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Naked to the Bone

Medical Imaging in the Twentieth Century

Bettyann Holtzmann Kevles

Helix Books
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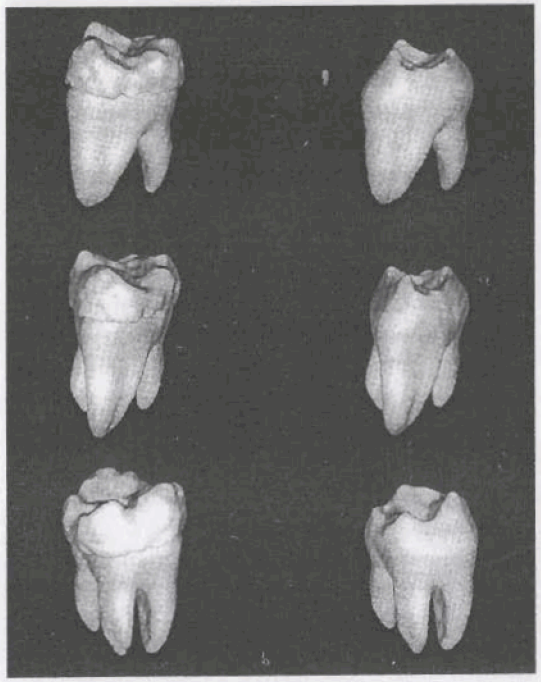


39. MRI of human molar by Pratik Ghosh (1995). The roots and air-dentine-enamel interfaces are easily distinguished. Computational removal of the enamel crown allows direct examination of the morphology of the dentine cap; it is here that the structure of the crown is initially determined as tooth development progresses. Courtesy of Pratik Ghosh.

In a bow to the cabarets in 1903 that featured dancers carrying glow-in-the-dark radium-filled cocktails, MRI has even found its way onto the New York stage. In 1994, the Feld Ballet featured a new production called *MRI*. In this abstract dance, the figures moved up and down in a metal cage because, as Feld explained, "changing the relationship of gravity changes the nature of time."[48] One critic likened the ballet spiritually to Auden's poem about "the body beneath the skin."[49] Another, more scientifically, wrote, "By referring to the medical diagnostic technique magnetic resonance imaging, Mr. Feld reportedly wanted to present the equivalent of objective data, to reveal images hidden below the surface without commenting on them."[50]

By 1994 MRI had become a catch-phrase for all medical scans. Representing the general confusion of the educated public, the critic in *New York Newsday* thought she was clarifying the technology when she commented: "MRI stands for 'magnetic resonance imaging'; you may have seen the initials if you've ever had a CAT scan." MRI had become synonymous with all imaging innovation and with its intimations of mystery, new age spiritualism, and hi-tech machines.[51]

Nine

From the Inside Out
PET (Positron Emission Tomography) in Nuclear Medicine

George Hevesy, a young Hungarian physicist, arrived in Manchester, England, in 1911 to learn the new techniques that the great Ernest Rutherford was using to study electrons. When he was asked to separate the radioactive isotopes of lead from a pile of ordinary lead ore—a procedure we now know is impossible by chemical means—he was stymied. But making the best of a bad situation, he grasped triumph from the jaws of defeat by turning the radioactive isotopes into tracers.

Hevesy had found a room in a boardinghouse and, familiar with such hostels, he suspected the integrity of its cuisine. One Sunday evening to satisfy his curiosity he performed an experiment. Bringing the laboratory to the dinner table, he added a speck of the radioactive metal to the fresh meat pie. The following Wednesday he brought an early radiation detector, an electroscope, to dinner and demonstrated to the collected guests that the leftover meat—marked with radioactive lead—had survived the chopper and the oven and been returned to the table in the form of a soufflé.[1] By "tagging" the pie, Hevesy had "traced" the meat through the kitchen back to the table. Some decades in the future similar tracers would enable scanners to obtain images of the body, from the inside out.

Seventeen years later and half a world away, the neurosurgeon Harvey Cushing at the Peter Bent Brigham Hospital in Boston examined a patient who complained of headaches, failing vision, and most curious of all, a loud

blowing sound inside his head whenever he used his eyes. Cushing operated but could not remove the vascular malformation he discovered near the man's visual cortex; when he closed the skull, he left a small bony defect sticking out beneath the scalp. This protrusion enabled Cushing to hear, and even record, the blowing sound (called a *bruit*) which increased in volume every time the man used his eyes to read. In the annals of brain research, this case remained a unique demonstration of the close connection between blood flow and cerebral function until 1983 when radioactive tracers, which Hevesy had pioneered, were used in the form of PET (positron emission tomography) scans to record and map the functioning of sight.

