One recent study showed that out of 64 patients with histologically proven differentiated thyroid cancer who had negative ^{131}I scans and elevated thyroglobulin levels, 44 had positive abnormal PET uptake. 34 out of 44 patients were shown to have a true positive PET study. Treatment was changed in 19 out of the 34 patients with additional surgery performed in 18 patients. PET can be valuable in patients with differentiated thyroid cancer who present with increased thyroglobulin levels and negative ^{131}I scan because it allows surgical treatment for select patients, which is often curative.[18]

New radiotracers have emerged that will increase the use of PET.

In the future, PET and ^{131}I scan may play complementary roles in the detection of recurrent or metastatic differentiated thyroid cancer. The reason for this is that recent studies have shown that poorly differentiated thyroid cancer is often negative for ^{131}I scan and positive for PET while highly differentiated thyroid cancer is positive for ^{131}I scan and negative for PET. Glucose metabolism is more likely to be increased in poorly differentiated than in well differentiated thyroid cancer, whereas radioactive iodine uptake is more likely to be preserved in well differentiated thyroid cancer. One study has shown that PET has a distribution pattern similar to ^{201}thallium even though they have different mechanisms of uptake. PET has much better image quality and sensitivity than ^{201}Tl scan. Thus for metastatic disease after total thyroidectomy, PET and ^{131}I scan will likely play complementary roles, while a ^{201}Tl scan may not be necessary as it has the same distribution of uptake as in PET.[19]

GYN

In terms of gynecologic tumors, FDG-PET has been examined for evaluating cervical and ovarian cancer. Studies comparing PET with CT and MRI have been performed. A recent study examined 35 cervical cancer patients with stage IB or II based on FIGO (International Federation of Gynecology and Obstetrics) staging, comparing MRI and PET with histologic findings after radical hysterectomy. Sensitivity and specificity was 91% and 100% with PET compared to 73% and 83% with MRI.[20] Similar results have been shown on studies comparing PET and CT.[21]

In patients with rising serum markers such as CA 125 where ovarian cancer is suspected, PET has been shown to be of some benefit. In one recent study, PET results were compared with the results of conventional imaging and CA125 levels as well as surgical findings and clinical 6 month follow-up. PET showed a sensitivity of 80% (16/20 patients), a specificity of 100% (5/5 patients) and an accuracy of 84% (21/25 patients) for the diagnosis of recurrent ovarian cancer. CT had a sensitivity of 55% (11/20 patients), specificity of 100% (5/5 patients) and accuracy of 64% (16/25 patients). PET detected recurrent lesions in seven of nine patients in whom conventional imaging was falsely normal.[22]

Neurology

PET has shown promise in diagnosing **Alzheimer's disease (AD.** Clinically diagnosing dementia early in patients who exhibit some cognitive decline is extremely challenging. PET has been shown in studies to have sensitivity of 83-96% and specificity of 55–70% based on autopsy. PET is

superior to conventional SPECT techniques for the early diagnosis of AD. Currently, PET is not reimbursed by Medicare for the diagnosis of AD, but this will likely change, with the development of better treatments for AD.

Psychiatric disorders have been a fertile ground for PET research, but PET has not yet been proven clinically effective in evaluating psychiatric conditions. This may in part be due to the clinical heterogeneity of many psychiatric disorders. With various different experimental PET tracers, it is possible to evaluate a variety of neurotransmitter systems with the dopamine, serotonin, **gamma-aminobutyric acid (GABA),** and opiate systems most extensively studied to this point. PET research has shown abnormalities of neuroreceptor uptake in a variety of diseases and it is anticipated that PET studies of receptors and transporters will demonstrate valuable information in the years ahead. One promising area of PET research in psychiatry is antipsychotic drug occupancy studies which may be useful in better defining effective and patient-specific medication doses with fewer side effects based on receptor occupancy levels.

Miscellaneous

PET has also shown potential for imaging inflammation and infection. FDG not only collects in tumors but in activated white blood cells such as granulocytes and macrophages that consume a lot of glucose to fight infection. New studies are being performed for using PET to diagnosis and monitor inflammatory bowel disease .[23] In contrast to other agents for imaging infection, FDG has no normal bone marrow uptake. This is particularly useful in evaluating hip prostheses for infection versus loosening.[24] In the future, PET may replace ^{111}indium white blood cell and ^{67}gallium scans for infection. In patients with fever of unknown origin or unknown sites of infection, PET/CT may be used to find and accurately localize an infection in any part of the body.

One of the most exciting future applications of PET may be in gene therapy. Currently more than 200 gene therapy trials are being performed worldwide. Many of these trials are studying **herpes simplex virus thymidine kinase (HSV1-tk)** marker gene. In these trials HSV1-tk marker gene is placed into tumors by retroviral or adenoviral gene transfer. HSV1-tk marker gene has been used as a target for nucleoside prodrug activation for herpes infection. PET has the unique ability to noninvasively demonstrate in vivo gene expression. ^{18}F labeled nucleoside analogs such as acyclovir, ganciclovir, and penciclovir allow PET to image HSV1-tk marker gene. Therefore as a clinical tool, PET may be used in the future to safely monitor the efficacy of clinical gene therapy trials. The future in gene therapy is limitless. For example gene therapy in prostate cancer has been studied. In a recent study, PET was able to successfully demonstrate the expression of HSV1-tk marker gene in severe combined immunodeficient mice with prostate tumor xenograft using fluorinated penciclovir as a radiotracer .[25-27]

The future of imaging will be a combination of functional and anatomic imaging.

PET and PET/CT will have many new oncologic and non-oncologic applications. PET is in its infancy with unlimited potential for growth due to future advances in PET technology and new radiopharmaceuticals.

