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Let's Play PET - Main Menu

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1. Overview of PET

2. Radioisotope Production

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Topics:

- **Cyclotron Operation**
- **The Carousel**
- **Target Chamber**
- **Computer Control**
- **Biosynthesis of Radionuclides**

PET Tracers: Structure and Function
Select a tracer from one of the following isotope groups:

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   - **Carbon Dioxide**
   - **Oxygen**
   - **Water**
2. **Nitrogen**
   - **Ammonia**
3. **Carbon**
   - **Acetate**
   - **Carfentanil**
   - **Cocaine**
   - **Deprenyl**
   - **Leucine**
   - **Methionine**
   - **N-Methylspiperone**
   - **Raclopride**
4. **Fluorine**
   - **Haloperidol**
   - **Fluorine Ion**
   - **Fluorodeoxyglucose (FDG)**
   - **Fluorodopa**
   - **Fluoroethylspiperone**
   - **Fluorouracil**
5. **Rubidium**
   - **82-Rubidium**

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- **Mathematical Models of PET Tracers**
  Select one of the following tracers:

1. Acetate
2. Ammonia
3. Carbon Dioxide
4. Fluorine Ion
5. Fluorodeoxyglucose (FDG)
6. Fluorodopa
7. Fluoroethylspiperone
8. Leucine
9. Oxygen
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6. Clinical Case Examples

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7. Credits

8. References

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LPP WWW Curator: Jim Strommer (jstrommer@mail.nuc.ucla.edu)
Last Updated: May 6, 1996

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Overview of PET

Positron emission tomography (PET) has enhanced our understanding of the biochemical basis of normal and abnormal functions within the body, and permitted biochemical examination of patients as part of their clinical care. These capabilities are important because:

1. The basis of all tissue function is chemical.
2. Diseases result from errors introduced into its chemical systems by viruses, bacteria, genetic abnormalities, drugs, environmental factors, aging, and behavior.
3. The most selective, specific, and appropriate therapy is one chosen from a diagnostic measure of the basic chemical abnormality.
4. Detection of chemical abnormalities provides the earliest identification of disease, even in the presymptomatic stages before the disease process has exhausted the chemical reserves or overridden the compensatory mechanisms of the brain.
5. Assessment of restoration of chemical function provides an objective means for determining the efficacy of therapeutic interventions in the individual patient.
6. The best way to judge whether tissue is normal is by determining its biochemical function.

Another principle relates to the value of examining these biochemical processes with an imaging technology. Because in most cases the location and extent of a disease is unknown, the first objective is an efficient means of searching throughout the body to determine its location. Imaging is an extremely efficient process for accomplishing this aim, because data are presented in pictorial form to the most efficient human sensory system for search, identification, and interpretation‹the visual system. Recognition depends upon the type of information in the image, both in terms of interpreting what it means and how sensitive it is to identifying the presence of disease.

PET provides the means for imaging the rates of biologic processes in vivo. Imaging is accomplished through the integration of two technologies, the tracer kinetic assay method and computed tomography (CT). The tracer kinetic assay method employs a radiolabeled biologically active compound (tracer) and a mathematical model that describes the kinetics of the tracer as it participates in a biological process. The model permits the calculation of the rate of the process. The tissue tracer concentration measurement required by the tracer kinetic model is provided by the PET scanner, with the final result being a three-dimensional (3-D) image of the anatomic distribution of the biological process under study.

Radiolabeled tracers and the tracer kinetic method are employed throughout the biological sciences to measure such processes as blood flow, membrane transport, metabolism, synthesis, and ligand-receptor Interactions; for mapping axonal projection fields through anterograde and retrograde diffusion; measurement of cell birth dates; marker assays using recombinant DNA techniques; radioimmunoassays; and the study of drug Interactions with chemical systems of the body. The tracer technique continues to be one of the most sensitive and widely used methodologies for performing assays of biological systems. PET allows the transfer of the tracer assay methodology to the living subject, particularly humans. PET builds a bridge of communication and investigation between the basic and clinical sciences, based upon a commonality of methods used and problems studied.

