A Brief History of Positron Emission Tomography (PET)

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The development of positron emission tomography (PET) illustrates how advances in basic science translates into benefits for human beings. In 1930 Ernest Lawrence and co-workers conceived of the cyclotron. By 1938 Lawrence, Livingston, et al had designed a "medical cyclotron." The subsequent production of C-11, N-13, O-15, and F-18 found many uses in medical and physiologic research. The introduction of F-18 deoxyglucose represents another major step toward practical clinical use of positron-emitting tracers. We have now achieved the transition from the postulation of the existence of positrons to their use in a wide variety of diseases.

The story of the invention and development of positron emission tomography (PET) is based on the creative genius of theoretical and experimental physicists, chemists, biologists, and physicians who did not initially foresee the great benefits the new technology would eventually provide.

Throughout history, advances in medicine have depended on research directed toward military purposes. Examples are the discovery of the element, iodine; the development of penicillin and other antibiotics; blood transfusion and blood typing; ultrasonography; computers; to name a few other striking examples in addition to PET. Unfortunately, in the case of PET, the continuing association in the mind of the public that all radiation is harmful and is to be avoided at all costs remains an obstacle to the development of the peaceful uses of atomic energy.

Theoretical physicist, P. Dirac, postulated the existence of positive electrons (positrons) on the basis of the equations of quantum mechanics and Einstein's theory of relativity.[1] He demonstrated how the energy of subatomic particles is equal to plus or minus the square root of the square of the momentum and rest energy of the particles. Thus, subatomic particles could be both positive or negative.

In 1932, experimental physicist, C.D. Anderson of the California Institute of Technology, proved the correctness of Dirac's prediction by observing experimentally that cosmic rays include particles with the mass of electrons but move in a strong magnetic field along a path indicating their having a positive charge.[2] He called these particles "positrons," or positive electrons.

FROM POSITRONS TO PHOTONS

Whenever a positron passes through matter, after dispersing its kinetic energy, it encounters an electron in the matter, and the positron and electron interact and are annihilated, emitting their rest energy (that is, their mass) in the form of two photons, each with an energy of 511 keV, according to Einstein's famous equation: E equals mc^2. The distance that the positron will travel in tissue before annihilation depends on the energy of the positron, this distance being about 1 mm in the case of the positrons emitted by the radionuclide fluorine-18 and about 2 mm in the case of oxygen-15. The travel of the emitted positron from the atom of interest before annihilation of the positron limits the spatial resolution of PET imaging in human beings to about 1 to 2 mm.

ARTIFICIAL RADIOACTIVITY AND CYCLOTRONS

In 1934 Curie and Joliot observed that when boron, magnesium, or aluminum were bombarded with alpha particles from radium or polonium, positrons continued to be emitted from the target for some time after the bombardment had stopped.[3] This was the first demonstration that artificial radioactive atoms could be produced.

Four years before, in 1930, Ernest Lawrence et al in Berkeley, California, conceived of the idea of accelerating particles between two D-shaped magnets, called a cyclotron, in order to produce progressively higher energy protons and deuterons that could then bombard elements to explore the nature of the atomic nucleus.[4] The cyclotron magnets in their first cyclotron were 4 inches in diameter, and their subsequent machines had 10, 37, and 60 inch magnets. Without their knowing it, between 1930 and 1934, the Lawrence group had been producing radioactive cobalt, copper, and other radionuclides

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from bombardment of the metal components of their cyclotrons. The report of the discovery of artificial radioactivity in 1934 by Joliot and Curie caused great disappointment within the cyclotron team at the Berkeley campus of the University of California because they had failed to be the first to demonstrate that one could make practically any element radioactive. They had failed to make this discovery because the power supply to their cyclotron and their radiation detection instruments were the same. Both were shut off simultaneously every evening.

As their cyclotrons progressively increased in size, the Berkeley group could produce and identify large quantities of artificial radioisotopes, including carbon-11, nitrogen-13, oxygen-15, and fluorine-18, each of which would subsequently prove of great significance to biomedical research.