The development of PET is the story of the merging of two separate technologies: the first, which began with Hevesy, is the creation and manipulation of biologically safe and useful radioactive tracers that have to be swallowed, inhaled, or injected into the body; the second, which began twenty-five years later, is the construction of instruments to detect those radioactive sources inside the body and from those signals extract tomographic pictures.

PET differs from the other computerized imaging technologies in the preponderance of physicians, or scientists employed in or collaborating with medical laboratories (who were sensitive to the hazards of radioactive isotopes) among its inventors. They solved the initial ethical dilemma of finding a human subject by following the medical tradition of experimenting on themselves. Hevesy was the first person to swallow radioactive deuterium. Indeed, some of these isotope pioneers were surprised, as the years passed, to discover that the radiation illnesses they had presumed would occur, never, in fact, did.

When Hevesy began his research in earnest after World War I, he was limited to a handful of naturally occurring radioisotopes, like the lead he had used to expose his landlady's recycled leftovers. Physicians in the 1920s simply moved their new Geiger counters manually over the surface of the patient's skin to track where these substances had gone. Like Bell's effort to "sound out" the bullet inside President Garfield, doctors listened to, rather than watched, the signals from their detectors.

In Copenhagen, and later in Freiburg, Germany, Hevesy explored the uses of radioisotopes by growing bean plants in a solution containing radioactive lead. At intervals, as the plants matured, he measured the radioactivity of their roots, stalks, leaves, and beans, in effect following the course of the leaded solution through the growing plant. This simple experiment, for which Hevesy received the Nobel Prize for chemistry in 1943, established three crucial principles: first, that radioisotopes of elements participate in biochemical and physiological processes in the same way as the chemicals they have replaced; second, that organisms absorb material selectively—the bean plants only absorbed the lead that was in the nutrient they needed, not as much nutrient as was available; and third, that there is metabolic turnover, that organisms continually cycle the substances they absorb—the lead isotope, having entered the plant, did not stay there indefinitely but passed through at a predictable rate; moreover, while it remained in the plant, it decayed at a predictable rate.

This discovery had a practical application after the disastrous meltdown at the Chernobyl nuclear power plant outside of Kiev, Ukraine, in 1986. One of the radioactive isotopes released was iodine. Polish health authorities distributed potassium iodide to people living beneath the path of the radioactive cloud, because it concentrates in the thyroid gland. They knew that once the thyroid was filled with as much potassium iodide as it could absorb, there would be no room for any additional iodine from radioactive fallout, that the "good" iodine would remain in the thyroid long enough for the "bad" iodine to lose its radioactive punch.[2]

Hevesy continued to work with naturally occurring radioisotopes, using lead, bismuth, thallium, radium, thorium, and actinium as tracers, but none of these elements plays a role in the normal development of living organisms. Then, in 1934, Irène and Frédéric Joliot-Curie bombarded the nuclei of nonradioactive elements with high-energy atomic particles and produced the first artificial radioisotopes. Then everything changed. Within a short time there were radioactive isotopes of sodium, phosphorous, and iodine.

The next year Hevesy fed these radioisotopes to laboratory rats and established, on autopsy, that the isotopes had, in each case, gone to particular organs and tissue. This demonstration triggered what would become an avalanche of new radiopharmaceuticals—radioactive isotopes that home in on and label specific organs. Physiologists were able at last to trace specific metabolic functions inside the human body.

At the same time, Ernest Lawrence at the University of California's Radiation Laboratory in Berkeley used his ingenious new cyclotron—a circular accelerator—to bombard a host of elements with high-speed neutrons. Inspired by the Joliot-Curies, Lawrence produced a radioactive isotope of sodium which could be introduced harmlessly into the body, and over the next few years he manufactured another seventeen biologically useful radioisotopes.[3]

John Lawrence, Ernest Lawrence's physician brother and an ardent supporter of the use of radioisotopic tracers, recalled the feelings of excitement and apprehension that accompanied this work in the mid-1930s. He could not forget the tragedies of radium workers and remembered making trips to New Jersey to confer with the doctor who had attended "the radium dial painters who later developed aplastic anemia, osteonecroses, and osteogenic sarcomata." These visits convinced him that artificial radioactivity would not produce the same diseases because these isotopes were not permanently deposited in bone or tissue.