The transfer of tracer methods from the basic biological sciences to humans with PET is made possible by the unique nature of the radioisotopes used in PET to label compounds: 11C, 13N, 150, and 18F. These are the only radioactive forms of the natural elements (l8F is used as a substitute for hydrogen) that emit radiation that will pass through the body for external detection. Natural substrates, substrate analogs, and drugs can be labeled with these radio isotopes without altering their chemical or biological properties. This allows the methods, knowledge, and interpretation of results from tracer kinetic assays used in the basic biological sciences to be applied to humans by the quantitative measurement abilities of the PET scanner.

[Excerpted from: Phelps, M.E., Positron Emission Tomography. In: Mazziotta, J. and Gilman, S., Eds., *Clinical Brain Imaging: Principles and Applications,* 1992, F.A. Davis Company, pp71-107]

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TUTORIAL: Radioisotope Production

Production of Radioisotopes

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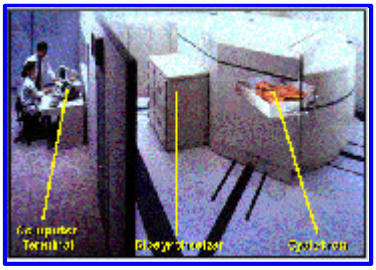
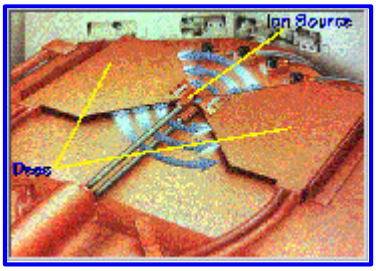


Click on image above to view full-size image.

Shown here are the three major components of a radioisotope delivery system (RDS). The cyclotron is a particle accelerator used for the production of radioisotopes. These radioisotopes are then attached to biologically relevant molecules using a biosynthesizer unit. The entire process is controlled by a personal computer.

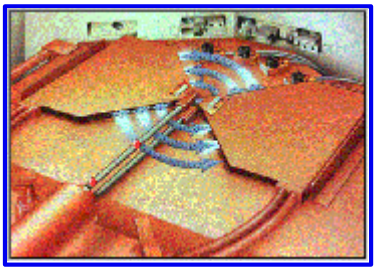
Cyclotron Operation



Click on image above to view full-size image.

A cyclotron consists of a pair of hollow, semicircular metal electrodes (called "dees" because of their shape), positioned between the poles of a large electromagnet (not shown). The dees are

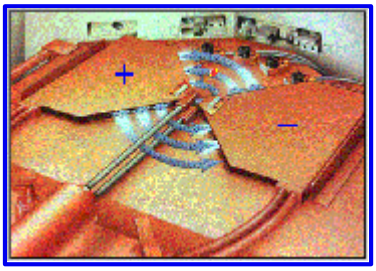
separated from one another by a narrow gap. Near the center of the dees is an ion source (typically an electrical arc device in a gas) that is used to generate charged particles.



Click on image above to view full-size image.

During operation, particles, such as the hydrogen ion depicted here, are generated in bursts by the ion source. A filament located in the ion source assembly creates a negative charge on the hydrogen ions through the addition of two electrons to the hydrogen (the electrons are depicted in yellow in the following screens).

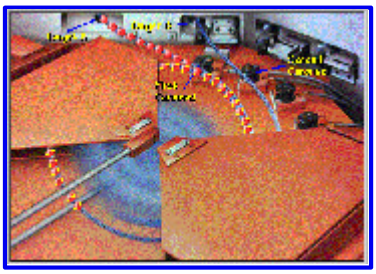
As the negative ions enter the vacuum tank, they gain energy due to a high-frequency alternating electric field induced on the dees. As the negative ions flow from the ion source, they are exposed to this electric field as well as a strong magnetic field generated by two magnet poles, one above and one below the vacuum tank. Because these are charged particles in a magnetic field, the negative ions move in a circular path.



Click on image above to view full-size image.

When the negative ions reach the edge of the dee and enter the gap, the RF oscillator changes the polarities on the dees. The negative ions are repelled as they exit the previously positive but now negatively charged dee. Each time the particles cross the gap they gain energy, so the orbital radius continuously increases and the particles follow an outwardly spiraling path.The particles are "pushed" from the first dee and drift along a circular path until they are attracted or "pulled" by the second dee which has become positively charged.The result is a stream of negative ions which are accelerated in a circular path spiraling outward.