References

1. Hany TF, Steinert HC, Goerres GW, et al. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiol* 2002; 225:575-81.
2. Sandrick K. Hybrid PET/CT captures best of both modalities. Supplement to Diagnostic Imaging 2002; 2-4.
3. Melcher CL. Scintillation crystals for PET. *J Nucl Med* 2000 41;1051-5.
4. New developments in PET instrumentation: quo vadis PET? *J Nucl Med* 2001 42:1831-2.
5. Chatziioannou AF, Cherry SR, Shao Y, et al. Performance evaluation of microPET: A high-resolution lutetium oxyorthosilicate PET scanner for animal imaging. *J Nucl Med* 1999; 40:1164-75.
6. Roivainen A, Forsback S, Gronroos T, et al. Blood metabolism of [methyl-11C]choline: implications for in vivo imaging with positron emission tomography. *Eur J Nucl Med* 2000; 27:25-32.
7. Price DT, Coleman RE, Liao RP, et al. Comparison of [18 F]fluorocholine and [18 F]fluorodeoxyglucose for positron emission tomography of androgen dependent and androgen independent prostate cancer. *J Urol* 2002; 168:273-80.
8. DeGrado TR, Baldwin SW, Wang S, et al. Synthesis and evaluation of (18)F-labeled choline analogs as oncologic PET tracers. *J Nucl Med* 2001; 42:1805-14.
9. Hara T, Kosaka N, Kishi H. Development of (18)F-fluoroethylcholine for cancer imaging with PET: synthesis, biochemistry, and prostate cancer imaging. *J Nucl Med* 2002; 43:187-99.
10. Hoh CK, Seltzer MA, Franklin FJ, et al. Positron emission tomography in urologic oncology. *J Urol* 1998; 159:347-56.
11. Oyama N, Akino H, Suzuki Y, et al. PET for evaluating the change of glucose metabolism in prostate cancer after androgen ablation. *Nucl Med Commun* 2001; 22:963-9.
12. Effert PJ, Bares R, Handt S, et al. Metabolic imaging of untreated prostate cancer by positron emission tomography with 18fluorine-labeled deoxyglucose. *J Urol* 1996; 155:994-8.
13. Nunez R, Macapinlac HA, Yeung HW, et al. Combined 18F-FDG and 11C-methionine PET scans in patients with newly progressive metastatic prostate cancer. *J Nucl Med* 2002; 43:46-55.
14. Hara T, Kosaka N, Kishi H. PET imaging of prostate cancer using carbon-11-choline. *J Nucl Med* 1998; 39:990-5.
15. Bachor R, Kotzerke J, Gottfried HW. Positron emission tomography in diagnosis of renal cell carcinoma [German]. *Urologe A* 1996; 35:146-50.
16. Hoh C, Figlin R, Belldegrun A. Evaluation of renal cell carcinoma with whole body PET. *J Nucl Med* 1996; 37:141P.
17. Albers P, Bender H, Yilmaz H, et al. Positron emission tomography in the clinical staging of patients with stage I and II testicular germ cell tumors. *Urol* 1999;53:808-11.
18. Schluter B, Bohuslavizki KH, Beyer W, et al. Impact of PET on patients with differentiated thyroid cancer who present with elevated thyroglobulin and negative 131I scan. *J Nucl Med* 2001; 42:71-6.
19. Shiga T, Tsukamoto E, Nakada K, Morita K. Comparison of (18)F-FDG, (131)I-Na, and (201)Tl in diagnosis of recurrent or metastatic thyroid car-

cinoma. *J Nucl Med* 2001; 42:414-9.
20. Reinhardt MJ, Ehritt-Braun C, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and PET. *Radiol* 2001; 218:776-82.
21. Sugawara Y, Eisbruch A, Kosuda S, et al. Evaluation of PET in patients with cervical cancer. *J Nucl Med* 1999; 40:1125-31.
22. Torizuka T, Nobezawa S, Kanno T, et al. Ovarian cancer recurrence: role of whole-body positron emission tomography using 2-[fluorine-18]-fluoro-2-deoxy- D-glucose. *Eur J Nucl Med Mol Imaging* 2002; 29:797-803.
23. Kresnik E, Gallowitsch HJ, Mikosch P, et al. (18)F-FDG positron emission tomography in the early diagnosis of enterocolitis: preliminary results. *Eur J Nucl Med Mol Imaging* 2002; 29:1389-92.
24. Manthey N, Reinhard P, Moog F, et al. The use of [18 F]fluorodeoxyglucose positron emission tomography to differentiate between synovitis, loosening and infection of hip and knee prostheses. *Nucl Med Commun* 2002; 23:645-53.
25. Blasberg R. PET imaging of gene expression. *Eur J Cancer* 2002; 38:2137-46.
26. Nichol C, Kim EE. Molecular imaging and gene therapy. *J Nucl Med* 2001; 42:1368-74.
27. Boerman OC, Oyen WJ, Corstens FH. Progress in gene therapy: Seeing is believing. *J Nucl Med* 2001; 42:1235-7.

Don Yoo, MD, is Senior Resident Department of Diagnostic Imaging, Rhode Island Hospital.

Richard B. Noto, MD, is Director of Nuclear Medicine, Rhode Island Hospital, and Assistant Professor (Clinical), Department of Diagnostic Imaging, Brown Medical School.

CORRESPONDENCE:
Richard B. Noto, MD
Department of Diagnostic Imaging
Rhode Island Hospital
593 Eddy St.
Providence, RI 02903
Phone: (401) 444-5184
Fax: (401) 444-5017
e-mail: Rnoto@lifespan.org

Certificate of Need Process: An Assessment of the Need for PET

John X. Donahue, MPA

In Rhode Island, health care providers and health care facilities proposing to undertake major capital investment for new high-cost medical equipment must receive **certificate of need** approval (**CON**).[1] CON is a public review process that assesses the community need and affordability of the proposed investment. One of the purposes of the CON is to avoid the costly duplication of high-cost medical equipment. For tertiary care services, assuring the quality of the new service is a key purpose of CON review.