All the same, no one knew what the biological effects of working with the cyclotron might be. One study made in 1935 predicted the postnuclear reactions of victims exposed to enormous dosages of radiation such as those at Hiroshima, but these developments were only theoretical. In 1955, John Lawrence wrote, "As a matter of fact, in the 20 years since we first used artificially produced radioisotopes in humans, we have not run into delayed effects or complications as some of the skeptics predicted we would."[4]

In 1939, physicists in America mulled over the implications of a German report that when uranium atoms were bombarded by neutrons, they released

energy as their nuclei broke apart. The discovery of nuclear fission stimulated physicists in the United States to consider the possibility of a nuclear explosion and to initiate what became the Manhattan Project to build an atomic bomb. Among the accomplishments of the project was the creation of nuclear reactors which produced, as by-products, short-lived radioisotopes.

World War II was not a radiologist's war, but the development of the atomic bomb was to have important repercussions for medical imaging technologies. After the explosions in August 1945, the United States was in the nuclear weapons business. At the Manhattan Project, Colonel K. D. Nichols foresaw a "virtually unlimited production" of isotopes and suggested they be distributed to "outsiders," by which he meant doctors.[5] The Atomic Energy Commission (AEC) agreed and announced in *Science* magazine on June 14, 1946, that isotopes were now available for research. On August 2, the AEC shipped radioisotopes to hospitals around the country.[6] Medical use of radioactive isotopes became the tip of the iceberg of nuclear research, the part that the public could see and that the AEC wanted to talk about. These isotopes became the cornerstone of the public relations program that became the "atoms for peace" program seven years later during the Eisenhower administration.

Positrons Are Different

Extracting an image from radioactive isotopes was not part of the original plan. That plan focused on distributing isotopes that could be used in therapy, such as iodine, which would go immediately to the thyroid and destroy tumors there. The instrument that would eventually extract a tomographic image from an internal source of radiation began to evolve in 1951.

In 1975, positron emission tomography scanners reached the clinic. The term *positron* refers to the particular particles that the scanner records. Detected for the first time in 1932, positrons are the positive antiparticles of electrons, having the same mass. In the course of radioactive decay, positrons are emitted from the nucleus of some atoms along with protons and neutrons. The positron travels a short distance and collides almost instantly with an electron. They annihilate each other, and in the process produce two photons, or gamma rays, that shoot off at 180-degree angles from each other.

This "coincidence" phenomenon is the key to the way a PET scanner works. A ring of electronic detectors, connected to a computing system, surrounds the body which has absorbed radioisotopes. Whenever two detectors at opposite sides of the ring are hit by photons at the same time, we can infer that a positron must have been emitted from inside the body. Then, using the same mathematics developed for CT, the computer reconstructs a picture of the spatial density of the area where the radioisotopes have come to rest.[7]

Emission refers to the place where the signals originate inside the body. Unlike CT or MR, the PET technique involves putting something into the body—radioactive molecules—and then tracking their position on the inside from the outside. Emission imaging differs from both CT and MR because, in PET, the source that emits radiation is also the site that is being imaged. In contrast, CT and MR are *transmission* techniques.

The T stands for *tomography*, in that PET makes images of planes through the body. But unlike either MR or CT, the aim is not to produce images of anatomical structures of the particular slice of the body being observed. Instead PET tracks metabolic functions. The image itself is a kind of graph, a two-dimensional map on a computer monitor. Each pixel corresponds to the projection of a unit of volume in the body. Each pixel also represents a third dimension, a quantity, presented in the form of brightness, color, or gray-scale that reflects the rate of flow of the radiopharmaceutical over a period of time.[8] This allows physicians to watch the flow rate of blood or the position of the tracer in the heart or lungs. Most astonishingly, they can track the way different parts of the brain use energy in the course of a mental process, recalling a particular face, doing a calculation, reading an unfamiliar word—in short, thinking.

Toward a Machine

The first step toward PET was a machine built by the physicist Benedict Cassen at the University of California at Los Angeles in 1951. Cassen, a man of many interests, was a good friend of William Oldendorf, with whom he would chat often about the engineering problems of medical, especially radiological, instruments. Flush with the gift of radioisotopes from the AEC, the UCLA medical physicists focused on the best way to track and record radioactive emissions mechanically. Cassen's idea was to link isotopic readings with the new photomultiplier tube.[9]

The photomultiplier tube (in the image intensifier) had just revolutionized the whole practice of radiology by, among other things, allowing ordinary movie cameras, at last, to capture moving pictures of fluoroscopic images from the new, extremely bright, scintillating screen.[10] Cassen replaced the hand-held Geiger counters with photomultiplier crystals, and harnessed them to a motorized arm attached to a pen. The automated pen recorded the relative number of gamma rays emanating from the isotopes inside the scanned area of the subject's body, moving back and forth over a grid placed on top of the area he was studying, zigzagging down, a line at each sweep, like a television beam. Cassen's "scintiscanner" produced a crude picture of the spatial representation of, for example, a radioactive thyroid gland, as tracks on carbon paper.