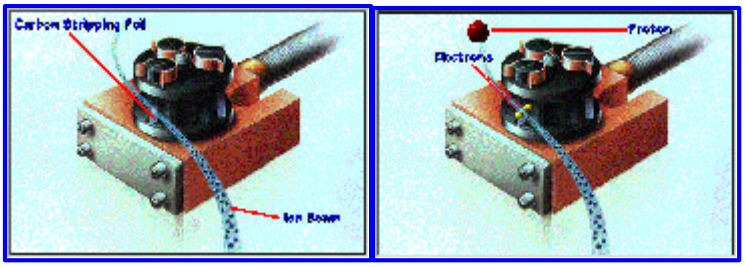
The Carousel



Click on image above to view full-size image.

The stream of negative ions is directed towards the first carousel positioned between the

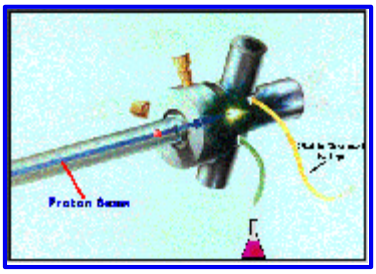
accelerators and target chamber A. The carousels contain thin carbon foils that strip each H- ion of its two electrons. When the negative ions lose both electrons, they become H+ ions or protons (indicated by the loss of the electrons, shown in yellow). Through computer-controlled movement of an extractor assembly, the proton beam can be split and directed to two separate targets. The stripping foil is positioned partway into the beam so that a portion of the beam is extracted. The remainder of the particles continue in a circular path completing an additional orbit.



Click on one or both of the images above to view full-size image(s).

In the negative ion systems, the proton beam is extracted by passing the (H-) ion beam through a thin carbon foil, located on one of the four carousels. The extraction foils strip each (H-) atom of its two electrons. When the negatively-charged hydrogen ions lose both electrons, they become (H+) ions or protons. The protons proceed through the foil; however because they now have the opposite charge, yet are still under the influence of the magnetic field, they follow a circular path, tangent to their former orbit away from the center of the cyclotron. This proton stream is directed toward a target chamber. Extraction foils range in thickness from 5 to 25 µm and have about a 100 hour lifetime.

Target Chamber



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The target chambers are integrated into the total RDS system to optimize performance of both the targets and the other RDS elements (cyclotron, beam transport lines, shielding, and computer control). The target chambers feature compact size for economical shielding, ease of removal and installation for maintenance, and a simple, reliable design.

In preparation for bombardment, a stable chemical isotope is loaded into the target chamber.

The proton beam from the cyclotron enters the target chamber and by means of a nuclear reaction, changes the stable target material into a radioactive isotope. These radioisotopes are unstable and decay by a process involving positron emission. It is this feature that is utilized in imaging studies involving Positron Emission Tomography.

Computer Control Unit

All functions of the RDS, including the cyclotron and biosynthesizer units, are controlled

through the use of a personal computer.

Production of a specific radioisotope is accomplished by stepping though a set of menu selections on the terminal display. The operator selects an item from the menu to produce the desired radioisotope. All other processes are carried out automatically. Operation of the RDS is oriented toward production of the final product rather than intermediate accelerator parameters. A separate "maintenance" mode is provided for monitoring and controlling the separate system components.

Complete computer control allows for a significant reduction in personnel requirements, allowing more time for other, more important tasks.

Biosynthesis of Radionuclides

Click on image above to view full-size image.

The biosynthesizer unit depicted above can be used to produce a variety of clinically useful radiolabeled compounds. Radioisotopes produced with the cyclotron are transfered to the biosynthesizer unit and attached to clinically useful biological markers.

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TUTORIAL: Radioisotope Production

PET Tracers: Structure and Function

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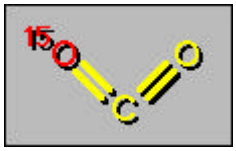
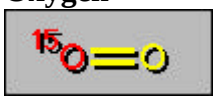
I. Oxygen
Oxygen-15 has a half-life of 2.1 minutes.

- **Carbon Dioxide**



Radiolabeled water and carbon dioxide have both been used to study local cerebral blood flow.