In the 1930s, recognizing the importance of the new radioelements in applying the tracer principle, first propounded by Hevesy using naturally occurring radiotracers, biologists, physiologists, and physicians flocked to Berkeley. In 1938, Lawrence, Livingston, et al designated their fourth cyclotron a "medical cyclotron" (Fig 1).

The subsequent history of the field that became known as nuclear medicine is the story of the production of ever more perfect radiotracers to examine the human body where there is always something more to be seen. They began with the clarification of the process of photosynthesis in plants with carbon-11, and examined the metabolism of carbon monoxide in human beings. They used phosphorus-32 to further clarify the dynamic state of body constituents.

THE REACTOR PUTS THE CYCLOTRON ON A BACK BURNER

Wartime research, beginning in the late 1930s and extending to the 1950s, led to the development of the nuclear reactor. Lawrence's work was supported initially by private sources, particularly the Rockefeller Foundation, but subsequent development of the Calutron, a magnetic radionuclide separator for isolating purified uranium-238 was strongly supported by the American government.

In 1939, physicist Niels Bohr of Copenhagen visited Princeton University to meet with Einstein. Just before he left Denmark, he was told of the experiments of O. Hahn and F. Strassmann, published in *Naturwissenschaften* in January 1939.[5] These physicists had reported that barium had been produced by neutron bombardment of uranium as a result of nuclear fission. At a meeting sponsored jointly by George Washington University and the Carnegie Institution of Washington, Enrico Fermi and Niels Bohr conceived of the idea of a chain reaction because of the demonstration that there were neutrons flying off from the fissioning uranium nuclei. Their calculations showed that, if all the atoms of a kilogram of uranium-235 were to undergo fission, the energy released would be equivalent to the energy released in the explosion of 20,000 tons of TNT. This was of obvious

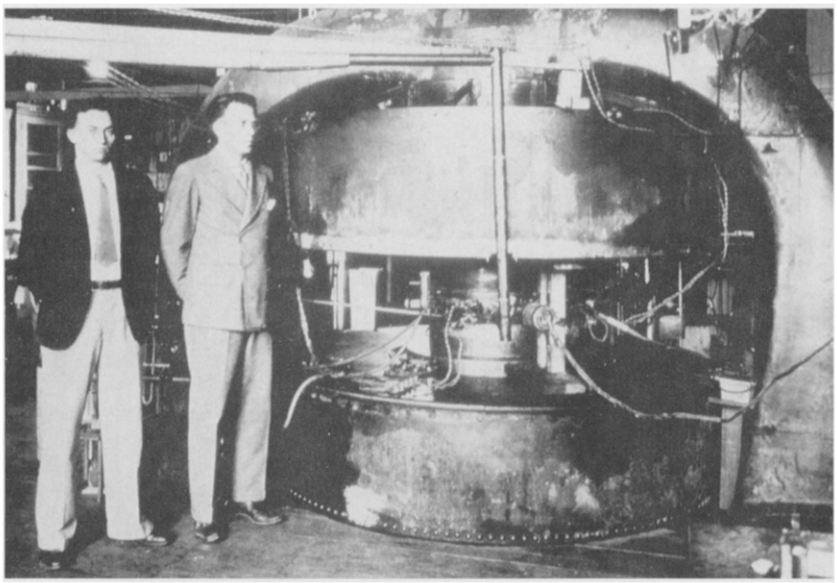

Fig 1. S. Livingston and E. Lawrence with the medical cyclotron developed in the late 1930s at the University of California in Berkeley.

military significance. Throughout history three domains of atomic energy have been inexorably linked: nuclear weapons, nuclear power, and nuclear medicine.