The scintiscanner was the state of the art until replaced by the "photoscan," which was invented in 1954 by David Kuhl, who was then a medical student at the University of Pennsylvania. Kuhl would later make the first transmission image of the lungs of a naval astronaut. But the transmission scan was only a detour for Kuhl on his way to perfecting *emission* images.

Throughout the summer of 1954, and over the next few years, Kuhl spent all his spare time tinkering in the hospital basement. Kuhl's photoscan captured the image of a patient's thyroid by sending the output from the photomultiplier tube directly to a moving beam of light and from there to a sheet of photographic paper or film. The photoscan registered different intensities of light, producing images that radiologists could examine in the conventional X-ray viewing boxes that they were accustomed to using.

Kuhl had actually begun to think about medical imaging while still in high school in Berwick, Pennsylvania. As a teenager, he had explored the distribution of uranium compounds in the bodies of mice by autoradiography. This is a process in which the experimental animal is injected with radioactive material, then sacrificed and its freshly killed body laid out in slices on X-ray film.[11] The exposure provides an image of the distribution of radioactivity similar to images now generated by CT. The clarity of those images remained a goal as Kuhl continued to build increasingly sophisticated emission detecting machines.[12]

Applying for a grant to the National Institutes of Health in 1959, Kuhl described his vision as "a whole new concept of scanning body organs in a manner analogous to body section radiography" using radioisotopes.[13] In the next few years he built a series of scanners, all bearing the name Mark, such as Mark I, Mark II, and so on (a tradition carried over from the military, he supposes). He was especially encouraged by the work of two of his former teachers at the University of Pennsylvania: Louis Sokoloff and Seymour Kety.

Sokoloff had practiced his first specialty, psychiatry, while on active duty in the army in the mid-1940s, but he became disillusioned with the talk therapies then in fashion. Convinced that mental illness arose from biochemical disturbances, Sokoloff returned to Penn to work with his former teacher, Kety, a pioneer in measuring cerebral blood flow. Sokoloff continued Kety's investigations when Kety became the first scientific director of the combined research programs at the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness, and in 1953, joined him at the NIH. During his years in Washington, Sokoloff developed the technique of using radioactive isotopes to track blood flow as well as the concentration of labeled substances in the brain. In 1955 his studies of the effects of retinal stimulation in cats were the first examples of imaging local cerebral functional activities.

In 1957 Sokoloff began experimenting with a radioactive analogue of sugar, a molecule with the awkward name "2-deoxyglucose," that approximates glucose consumption in the brain. He suggested it could be used as a tracer for studying cerebral blood flow because, like glucose, it would go to whatever part of the brain needed energy most. Almost twenty years later, in 1979, Kuhl and two colleagues, Alfred Wolf and Joanna Fowler, figured out how to attach radioactive fluorine to deoxyglucose. This new radio-labeled chemical, FDG, quickly became the most frequently used short-lived radiopharmaceutical because it enabled PET to image the brain at work.

By the 1970s, the pharmaceutical branch of what was now called *nuclear medicine* had successfully pioneered the use of oxygen isotopes to track blood flow throughout the body. The instrument makers were hard at work, too, and increasingly better detectors suggested that emission methods would take the lead in medical imaging. The teams, scattered in hospital laboratories throughout the United States and Europe, were unaware that EMI was about to launch CT, and alter the playing field.

Nuclear Imaging and SPECT

The simple mapping of internal organs with radioactive tracers for medical purposes began with Hevesy in the 1930s. The development of injected radioactive tracers was accelerated by the discovery of technetium in the new Berkeley cyclotron before the end of that decade. But radioisotopes were not used routinely until 1961 when, starting with technetium, which became the warhorse of scanning, radioactive isotopes were radiotagged to chemical carriers, creating radiopharmaceuticals. Thus tagged, radiopharmaceuticals are used to scan almost every vital organ. These scans are not glimpses of the insides of the body, and are not really images. Rather, they highlight "hot" or "cold" areas, recording either functional or anatomical changes. They resemble silhouettes rather than three-dimensional pictures of the body's interior.

The invention of actual three-dimensional emission imagers began with the announcement of the first SPECT machines in 1968. SPECT (Single Photon Emission Computed Tomography) was the most versatile, convenient, and relatively inexpensive imaging technology of this new generation of machines and the first triumph of emission imaging. It evolved out of SPET (Single Photon Emission Tomography), Kuhl's first system for mapping photon emissions from internal radioactive substances, which did not use computers. He used cameras, which he kept steady while rotating a patient. The cameras recorded photons as single lines of data which were back-projected onto a film cartridge that rotated in synchrony with the patient. These projection strips were then built up into pictures, as Bracewell had done with data "strips" of sunspots.