- **Oxygen**



[15O]-labeled water and oxygen are being evaluated for the quantification of myocardial oxygen consumption and oxygen extraction fraction. [15O]-labeled oxygen can also be used to measure tumor necrosis.

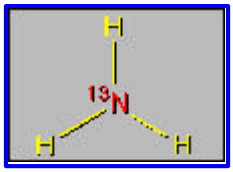
- **Water**

15O-labeled water and oxygen are being evaluated for the quantification of myocardial oxygen consumption and oxygen extraction fraction. 15O-water is also used by many PET centers as a tracer for myocardial blood perfusion (in contrast to 13N-ammonia). Use of [15O]water has the advantage of a nearly 100% extraction fraction in myocardium. The extraction is unaffected by metabolism, which conceivably could modify the extraction fractions of other tracers such as [82Rb] or [13N]ammonia; a disadvantage is the high [15O] activity concentrations in the vascular compartment of myocardium, the cardiac chambers, and the lungs. Accurate measurements of the tracer concentrations in myocardial tissue are therefore difficult.

II. Nitrogen

Nitrogen-13 has a half-life of 10.0 minutes.

- **Ammonia**



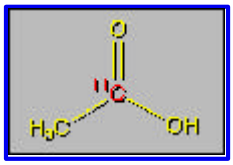
Click on image above to view full-size image.

[13N]-labeled ammonia can be used to measure blood flow. This tracer moves from the vascular space to tissue by both active transport (sodium-potassium pump) as well as by passive diffusion. Once inside cells, this tracer is primarily metabolized by the glutamic acid-glutamine pathway. [13N]-ammonia has been found to be an excellent measure of regional myocardial perfusion in both normal and diseased states. An added advantage of [13N]ammonia is the relatively short physical half-life, which allows for repeat studies. Clearance of [13N]ammonia from blood is rapid, with high tissue retention fractions, resulting in high-contrast cross-sectional images of the myocardium. [13N]ammonia studies are often combined with [18F]FDG to compare myocardial blood flow with glucose metabolism in an effort to detect "mismatch", an index of viable but

compromised tissue.

III. Carbon
Carbon-11 has a half-life of 20.4 minutes.

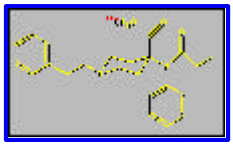
- **Acetate**



Click on image above to view full-size image.

11C-labeled acetate is used for measuring oxidative metabolism. The primary metabolic fuel for the myocardium are fatty acids, and therefore this tracer is very useful in assessing the metabolic status of the heart.

- **Carfentanil**



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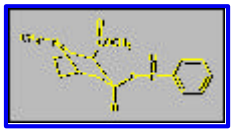
Carfentanil is a mu-opiate receptor agonist that is approximately 8000 times more potent than morphine. [11C]-labeled carfentanil is use with PET to study opiate receptors in the brain (Dannals, et al., 1985, 1993).

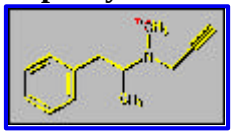
- **Cocaine**



Click on image above to view full-size image.

PET can be utilized for the identification and characterization of drug binding sites in the brain. [11C]-labeled cocaine has been utilized in human and monkey brain to study the distribution and pharmokinetics of this agent. For example, it was demonstrated that cocaine is rapidly taken up and cleared from the striatum, and the time course of this parallels the temporal pattern of the "high" experienced with cocaine. PET has also been used to study the biochemical effects of cocaine. It has been demonstrated that while acute doses of cocaine have little, if any, effect on dopamine D2 receptor availability (measured with [11C]N-methylspiroperidol), chronic cocaine results in a down regulation of D2 receptors. Dopamine metabolism is also reduced in chronic cocaine abusers (measured with 6-[18F]fluoro-L-DOPA). (See Fowler, et al. for review).

- **Deprenyl**

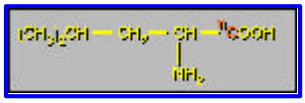


Click on image above to view full-size image.

The distribution of monoamine oxidase (MAO) type B, the isoenzyme that catabolizes

dopamine, has been monitored in the human brain by PET following injection of radioactive [11C]-deprenyl (Fowler, et al., 1987). Deprenyl is a potent MAO B inhibitor and has been shown to be effective in the treatment of early Parkinson's disease.