The nuclear reactor, invented by Fermi et al at the University of Chicago led to the production of great quantities of carbon-14, tritium, phosphorus-32 and other radionuclides, which resulted in the development of biochemistry as we know it today. The longer half-lives of these tracers greatly facilitated their availability, use and cost, compared to cyclotron-produced radionuclides. Because of its short half-life (20 minutes), carbon-11 lost its appeal. However, carbon-14 and tritium emitted only beta particles with a very short range in tissue, so that they could not be used to examine regional biochemistry within the living human body or experimental animals. Three decades were to elapse before physicians' desire to measure *in vivo* regional biochemistry led to a rebirth of interest in cyclotrons in biomedical research.

Initially, nuclear medicine physicians directed their attention to the imaging of organs, such as the liver and spleen, that could not be seen with conventional x-rays passing through the body. Radiation coming from radionuclides within the body could reveal the structure and defects in these organs.

The physical characteristics of technetium-99m (the 140 KeV energy of its emitted photons and its failure to emit particles) made it ideal for *in vivo* imaging with scanners and cameras detecting the photons to produce functional images. However, technetium-99m is a man-made element that does not exist in the human body. Organic chemistry is defined by carbon, and the only photon-emitting radionuclide of carbon is carbon-11, which requires a cyclotron for its production.

The development of "competitive" imaging methods, computed tomography (CT) and magnetic resonance imaging (MRI), redirected the attention of the nuclear medicine community back to the "biological" elements, carbon-11, fluorine-18, nitrogen-13, and oxygen-15.

IN VIVO BIOCHEMISTRY

External measurement of radiotracers in the body had been made since the earliest days of nuclear medicine in the 1940s. Initially, hand-held Geiger-Muller counters were moved systematically in a grid pattern to measure the rate of accumulation of radioactive iodine by the thyroid gland in order to help decide whether a thyroid nodule was benign or malignant. The radioactivity emitted at multiple points across the grid with markers 1 cm apart was used to map out the images of the distribution of the radioiodine.

In 1950, Benedict Cassen at UCLA automated the movement of the detector over the region of the thyroid and replaced the GM detector with newly developed thallium-activated sodium iodide crystals, producing what was called a "scanner."[6] This device was soon used to produce nuclear images of other organs, such as the liver, spleen, and lungs. *In vivo* molecular imaging was born.

POSITRON IMAGING

In 1948, Kety and Schmidt first used the nonradioactive tracer, nitrous oxide, to apply the Fick principle to measure cerebral blood flow.[7] Later they replaced nitrous oxide with krypton-79 to facilitate the measurements, and obtained values for cerebral blood flow almost identical with those obtained with nitrous oxide. Lassen and Munck used krypton-85 to modify the nitrous oxide method, and in 1961 substituted xenon-133 for the quantitative measurement of regional cerebral blood flow in human beings using multiple small single crystal radiation detectors.[8]

Kety's close associate, Louis Sokoloff, knew that measurement of blood flow to the brain as a whole was not able to fulfill his dream of relating mental function to brain function. He knew he had to examine regional, not global, brain function. In 1964 he wrote that: "Since the functional activities of these component structures vary independently of one another, it might be expected that their rates of blood flow would also differ widely and vary independently of one another."[9] Therefore, he directed his research to the study of cat brains with I-131 labeled trifluoroiodomethane and autoradiography to measure the blood flow to discreet small cerebral regions.[10]

In 1953, Brownell and Sweet described a multidetector system for localization of brain tumors with positron-emitting radionuclides, copper-64 and arsenic-75.[11] In 1966 Yamamoto et al at the Brookhaven National Laboratory (BNL) constructed the device shown in Fig 2 to be used to measure regional cerebral blood flow with positron emitting radiotracers. After preliminary studies of the instrument at BNL the instrument was moved to