By adding a computer (and eventually a rotating camera with an immobile patient), Kuhl turned SPET into SPECT—the C standing for the computer—and got a crude, but useful, three-dimensional image of the distribution of radioisotopes in an organ.[14] In 1972 Niels Lassen, in Copenhagen, began using SPECT to track blood flow in the brain to map function, especially the way movements by the right hand activated areas in the left cerebral cortex. Lassen also introduced the use of color into the computer-reconstructed images.[15] Ever since then the use of color in all computerized imaging has been a matter of controversy. Those who defend it point out that there is no light inside the body so that there is no "real" color or real illumination to be reproduced and the use of color dramatically delineates one kind of tissue from another. Opponents deride its use, asserting that color exaggerates the differences

between tissue and is really used for public relations and to attract investors.

Two years later at Berkeley's Donner Laboratory, Thomas Budinger presented the first study of a patient with quantitative SPECT. Budinger, who had earlier in his career studied oceanography and helped map underwater icebergs, found his interest in visualization redirected to a different kind of unmapped territory—the brain. Under his direction, Berkeley's lab would perfect SPECT and, turning to PET, generate the highest-resolution images of any PET scanner.

SPECT, which provides a generalized tomographic image by using rotating cameras (or a single camera) to detect and reconstruct gamma-ray emissions, can use only a limited number of radioisotopes.[16] Relatively inexpensive and easy to operate in a clinical setting, SPECT is the most frequently used emission-scanning technology all over the world.

Yet SPECT has major drawbacks. Its images have only half the spatial resolution of PET, and in some instances individual pixels are so large they give the impression of a Cézanne landscape.[17] This limits its use for delicate organ mapping. Moreover, SPECT exposes the whole body to small doses of radioactivity for periods as long as several days. The length of exposure is a result of using isotopes with a shelf-life long enough to be shipped to hospital pharmacies. These over-the-counter isotopes are a cheaper, but less subtle tool.

The Center of the Road: PET

In the United States, with the blessings of the AEC, scanning experiments with positron detectors were part of the research protocol beginning in the 1950s at the National Laboratories of Brookhaven in New York, the Donner Laboratory in Berkeley, and at medical-school laboratories in St. Louis, Los Angeles, and Philadelphia. During a joint trip to Brookhaven, Gordon Brownell, a physicist at MIT, and William Sweet, a neurosurgeon at Massachusetts General Hospital, became fascinated with the possibilities of positron detection. By 1952, they were operating the first positron scanner to image brain tumors in patients. They would place the patient between two detectors, one on each side of the head, and the machine recorded data when both detectors were hit simultaneously. Alan Cormack tried then to interest the team in his computerized tomographic algorithms, but Brownell was indifferent. Like Kuhl at Penn, that failure to see that there was a connection between transmission scans and emission scans contributed to the delay in making PET until EMI demonstrated the CT scanner in 1972.[18]

British physicians, who also had access to cyclotrons, were likewise interested in emission tomography. London's Hammersmith Hospital, with its tradition of medical instrument innovation, attracted Americans interested in postdoctoral research. It was there that two American visitors who would play leading roles in PET scanning, Michel M. Ter-Pogossian and Henry Wagner, met in 1964. They discussed working together to develop PET, but they

couldn't raise enough money. Wagner went on to head the PET program at Johns Hopkins University, where almost twenty years later, under his leadership, the first imaging of a dopamine neuroreceptor, the focus of degeneration in Parkinson's disease, took place.[19] Ter-Pogossian went on to head a program at Washington University in St. Louis, where the first PET scanner would be built eleven years later.

Research in nuclear medicine continued apace in Great Britain, France, and Scandinavia where radioactive isotopes were available from their respective national nuclear power programs. There would be constant feedback between the European and North American laboratories with a surprising lack of secrecy or overt competition, perhaps because clinical applications did not seem promising, and there was relatively little money invested in the research. Chemists manufactured radiopharmaceuticals where medical facilities had access to cyclotrons, which in the United States meant that PET research was centered at UCLA and Berkeley in California, at Massachusetts General Hospital in Boston, and at the Mallinckrodt Institute in St. Louis, all laboratories attached to research-oriented medical schools.

The breakthrough occurred in St. Louis in 1973. Ter-Pogossian had installed the first hospital-based cyclotron there in 1964 and had pushed ahead with research in positron scanning. By 1972 his group had built a cumbersome positron imaging device that looked like a helmet spiked with 26 detector probes. Everyone called it the "lead chicken."[20] The chicken did not capture much of a picture because the researchers had to process the data manually. They did not yet have the algorithms that would make a computer useful.