Positron Emisson Tomography (**PET**) is a capital-intensive diagnostic procedure in which very small amounts of radiotracers are injected and sensitive imaging equipment is used to detect biochemical and physiological reactions in the human body. A major application of this technology is for the detection, staging, and monitoring of cancer because tumor cells show high uptake of some radiotracers.[2] When the Department of Health reviewed PET, it looked at machines costing approximately $1.7 million, and considered $1700 the average insurance reimbursement per scan.

PET is subject to CON review for two reasons: (1) the total costs exceed the capital cost review threshold of $1 million, and; (2) PET is classified as a tertiary care service and is reviewable regardless of capital or operating costs.

In general, the CON process involves a formal application, public comment period, review by the **Health Services Council** (**HSC**), an assessment of public need and affordability, a recommendation by the HSC and, a final determination by the Director of Rhode Island **Department of Health** (**HEALTH**). For tertiary care services, the due process steps remain the same, but greater scrutiny is applied to issues related to quality of care including, programmatic oversight, staffing, efficacy, access and cost effectiveness.

Historical Background

PET is not a new medical technology, but its capabilities and applications in clinical practice have been refined and expanded over the last few years. Limitations on PET marketing and diffusion have included high costs and reimbursement constraints. For example, until recent developments in isotope production, PET required onsite capacity of cyclotrons (approximately $2 million alone). Also, in December 2000, Medicare finally approved for reimbursement an expanded list of diagnostic categories for PET scanning services[3]

In Rhode Island, a number of hospitals had, for many years, identified PET as a potential CON project in their individual hospital annual short and long range plans but never filed for review. In 1991, Eastern Bio-Medical, Inc. submitted a CON to establish PET scanning services. The capital costs were in excess of $5.5 million and included a cyclotron. The proposal was not approved, but it generated much discussion on costs, organizational structure, research, medical education and efficacy particularly within the medical community.

Recent Developments

Following the December 15, 2000, Medicare decision to expand reimbursement, local interest in providing PET services rapidly changed. In January 2001, three separate CON applications were filed. Two proposals were submitted by physician practices specializing in diagnostic imaging, and the third application was a joint venture between a for-profit entity and a hospital. The capital costs of the different proposals ranged from $1.3 million to just under $2 million.

The CON applications were referred to the HSC for review. Given the evolving nature of PET, the HSC/HEALTH requested that an independent consultant undertake a need assessment for this tertiary service in Rhode Island. Spectrum Research performed an in-depth analysis of PET and, in May 2001, presented its Report, "An Assessment of the Need for Positron Emission Tomography Scanners in Rhode Island," to the HSC and the applicants. The Report highlighted the annual predicted patient volume to be 2,806 scans while the annual through-put per scanner was estimated to be 1,500. Important factors for siting PET scanners included: 1) proximity to inpatient services; 2) availability for research; 3) access for teaching residents and medical school students; 4) board certification and experience requirements for PET program directors and PET physician readers; 5) co-location with other clinical services; 6) radiation safety issues for PET staff; 7) state-of-the-art equipment capabilities; and, 8) cost effectiveness factors.[4]

The HSC was cognizant of the value that PET would contribute to the health care system in Rhode Island. The HSC weighed each application and recognized that each proposal had certain strengths and weaknesses. In the final analysis, however, the HSC was not convinced that those proposals then under review satisfied the factors identified above for siting this tertiary care service in RI, particularly with reference to the equipment, training, co-location of services and the organization/delivery of PET services as proposed.

The HSC recommended denial of applications, but also recommended that the HEALTH prepare a **Request for Proposal** (**RFP**) for PET Services incorporating the most recent research and standards for PET services delivery. In taking this position, the HSC sought to establish a high quality standard for the initial deployment and diffusion of this tertiary level technol-

ogy in RI. This approach has been utilized previously by the HSC and HEALTH in the case of other tertiary care services.

Request for Proposals

After circulating a draft RFP to interested parties, HEALTH, in December 2001, issued the formal PET RFP with a February 1, 2002, submission date. The RFP contained a number of factors, standards and measures that each applicant was required to address including: 1) planning process; 2) demonstrated demand; 3) teaching hospital role for medical education and research; 4) physician qualification and experience; 5) location and organizational relationship to existing diagnostic and medical services; 6) quality assurance standards; 7) state of the art equipment, and; 8) access for all patients regardless of ability to pay.

On February 1, 2002, two applicants responded to the RFP. Rhode Island Hospital proposed to establish the PET service on its campus adjacent to its nuclear medicine department. **Rhode Island PET Services, LLC (RIPS)** proposed to offer a mobile PET service involving six hospitals statewide (Landmark Medical Center, Memorial Hospital of Rhode Island, Roger Williams Medical Center, St. Joseph Health Services, Kent County Memorial Hospital and South County Hospital Healthcare System).

Overall, there were several noticeable differences between the 2002 RFP proposals compared to the 2001 PET proposals. These included: 1) provision for state-of- the-art equipment (LSO/GSO); 2) identification of the means to satisfy the professional competence requirements of PET directors, PET readers, and PET trainers; 3) hospital-based service to address the issue of co-location to other diagnostic and medical services; 4) the role of teaching hospitals for medical education and research, and; 5) health facility licensure, quality assurance and access provisions.