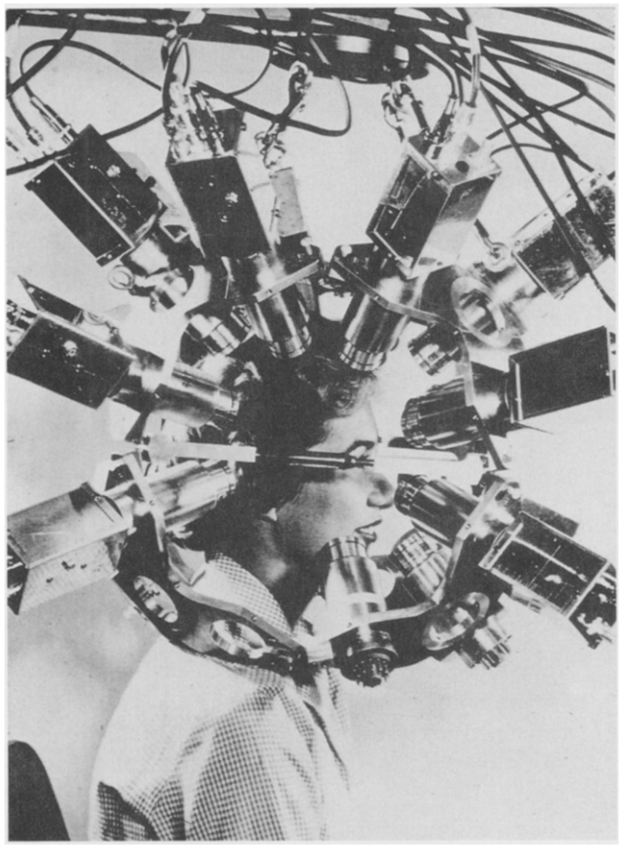

Fig 2. Original design of the device for examining positron emitting radiotracers in the brain at Brookhaven National Laboratory by Yamamoto, Robertson et al. The idea of a circular array of detectors in a single plane had not yet been invented.

the Montreal Neurological Institute and the detectors were arrayed in a single plane surrounding the patient's head. These investigators tried several reconstruction methods but never hit upon the filtered back projection method that was to prove successful in computed tomography (CT) of conventional x-ray imaging, and subsequently was to be applied to PET imaging.

TOMOGRAPHY

In 1968 Kuhl and Edwards introduced the concept of reconstruction of source distributions by superimposing multiple cross sections of transverse axial scans in conventional nuclear imaging, and built a device for constructing such images (Fig 3).[12] The method of reconstruction was very primitive, and the development of PET was accelerated by the development of transverse axial tomography for radiography by Hounsfield.[13,14] Mathematical reconstruction algorithms developed for CT were applied to PET. In 1975, Ter-Pogossian, Phelps, and Hoffman described a PET instrument that employed the filtered back projection method of reconstruction (Fig 4).[15-17]

The Renaissance of C-11, N-13, O-15, and F-18

In the mid-1950s while looking for a method to examine the oxygenation of tumors, Ter-Pogossian and Powers (1958) at Washington University in St. Louis, MO, worked with oxygen-15 (half-life 2½ minutes) produced by the cyclotron built in the early 1940s in the physics department to study mice with mammary adenocarcinomas, using autoradiography to map the distribution of the injected oxygen-15 (18) (Fig 5). These early experiments stimulated interest in the use of short-lived radioactive gases, and led in 1955 to the building of the first medical cyclotron located on the grounds of a hospital, namely, Hammersmith Hospital in London. The initial success of these experiments led to the installation of a National Institutes of Health (NIH)-funded cyclotron in the Washington University Medical Center. Subsequently, the Department of Energy funded hospital cyclotrons at UCLA, the