A year later, following Hounsfield's publication of his description of the CT system, PET investigators like Kuhl realized that the image-retrieving formulas that worked with *transmission* tomography—passing rays through the body—would also serve *emission* tomography—tracking the radioactive source within.[21] Then it was only a matter of time before two assistant professors in Ter-Pogossian's laboratory, Michael Phelps and Edward Hoffman, both chemists, disassembled the clumsy lead chicken to salvage its probes and rearranged them as a hexagonal array. Phelps and Hoffman linked the hexagonal detectors electronically so that a positive signal registered only when two opposite detectors picked up a positron at the same time. The computer stored these signals and then processed them mathematically, employing formulas like those used in CT scanning—first an iterative algorithm and later Fourier transforms—to reconstruct a slice. This process was dubbed PETT (positron emission transaxial tomography) in a paper published by Phelps and Ter-Pogossian in 1975.

Phelps, a former Golden Gloves boxer whose pugilistic skills may explain his combative approach to science, had worked out the considerable computational and engineering problem of PET. But he clashed with the hierarchy in Ter-Pogossian's laboratory, which he described as having a different ethic because it was medical rather than purely scientific, and where he, as a junior member of the staff when he solved the PET instrument problem, had to

share credit with the laboratory director. In 1975 he and Hoffman left to join Kuhl at the University of Pennsylvania. The following year, 1977, Phelps, Hoffman, and Kuhl moved to UCLA where they secured a strong beachhead for PET and nuclear medicine.

Throughout these improvements in theory and practice, the symbiotic connection between the development of the PET machine and the development of radioisotopes continued. The usefulness of the machine depended on the ingenuity with which complex molecules were tagged. Detectors became better at extracting data and reconstructing images as radioisotopes underwent a revolution of their own. Once thought of as "throw-away" by-products of nuclear reactors whose very short half-lives made them useless therapeutically, short-lived radioisotopes came to be recognized as ideal tracers. Ter-Pogossian, for example, had encouraged his laboratory to use isotopes like Oxygen –15, which decays in two minutes, and Fluorine –18, which decays in two hours, because he recognized them as excellent ambassadors to diseased organs that could be used with the cumbersome "lead chicken."

Researchers first targeted the iodine-hungry thyroid gland, then moved on to the heart, and then to the brain. The next major advance came from the 1979 production of the radiopharmaceutical FDG, or deoxyglucose, the key to both clinical explorations, especially of Parkinson's and Huntington's diseases, and activational studies of the working brain. The subsequent development of additional radiopharmaceuticals targeting specific neuroreceptors has helped in the study of Alzheimer's disease, depression, anxiety, schizophrenia, pain, and drug addiction.

By the mid-1980s the hardware of PET scanners and radiopharmaceutical manufacturing had reached a stage where the emphasis shifted from invention to fine-tuning and simplifying the machinery to make it less cumbersome and simpler to operate. Well ensconced in government laboratories, PET thrived as a research tool; but the efforts of its advocates to move it into the world of clinically accepted procedures that are reimbursable by Medicare and private health insurance were not very successful, and for that reason PET remains an expensive option.

The Market

PET faced a series of problems that neither CT nor MR confronted when it moved into the world of the clinic. First of all, PET requires more skill to produce and to interpret, and skill is not cheap. Because the radio-tagged molecules used in PET have very short half-lives, the intensity of the radiation they emit rapidly diminishes as the molecules move through the body. All the time that the isotopes are accumulating in the targeted areas, they are losing radioactivity. Figuring out precisely how to measure the fading radiation of short-lived radioisotopes as they head to their targets requires complex kinetic mathematics, which translates into dollars to pay for mathematicians.

PET was also different from CT and MR in its financial base. Where the other technologies developed on the margins of state subsidies and had to wait for the right moment to win private investment, from the start PET was funded, organized, encouraged, and distributed by the U.S. government. The AEC (later the Department of Energy, or DOE) funded the research at the Argonne National Laboratory in Illinois, the Brookhaven National Laboratory in New York, the Oak Ridge National Laboratory in Tennessee, the Donner Laboratory at Berkeley in California, and at Los Alamos in New Mexico. The DOE eventually supported work at universities including UCLA and UC Berkeley, the University of Chicago, Harvard's Massachusetts General Hospital, the University of Michigan, University of Pennsylvania, University of Rochester, and Washington University in Missouri.