The proposals were referred to the HSC for review. The HSC/HEALTH requested that Spectrum Research update its 2001 Needs Analysis. The 2002 Update noted that recent reimbursement changes in coverage for PET resulted in an estimated doubling of potential scan volume for Rhode Island. Spectrum Research now estimated the annual volume of scans to be 5,600. The 2002 Update also factored into account the more efficient nature of the equipment (LSO/GSO) proposed, resulting in greater annual thru-put of 3,000 PET scans. Finally, the Update continued to confirm the professional competence requirements and other siting considerations for PET originally identified in the 2001 Needs Assessment Report and as reflected in the RFP standards.[5]

The Department retained an out-of-state expert, R. Edward Coleman, MD, Director of PET Services at Duke University Medical School, to evaluate the RFP responses and to review physician credentials for the positions of PET directors, PET readers, and PET trainers for both applicants.

Beyond the hardware issues of the number of scanners needed and equipment capabilities, the HSC/HEALTH were also concerned about the professional componen t to operate the PET service. The Department retained an out-of-state expert, R. Edward Coleman, MD, Director of PET Services at Duke University Medical School, to evaluate the RFP responses and to review physician credentials for the positions of PET directors, PET readers, and PET trainers for both applicants. The RFP requirements for each were as follows: PET director – board-certified in nuclear medicine/nuclear radiology and completed a PET fellowship or nuclear medicine fellowship and having read at least 600 PET scans; PET reader – board-certified in nuclear medicine with specialty PET training or experience as demonstrated by having read at least 600 PET scans; PET trainer – board-certified in nuclear medicine and having read over 2,000 PET scans.

Dr. Coleman also reviewed the RIPS proposed 6-month PET training and education program (4 hours per session) for physicians to be sponsored by Alan Fischman, MD, Director of PET Services for Massachusetts General Hospital. In addition, he advised on volume standards for maintaining proficiency and competency in PET readings. Dr. Coleman provided a written Report which: 1) evaluated the qualifications of each proposed physician against the RFP standards; 2) commented on the adequacy of the proposed RIPS training program; and 3) recommended that any physician with limited PET experience (600 interpretations via a training program) needs to read a minimum of 5 scans per week (250 annually) to maintain proficiency.

CON Decisions

After consideration of all of the materials including the RFP applications, the 2002 Needs Assessment Update Report and the Report of the medical consultant, the HSC recommended to the Director of Health that the RIH and the RIPS PET proposals be approved. The recommendations included the standard CON conditions of approval regarding cost, access and regulatory compliance. The HSC included an additional condition to the RIPS proposal that required that each physician have his/her scans over-read by the RIPS medical director (Dr. Fischman) until such time that physician has read five scan per week on a consistent basis.

In June 2002, the Director of Health accepted the HSC recommendations and approved the proposals with the inclusion of conditions for PET site accreditation for both appli-

cants and certain physician certifications to the RFP requirements be forthcoming primarily from the RIPS proposals.

Discussion

As a result of the RFP, the HSC/HEALTH have established a high standard for the introduction and initial deployment of PET services in RI. The framework of the RFP required the applicants to address quality considerations pertinent to tertiary care services in general and to PET services in particular. For example, both RIH and RIPS have committed to acquiring state of the art equipment and both will be using professional staff that have met or will meet the physician standards for rendering PET services. In addition to quality of care factors, patients will also experience enhanced access and choice of location and PET service provider.

In summary, current needs assessment and reimbursement policies indicate that patient demand for PET will be more than adequately served by RIH and RIPS, at least in the near term. As PET becomes operational early in 2003, quality oversight activities should be an integral component of the service on an ongoing basis and public need for additional PET capacity will be periodically assessed.

References

1. Rhode Island General Assembly. Chapter 23-15 Determination of Need for New Health Care Equipment and New Institutional Health Services.
2. Balk E, Lau J. PET scans and technology assessment. *JAMA* 2001;285:936-7.
3. Medicare coverage policy decisions memorandum: FDG positron emission tomography (CAG-00065); December 15, 2000.
4. Zimmerman H. An Assessment of the Need for Positron Emission Tomography Scanners in Rhode Island; May 2001.
5. Zimmerman H. An Assessment of the Need for Positron Emission Tomography Scanners in Rhode Island; Revised May 2002.

John X. Donahue, MPA, is Chief of the Office of Health Systems Development, Rhode Island Department of Health.

Correspondence:
John X. Donahue, MPA
Rhode Island Department of Health
3 Capitol Hill
Providence, RI 02908
Phone: (401) 222-2788
Fax: (401) 273-4350
e-mail: JohnD@doh.state.ri.us

What s in a Name?

By Marcia K. Petrillo, MA

Recently, Rhode Island Quality Partners became Quality Partners of Rhode Island—a change that reflects our commitment to community partnership. Partners include hospitals, nursing homes and physicians, as well as healthcare professional and consumer groups. Working together, we have improved the quality of healthcare for Rhode Islanders.

For example, as a founding member of the Ocean State Adult Immunization Coalition, we are proud that Rhode Island has one of the highest flu and pneumonia immunization rates in the country. Most recently, we have established a Physicians Quality Network to improve healthcare delivered in primary care offices.

These successful local partnership efforts have been expanded to include initiatives that impact the delivery of care nationally. In 2002, Medicare released quality-of-care data on 17,000 nursing homes nationwide for the first time, providing information for people trying to choose a nursing home and for nursing homes to target their quality improvement efforts. Quality Partners tested the data release program for Medicare in Rhode Island and facilitated similar work in five other states.

Today, we are building the program that Medicare offers to support quality improvement in nursing homes throughout the nation. These efforts were recently recognized by Medicare and quality improvement organizations across the country when Quality Partners received the award for *Outstanding Customer Service* as the National Nursing Home Quality Improvement Organization Support Center.