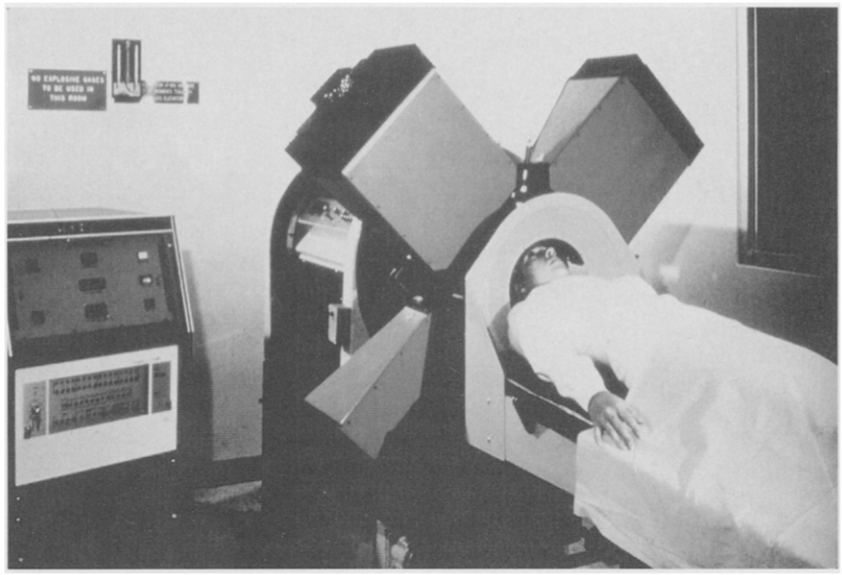

Fig 3. Mark IV tomographic scanner developed by Kuhl et al at the University of Pennsylvania for the study of single photon emitting radiotracers. Arranging the detectors in a ring surrounding the patient's head was an important advance.

University of Chicago, and Memorial Sloan Kettering Institute in New York. Existing cyclotrons at UC Berkeley and Ohio State continued to be used for the production of radionuclides of biological importance.

THE FDG STORY

Långström wrote: "Carbon-11 fulfills Claude Bernard's dream of a tracer for examining physiological processes in complex living systems."[19] In 1977, after a decade of development, Sokoloff et al described in a classical paper the carbon-14 deoxyglucose method for measurement of local cerebral glucose utilization.[20]

Prior to this work, the Kety-Schmidt method for measurement of cerebral blood flow made it possible to determine in living persons the average rate of glucose use in the brain as a whole from measurements of blood flow and the cerebral arteriovenous difference in glucose levels. Reivich et al (1979)[21] extended the carbon-14 radiographic method to measurements of regional glucose utilization with the use of fluorine-18 deoxyglucose. This tracer had been developed by Ido and colleagues.[22]

The first images of ^{18}F- FDG in the brain were performed with the Mark IV tomography system of Kuhl et al, but were of poor quality because filtered

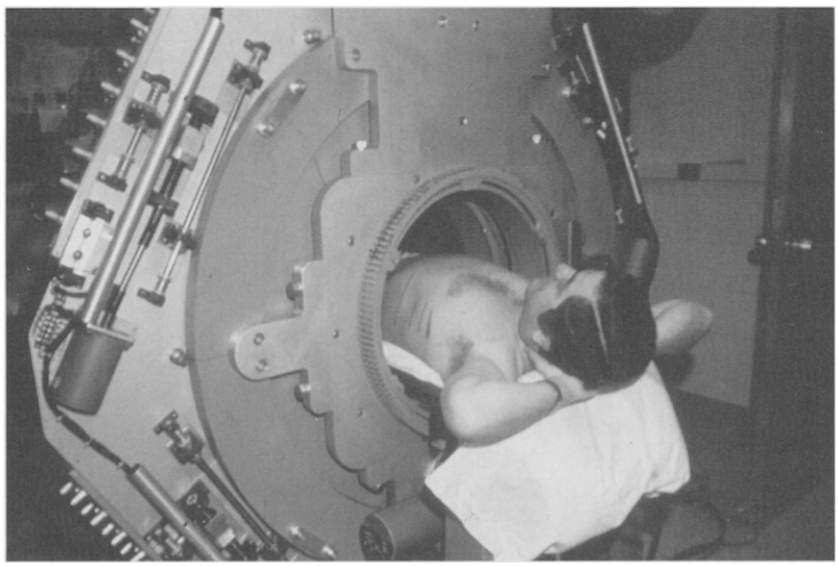

Fig 4. The author being examined by Ter-Pogossian et al in the original PETT scanner at Washington University in Saint Louis. The tracer was carbon-11 carbon monoxide.