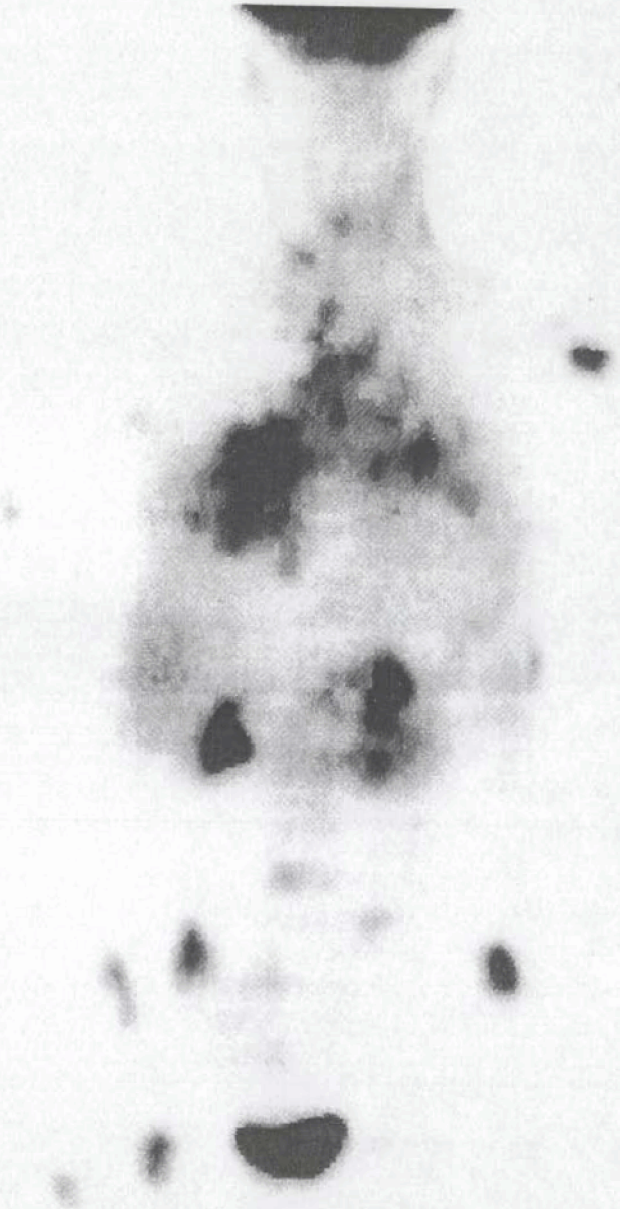
In 1979 the National Institutes of Health gave grants to support research in clinical applications, complementing DOE's support for improved instrumentation and the transfer of PET technology to industry. Although sales of PET scanners never ballooned like the sales of CTs, they held steady until 1995 when the market for all medical instruments sagged. The major PET producers are now the same companies whose names have been associated with imaging for almost a century, Siemens and General Electric, who, by the end of 1995 had placed a PET scanner within two hundred miles of most Americans.

It is doubtful that there would have been any PET without considerable government support. However, what the government provided with one hand it withheld with the other. While the NIH and DOE used PET in research, the Health Care Finance Administration, which administers Medicare and Medicaid, did not cover any PET procedures until 1995. Many private health insurers did pay, however, impressed by PET's ability to distinguish different kinds of heart disease, to determine the viability of heart tissues in preparation of bypass surgery and transplants, and to identify metastatic cancers.