We will work in partnership with hospitals, nursing homes, physicians, healthcare professionals and consumer groups to create the best possible healthcare system and make our state a model for America.

Partnership is the key to improving healthcare quality. Given the complexity of the healthcare system, positive change is almost impossible to implement unless the effort to change includes all of the people and organizations that impact healthcare. That is why we have chosen to recognize the value of partnering for quality in our new name. Thank you for helping us advance excellence in healthcare, and striving to make our state a model for America.

Marcia K. Petrillo is Executive Director for Quality Partners of Rhode Island, a not-for-profit designated by the federal government to evaluate and improve healthcare quality.

QUALITY PARTNERS OF RHODE ISLAND

This message was prepared by Quality Partners of Rhode Island under a contract with the Centers for Medicare & Medicaid Services (CMS). Contents do not necessarily reflect CMS policy.

(401) 528-3200 **www.qualitypartnersri.org**

Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Jay S. Buechner, PhD

Damp Housing Conditions and Asthma in Rhode Island

Leanne C. Chiaverini, Jana E. Hesser, PhD, and John P. Fulton, PhD

Exposure to environmental agents can play an important role in the development and exacerbation of asthma, a condition that affects an estimated 84,000 persons in **Rhode Island (RI)**.[1] Considering the amount of time spent indoors, housing conditions are of particular interest. More specifically, several studies in the U.S. and elsewhere have found that the prevalence of asthma and other respiratory symptoms among both children and adults are higher in homes with reported dampness or mold.[2-5] Mildew (mold in early stage) and molds are fungi that grow on organic materials almost anywhere indoors and outdoors.[6] They thrive in moist environments—mold growths or colonies can develop on damp surfaces within 24 to 48 hours—and reproduce by making small, lightweight spores that travel through the air.[6] The work presented here examines the relationship between home dampness/mildew odor and asthma in RI.

At the national level, Healthy People 2010 includes the following objective relevant to environmental risk factors: increase the number of "persons with asthma who receive assistance with assessing and reducing exposure to environmental risk factors in their home, school, and work environments."[7]

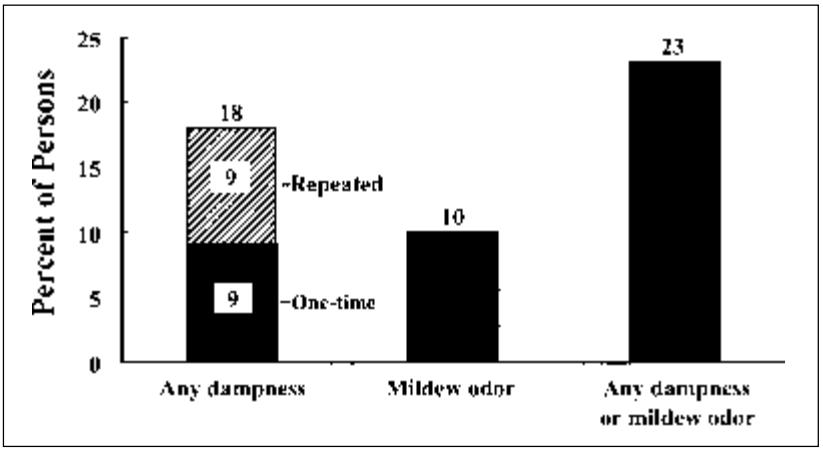


Figure 1. Prevalence of dampness and mildew odor in housing, Rhode Island, 2001.

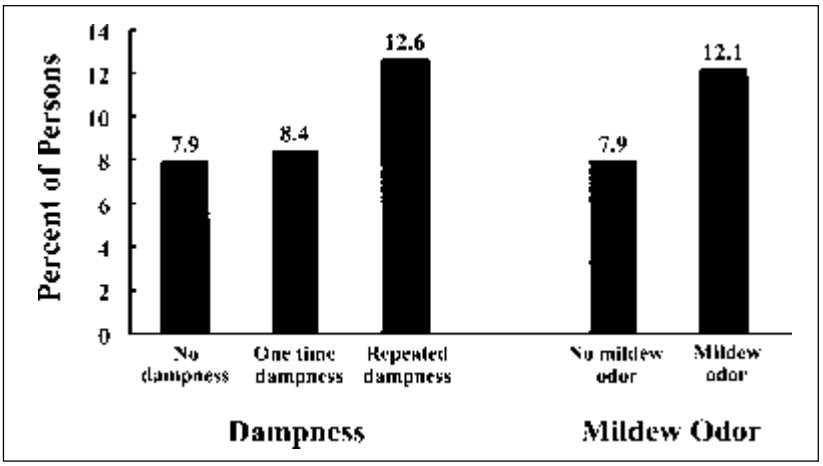


Figure 2. Prevalence of asthma, by presence of dampness and mildew odor in housing, Rhode Island, 2001.

Methods

Data on persons reported with asthma, dampness in the home, and mildew odor in the home were obtained from the RI Health Interview Survey,[1] a periodic telephone survey of approximately 2,600 households including 6,500 individuals per iteration. Percentages and estimated populations are based on weighted data for 2001.

Prevalence of asthma is defined as persons who answered "yes" to "Does anyone in the household have asthma?" and "Did a doctor say that you/he/she have/has asthma?" Dampness in the home is determined from two questions as shown in Table 1: (a) "During the past 12 months, has there been water or dampness in the apartment/house where you live caused by broken pipes, leaks, heavy rain, or floods?" and (b) "Has this happened more than once in the past 12 months?" Mildew odor in the home is defined as persons who answered "yes" to "Does the apartment/house where you live frequently have a mildew odor or musty smell?" All data exclude respondents who answered "I don't know" or who refused to answer the question.