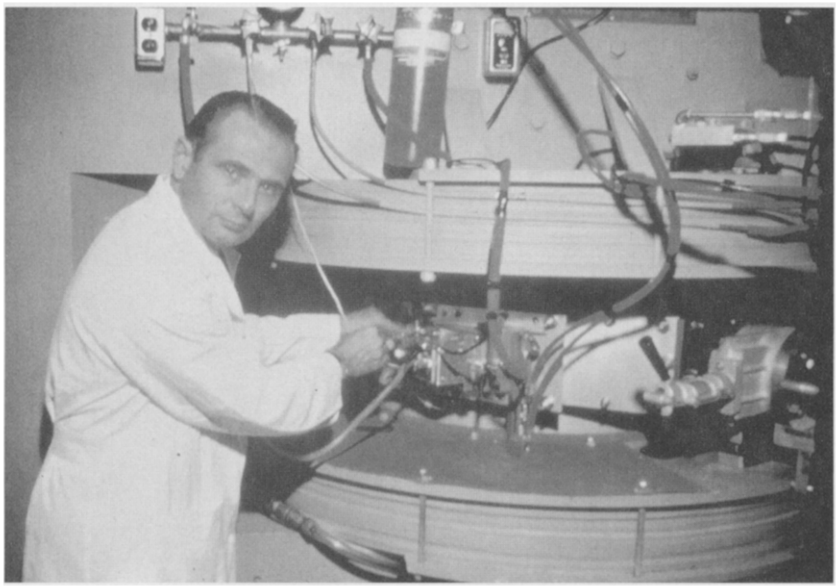

Fig 5. Michel Ter-Pogossian with the cyclotron at Washington University.

back projection was not used in the reconstruction. Nevertheless, it was a significant accomplishment to have produced and imaged this tracer in the human brain. The development of this tracer and the modeling of its use to reveal regional cerebral glucose utilization, together with measurement of regional cerebral blood flow with oxygen-15 water, gave birth to functional mapping of the human brain.

NUCLEAR ONCOLOGY

Over the past decade, numerous studies with fluorine-18 labeled deoxyglucose (^{18}F-FDG) and dedicated PET scanners have shown how measurement of ^{18}F-FDG accumulation by cancerous lesions can help in the solution of many problems in the care of patients with cancer.[23–35] These uses are summarized in Table 1.

Many types of cancer have been found to have increased anaerobic breakdown of glycogen to glucose as an energy source compared with normal tissue. There is often an increase in the enzyme hexokinase HKII which enhances the glycolytic process, converting glucose to lactate, rather than to carbon dioxide and water.

MOLECULAR COINCIDENCE DETECTION (MCD)

A new approach to imaging FDG accumulation by neoplasms occurred in 1994 when Gerd Muehllehner and his engineering team at ADAC Laboratories modified a single photon emission tomography (SPECT) scanner to perform coincidence imaging of the 511 keV photons emitted by decay of positron-emitting radiotracers, such as ^{18}F-FDG, without a lead collimator.[36] The process was called "Molecular Coincidence Detection" (MCD). This advance offered a whole new approach for imaging ^{18}F-FDG in the care of patients with cancer, initially to determine whether curative surgical treatment would be possible.

The increasing availability of commercially produced ^{18}F-FDG was another factor in making possible the greater use of ^{18}F-FDG studies in the care of patients with cancer.