- **Leucine**



Click on image above to view full-size image.

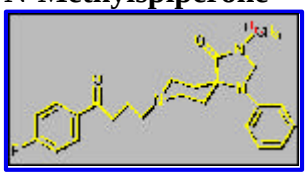
[11C]-labeled methionine and leucine can be used to evaluate amino acid uptake and protein synthesis, providing an indicator of tumor viability.

- **Methionine**

Click on image above to view full-size image.

[11C]-labeled methionine and leucine can be used to evaluate amino acid uptake and protein synthesis, providing an indicator of tumor viability.

- **N-Methylspiperone**



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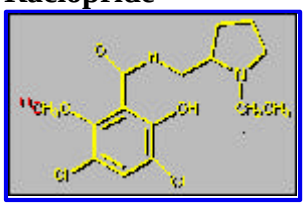
N-methylspiperone (N-methylspiroperidol) binds to dopaminergic D2 receptors. [11C]-labeled N-methylspiperone has been used to study the neurochemical effects of various substances on dopaminergic function.

- **Raclopride**



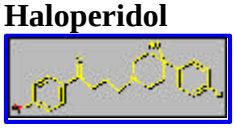
Click on image above to view full-size image.

[11C]-labeled raclopride is used in PET to study the function of dopaminergic synapses. Raclopride binds to dopamine D2 receptors and is a selective, reversible inhibitor of dopaminergic D2 receptor function (Farde, et al., 1986).

IV. Fluorine

Fluorine-18 has a half-life of 109 minutes.

- **Haloperidol**



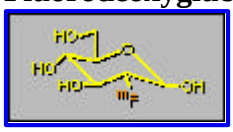
Click on image above to view full-size image.

PET has been used to study the binding sites of haloperidol, a widely used antipsychotic and anxiety reducing drug. Haloperidol is a potent antagonist of the neurotransmitter dopamine, and acts on dopamine D2 receptors. Recent evidence suggests that haloperidol may also act on other types of dopamine receptors, since [18F]-haloperidol binding is seen in the cerebellum, a structure devoid of D2 receptors (Fowler, et al., 1990).

- **Fluorine Ion**

Radiolabeled fluorine ion [18F-] was once a standard agent for clinical bone scanning. The pattern of skeletal uptake of [18F-] is similar to that of Technetium-99m-diphosphonate (conventional gamma camera tracer); normal bone structures demonstrate uniform uptake of [18F-]. Both [18F]- and [99mTc] are quite sensitive indicators of skeletal pathology but are limited in terms of pathological specificity (i.e., benign and malignant processes both result in stimulated osteoblastic activity and increased uptake). However, because [18F-] has a better bone-to-soft-tissue uptake ratio compared to [99mTc] diphosphonate, a whole-body PET bone scan may be both more anatomically accurate and more numerically precise than a comparable gamma camera study.

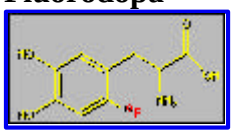
- **Fluorodeoxyglucose**



Click on image above to view full-size image.

[18F]-labeled 2-deoxyglucose (FDG) is used in neurology, cardiology and oncology to study glucose metabolism. In cardiology, [18F]-labeled FDG can be used to measure regional myocardial glucose metabolism. Although glucose is not the primary metabolic fuel of the myocardium, glucose utilization has been extensively studied as a metabolic marker in both diseased and normal myocardium. Because [18F]-labeled FDG measures glucose metabolism it is also useful for tumor localization and quantitation. FDG is potentially useful in differentiating benign from malignant forms of stimulated osteoblastic activity because of the high metabolic activity of many types of aggressive tumors.

- **Fluorodopa**



Click on image above to view full-size image.

18F-labeled PET tracers are used in neurology to study metabolism, neurotransmission, and cell processes. L-[18F]DOPA can be used to examine the presynaptic distribution of stored neurotransmitter. L-DOPA is the precursor for the neurotransmitter dopamine and radiolabeled L-DOPA is taken up by dopaminergic terminals and becomes incorporated into the neurotransmitter. L-[18F]DOPA has been used clinically in the study of Parkinson's disease.