Results

Among all persons in RI, 18% report the presence of any dampness (9%

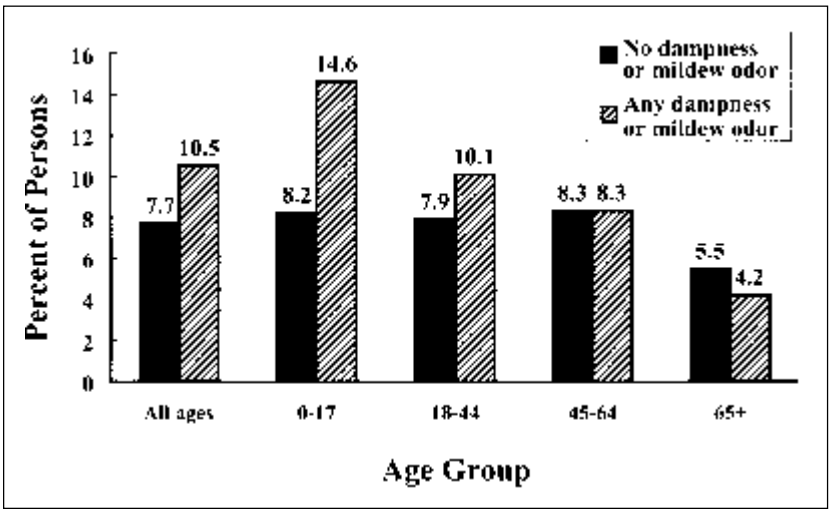


Figure 3. Prevalence of asthma, by age group and presence of dampness and mildew odor in housing, Rhode Island, 2001.

report one time dampness; 9% report repeated dampness), 10% report mildew odor, and 23% report either any dampness or mildew odor in the home. (Figure 1) The percent of Rhode Islanders who report dampness and mildew odor in the home varies by several demographic variables. Damp housing/mildew odor was reported less among homeowners (versus renters), Hispanics, and persons of older age. The observed relationship between demographic variables and home dampness/mildew odor was independent of gender and income.

According to this study, 8.6% of Rhode Islanders are reported to have a doctor's diagnosis of asthma. The burden of asthma varies according to dampness/mildew odor housing conditions. (Figure 2) The percent of persons in RI who have asthma is 7.9% among those with no dampness in the home, 8.4% among those with one-time dampness in the home, and 12.6% among those with repeated dampness in the home. The percent of persons in RI with asthma is 7.9% among those with no mildew odor in the home. This number jumps to 12.1% among persons who report mildew odor in the home. Odds ratios (ratio of event occuring with risk condition to event occuring without risk condition) for associations between asthma and home dampness/mildew odor range from 1.14 to 1.60. (Table 2)

Age is a significant variable when considering the relationship between asthma and home dampness/mildew odor. (Figure 3) Among persons who report no dampness or mildew odor in the home, the burden of asthma is distributed evenly across all age groups (about 8%) except for those 65 years and over (asthma prevalence of 5.5%). Among persons who report any dampness or mildew odor in the home, the percent with asthma decreases as age increases. The strongest association between asthma and any dampness or mildew odor is among 0-17 year-olds. In this age group, the percent of persons with asthma is 8.2% among those with no dampness or mildew odor, and 14.6% among those with any dampness or mildew odor in the home. A smaller association is seen among persons ages 18-44 (7.9 versus 10.1%). No difference is observed among persons ages 45-64 (8.3% for both no dampness/mildew odor and any dampness/mildew odor), and there is a small inverse relationship among those 65 years and over (5.5 versus 4.2%).

Table 1. Definition of Groupings Based on Dampness in the Home Questions

Grouping	Questions	
	a) Dampness in house, past 12 months	b) More than one occasion
No dampness	No	[Not asked]
Any dampness	Yes	Yes or No
One-time dampness	Yes	No
Repeated dampness	Yes	Yes

Table 2. Odds ratios for association between asthma and home dampness/mildew odor

Housing Conditions	Odds Ratio
One time dampness	1.14
Repeated dampness	1.54
Mildew odor	1.60
Any dampness or mildew odor	1.42

Assessment

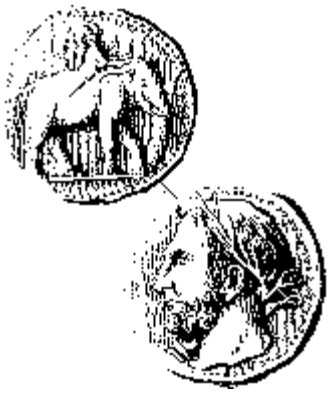
Published research[2-5] has demonstrated that dampness and mildew odor in the home are potential risk factors for asthma. We have observed a similar association in RI survey data. The prevalence of asthma in RI is elevated among persons who report one time or repeated dampness or mildew odor in the home compared with those who report no dampness or mildew odor in the home. This relationship between home asthma and dampness/mildew odor was strongest among persons ages 0-17. The burden of asthma in this age group was disproportionately higher than in other age groups. Results suggest that children and young adults are more susceptible than adults to developing asthma as a result of exposure to home dampness/mildew odor.

Future investigations may want to examine other exposures in the home environment, such as environmental

tobacco smoke or the presence of adequate ventilation, as well as the relationship between asthma and dampness/mildew odor in other indoor environments such as workplaces and schools.

This and future studies will be instrumental in designing public health interventions to reduce exposure to environmental triggers of asthma in order to reduce asthma morbidity. Asthmatic patients should be encouraged to deal with mold problems effectively and efficiently, and to take the following steps to prevent mold and mildew problems in their homes:[6]

- Fix leaks in pipes or other sources of water.
- Be sure the home has adequate ventilation.
- Use dehumidifiers during humid months.
- [a] Clean bathrooms with mold killing products.