Dual-detector scintillation cameras operating in coincidence mode do not use lead collimators to determine the location of the radiotracer within the body. Because the two 511 keV photons associated with positron decay are emitted at 180° from each other, electronic means, called coincidence detection, are used to localize the site of positron

Table 1. Uses of PET Scanners for Patients With Cancer

(1) Detecting primary sites of cancer
(2) Differentiating benign and malignant lesions
(3) Grading the degree of malignancy of a lesion
(4) Staging the extent of disease
(5) Assessing whether lesions seen with CT or MRI are cancerous
(6) Planning treatment
(7) Monitoring the response to treatment
(8) Detection of recurrent disease

emission. Two photons must be detected within a narrow timing window (less than 15 nanoseconds). The crystal thickness of the dual head detectors was increased from 3/8 to 5/8 inches to improve detection efficiency. New high count-rate digital electronics were developed which increased accepted count rates from 200,000 counts per second (cps) to 2,000,000 cps. The electronics use one analog to digital converter for each photomultiplier tube which enables virtually simultaneous counting of two coincident events. The digital electronics make it possible for the system to use the thicker crystal without compromising the performance of the system as a single photon SPECT scanner. In MCD imaging, the two detectors rotate around the body, acquiring counts from photons coming from different angles surrounding the region of interest. These are then processed by computer to yield transverse, coronal, and sagittal images.

The cover of the Journal of Nuclear Medicine proclaimed in 1991: "Clinical PET: Its Time Has Come" (Fig 6). It has taken a long time for PET to reach the stage of clinical applications, but its future seems assured. No other technology reveals the chemistry of different regions of the living human body by means of external radiation detectors safely and noninvasively. Many institutions throughout the world have made the decision to take on the complexity and expense of establishing a PET capability, because the value of the information provided is clearly a major advance in biomedical science, research, and clinical practice. Positron emitting tracers are increasingly being provided by a regional supplier, either an academic medical center or a commercial radiopharmacy.

The ability to carry out whole body imaging of patients at high risk of developing cancer, for example, persons with a strong family history of multiple endocrine neoplasms, is helpful not only in diagnosis, but also in making it possible to begin specific therapy early in the course of the disease.

Studies of the brain with PET have begun to close the circle between brain chemistry and behavior. The difficulty lies not in new ideas but in escaping the old ones. An old idea is to classify disease primarily on the basis of histology. A diagnosis based on regional biochemical abnormalities is much more likely to lead to better design and development of drugs as well as individualization of patient therapy.

Today advances are being made chiefly in oncology, cardiology, and neurosciences. In the present climate of changing medical practice, it is increasingly clear that ignorance is what is expensive in medicine. Better selection of patients for specific therapy, whether it is surgery, radiation, or chemotherapy, and better monitoring the effect of therapy is where revolutionary advances are being made. History repeats itself, because no one listens the first time. The messages being sent by the pioneers in the development of PET are now being heard loud and clear.

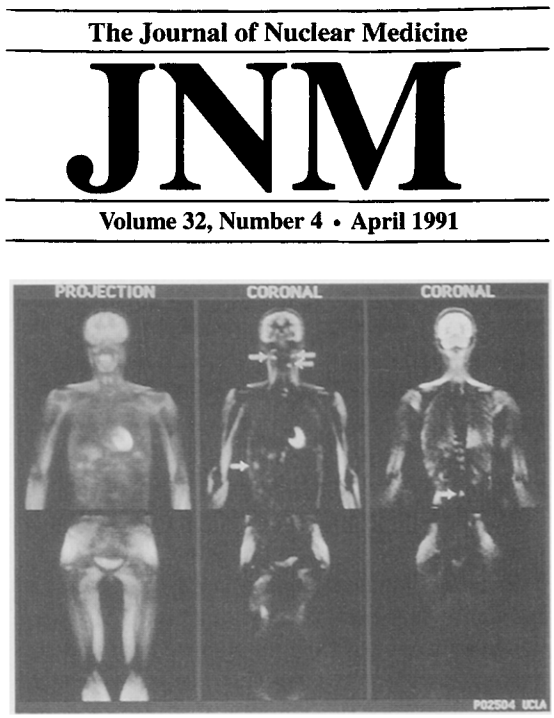

Fig 6. Cover of the *Journal of Nuclear Medicine* in 1991, referring to an editorial in the journal.

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