Leanne C. Chiaverini is Research Associate, Division of Disease Prevention and Control, Rhode Island Department of Health.

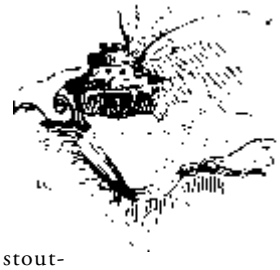
Jana E. Hesser, PhD, is Program Manager for Health Surveys, Office of Health Statistics, Rhode Island Department of Health, and Clinical Teaching Associate in Community Health, Brown Medical School.

John P. Fulton, PhD, is Associate Director, Division of Disease Prevention and Control, Rhode Island Department of Health, and Clinical Associate Professor of Community Health, Brown Medical School.

References

1. Rhode Island Health Interview Survey, Office of Health Statistics, RI Department of Health, 2001.
2. Thorn J, Brisman J, Toren K. Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. *Allergy* 2001;56:287-92.
3. Hu FB, Persky V, Flay BR, Richardson J. An epidemiological study of asthma prevalence and related factors among young adults. *J Asthma* 1997;34:67-76.
4. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Home dampness, current allergic diseases, and respiratory infections among young adults. *Thorax* 2001;56:462-7.
5. Yang CY, Chiu JF, Chiu HF, Kao WY. Damp housing conditions and respiratory symptoms in primary school children. Pediatr Pulmonol 1997;24:73-7.
6. Federal Emergency Management Association, Mitigation Division. Dealing with Mold and Mildew in your Damaged Home. http://www.fema.gov/pdf/reg-x/mold_mildew.pdf
7. US Department of Health and Human Services. *Healthy People 2010*. 2nd ed. *With Understanding and Improving Health and Objectives for Improving Health.* 2 vols. Washington, DC: US Government Printing Office, 2000.

– A Physician's Lexicon –



The Verbiage of Obesity

The word epidemic, by custom if not by etymology, is generally applied to any disorder, infectious or otherwise, originating elsewhere, newly attacking large numbers of humans living in a geographically defined area, and coming down with the disease within a restricted time interval. The United States is currently experiencing unprecedented increases in overweightedness and obesity. And so, in the words of the Rhode Island Department of Health, the disorder of obesity has reached "epidemic proportions in the United States." To illustrate, in 1991 no state had an obesity rate of 20% or more involving its overall population. By 2000, 22 states reported obesity rates of 20% or higher in their populations, and in the past decade, the adult obesity population in Rhode Island has almost doubled.

Obese individuals are now defined as having a Body Mass Index [calculated by a person's height and weight] equaling or exceeding 30. The synonyms of the word, obese, are numerous.

The word obesity is derived from a Latin word, ***obesus***, which in turn is a contraction of two Latin words, ***ob-*** and ***edere***, meaning to devour, to eat away. The ***edere*** root also produces such current English words as edible. Adipose, and similar words such as adiposity, come from a Latin word ***adeps***, meaning fat. The anatomic phrase, ***panniculus adiposus*** [the superficial abdominal fascia with much incorporated fatty tissue] is also derived from the Latin ***pannus***, meaning sheet or layer.

The word corpulent comes directly from the Latin ***corpulentia***, meaning an augmentation of the body [***corpus***]. And with an added diminutive ending one arrives at the Latin word, ***corpusculum***, meaning little body as in its English derivative, corpuscle. Portly, from the Latin ***portare***, meaning to carry, has, as in English words such as comport, gradually evolved to mean how one carries or conducts oneself, as in the sentence, "He comported himself with dignity." Portly has then come to mean dignified, imposing, stout.

The word stout [an old German word originally meaning courageous or dauntless, as in stout-hearted] has now gradually come to mean fleshy or corpulent.

And the word weight comes from an Anglo-Saxon word ***gewiht***, meaning fatty. The word fat is similarly of Anglo-Saxon origin, taken from the word, ***faet.***

Words such as lipid, lipase, lipoma and lipemia are all derived from a Greek word meaning greasy or fatty. In general, when there is both a Latin as well as a Greek term available to define a specific anatomic structure, the pathologic states tend to use the Greek rather than the Latin root. Thus we have the word pulmonary, from the Latin, but pneumonitis from the Greek; or renal, from the Latin, but nephritis from the Greek; or vascular from the Latin, but angiitis, from the Greek. This pattern of assigning pathologic states or lesions solely to Greek-derived words is diminishing since words such as pu;monitis or vasculitis now appear occasionally.

– Stanley M. Aronson, MD, MPH

Vital Statistics

Rhode Island Department of Health
Patricia A. Nolan, MD, MPH, Director of Health

Edited by Roberta A. Chevoya

Rhode Island Monthly Vital Statistics Report

Provisional Occurrence Data from the Division of Vital Records

Underlying Cause of Death	Reporting Period			
	May 2002	12 Months Ending with May 2002		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	243	3,069	292.8	3,894.0
Malignant Neoplasms	188	2,403	229.2	7,483.0
Cerebrovascular Diseases	40	529	50.5	720.0**
Injuries (Accident/Suicide/Homicide)	21	400	38.2	7,385.0***
COPD	32	517	49.3	462.5

Vital Events	Reporting Period		
	November 2002	12 Months Ending with November 2002	
	Number	Number	Rates
Live Births	1,120	13,649	13.0
Deaths	821	10,289	9.8
Infant Deaths	(6)	(101)	7.4
Neonatal deaths	(5)	(71)	5.2
Marriages	557	8,306	7.9*
Divorces	248	3,389	3.2
Induced Terminations	416	5,563	407.6#
Spontaneous Fetal Deaths	89	1,123	82.3
Under 20 weeks gestation	(86)	(1,052)	77.1
20+ weeks gestation	(3)	(71)	5.2

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.

(b) Rates per 100,000 estimated population of 1,048,319

(c) Years of Potential Life Lost (YPLL)

Note: Totals represent vital events which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.

* Rates per 1,000 estimated population
** Excludes one death of unknown age.
*** Excludes two deaths of unknown age.
# Rates per 1,000 live births

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publications Committee

VOLUME 1
NUMBER 1

PROVIDENCE, R.I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

Ninety Years Ago

[May, 1913]

An editorial explained the Medical Society's reluctant decision to expel two members. The first, Dr. J.B. Archambault, of Woonsocket, "although a graduate of Laval [and] a licensed practitioner of this state," had "publicly lent his name and the profession to a …quack medicine." Dr. Archambault had placed an advertisement in a local newspaper for his elixir, a "Long Life Tonic for Dyspepsia and all Female Disturbances, also a Wonderful Cough Syrup for Tuberculosis, Bronchitis, Pneumonia, Whooping Cough." The Society also expelled Dr. George M. Bailey, MD, LLB, President of the Rhode Island College of Nursing. Dr. Bailey had advertised the school in *JAMA*. This correspondence course (the time could range from a few months to a year) was replacing the Rhode Island Training School for Nursing and Allied Sciences. Dr. Bailey proposed to give physicians stock in the school, in exchange for sending "fully paid students." The advertisement promised physician-investors that they might also gain some free labor from the students.

Governor Pothier had invited Dr. Friedrich F. Friedmann of German to demonstrate at public clinics (Woonsocket Hospital, St. Joseph's Hospital, City Hospital, and an improvised laboratory at the Narragansett Hotel) his treatment for tuberculosis. Dr. Friedmann refused to publish details of his cure. The Journal decried the visit: "That he has infected others with his sensationalism is evidenced by the hectic and perfervid comparison of his coming to America by a local minister to that of the coming of Jesus Christ."

Henry C. Hall, MD, President, Providence Medical Association, gave the Annual Address, "Practical Aspects of Psychotherapy." He wrote: "In the present era of medical science . . . may it not be well to pause and seriously question whether some of the old-time methods of cure are not neglected?" Specifically, he cited "suggestion" (as in faith healing, mesmerism, animal magnetism), but conceded that modern medicine was "antagonistic" to these treatments.

Henry W. Kimball, MD, in "Carbon Dioxide and its Uses in Dermatology," noted that in 1905 Julius Berg of Breslow sprayed carbon dioxide on body parts; later Pusey of Chicago used the solid form. He described the technique of collecting and molding the snow, using a chamois sheet and a test tube. He recommended carbon dioxide for congenital deformities of the skin, abnormal overgrowth, small epithelomata, hypertropic scars, lupus vulgaris, even tattoo marks.

Fifty Years Ago

[May, 1953]

Arthur E. O'Dea, MD, Research Fellow in Pathology and Legal Medicine, Harvard Medical School, presented "Medicolegal and Pathological Aspects of Suicide," at the Providence Medical Association annual meeting. He cited the duties of a forensic pathologist: "He not only documents homicide but also guards the public interest by removing unwarranted suspicion arising over a given death and assists law enforcement officers acting as an impartial arbiter in investigating sudden and apparently unexplainable deaths." Identifying suicide was a challenge because the pathologist rarely had a correct family history. Instead, the family would try to make the cause of death seem natural or accidental.

Norman L. Loux, MD, Clinical Director, Butler Hospital, in "Some Clinical Aspects of Suicide," said that men were more likely to use firearms and hanging; women, poison and gas.

Anthony Caputi, MD, and Louis E. Burns, MD, in "Coronary Occlusion and Myocardial Infarction," reviewed 188 cases of coronary occlusion seen at Newport Hospital from January 1, 1946, to December 31, 1950. Only 12 patients received anticoagulant therapy. The mortality rate was 40.5 %; 76.3% of them died within two weeks after onset of the occlusion.

Barry B. Mangillo, MD, contributed "Videotherapy as an Office Procedure." For example, the cartoon film, "Johnny Learns His Manners," was "of great value in treating children with behavior problems." The film featured "Badself," "nasty imp whose mission is to get Johnny into trouble", versus "Goodself." One scene, promoting neatness, showed Johnny in the room of a West Point cadet.

An editorial praised the Providence Tuberculosis League, which provided chest x-rays and advice to 6,341 individuals at facilities and took 22,214 small films at the trailer.

An editorial on Foreign Medical Graduates noted, on the one hand, that state licensing boards had found the foreign training deficient, on the other hand, that hospitals needed these staff. The editorial saw "no easy solution."

Twenty Five Years Ago

[May, 1978]

In "Message from the Dean," Stanley M. Aronson, MD, MPH, described the 63 students from the Class of 1978, Brown Medical School's fourth group. The journal featured photographs of graduates, with their residency destinations.

In "Medicine in the Year 2000 : A Symposium," Stanley M. Aronson, MD, Paul Calabresi, MD, Pierre M. Galletti, MD, PhD, Henry T. Randall, MD, Leo Stern, MD, Albert F. Wessen, PhD, and Robert J. Westlake, MD, peered into the crystal ball two years hence. [They did not foresee managed care.]

Milton W. Hamolsky, MD, gave a eulogy for Marshall Fulton, MD [1899-1977], an Iowa-born Brown graduate and Rhodes Scholar who went on to become Brown's first University Professor of Medicine in Brown's new program in medicine.

The Journal reprinted from the *Harvard Medical Alumni Bulletin* "Sir William Osler's Better Half," which Dr. Fulton wrote for the American Osler Society.