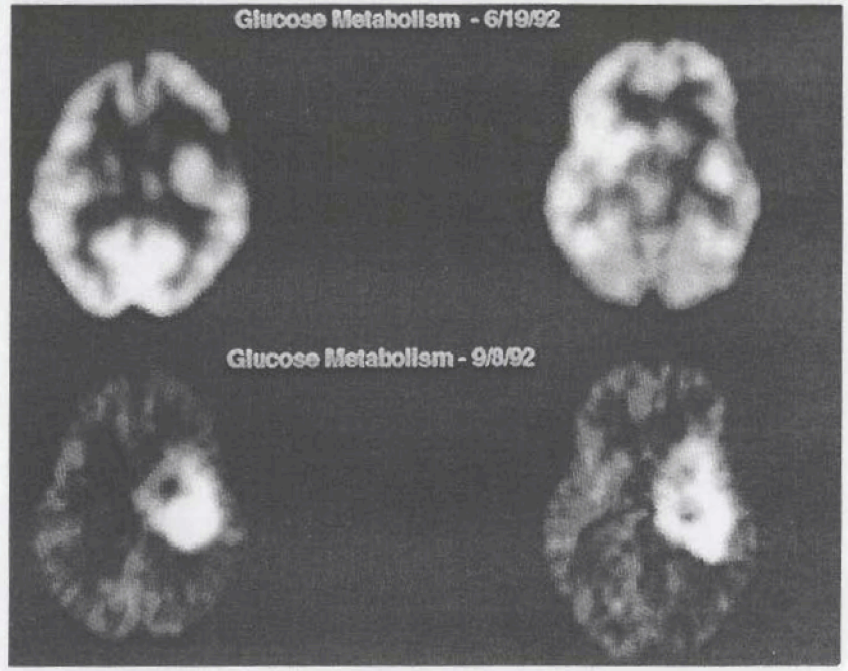
PET and Cancer

The newest generation of PET scanners in the early 1990s introduced whole-body PET into the imaging competition. It was often a matter of comparing apples and oranges, and PET found itself competing with other forms of nuclear scans, such as SPECT, where the resolution is several times larger but the expense several times smaller, or with the other functional imaging technique, fMR. Whole-body PET is used almost exclusively for cancer detection it can discover metastatic tumors as well as track the functional development of cancers. Moreover, PET can monitor the success or failure of chemotherapies as the various drugs are introduced in the body, rather than waiting weeks for symptoms to appear.

In treating a malignancy such as a brain tumor, PET provides information about the regional chemistry of a tumor and can detect changes before any structural signs are visible. This kind of early diagnosis precludes evaluation



40. Whole body PET/FDG study of patient with widely disseminated anaplastic thyroid carcinoma (1992). Courtesy of Dr. Peter Conti.

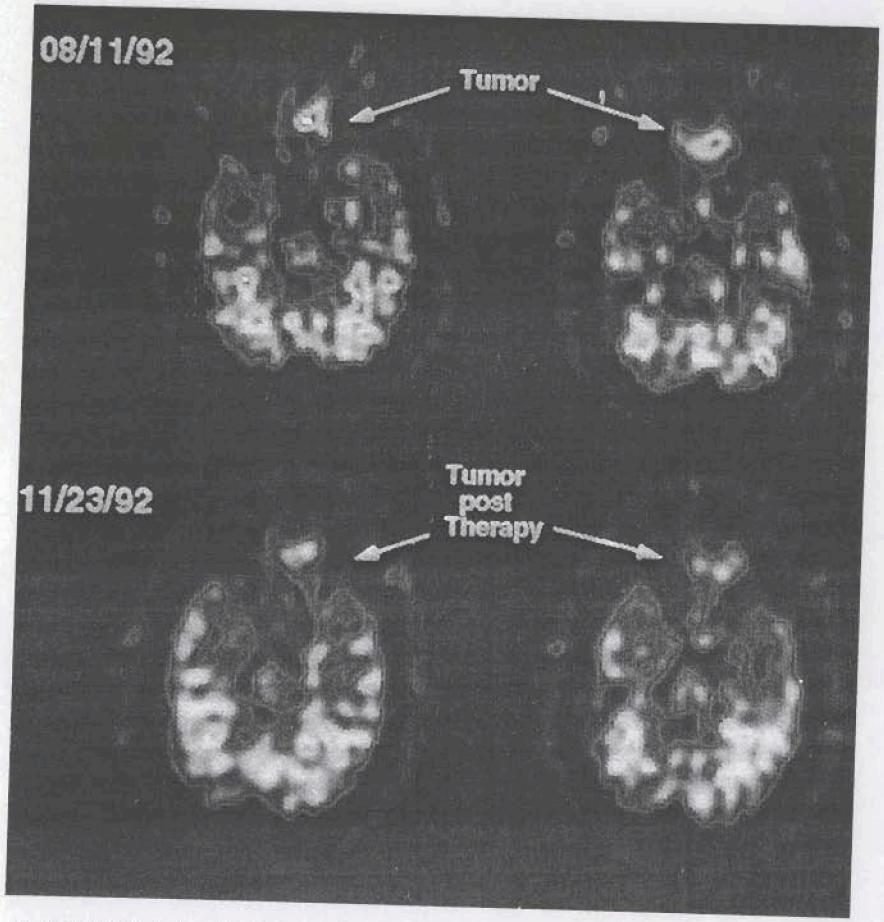


41. Serial PET study of glucose metabolism of a patient with glioblastoma (1992). Courtesy of Dr. Peter Conti.

based on biopsies and clinical responses. Oncologists can assess the effectiveness of surgery, radiation, or chemotherapy in treating tumors early, and modify treatments if necessary.[22]

Research has shown that tumors are seldom homogeneous in the same patient, and a combination of radiotracers injected serially offers an opportunity to profile multiple biochemical processes. These have included markers O^{15} for water, and FDG for glucose. This list may, in the future, be expanded to measure other substances that prove appropriate for evaluating particular tumors.[23]

Exploring disease at the molecular level is one of the great advances in modern medicine. The physicist Karl Darrow once said, "One of the things which distinguishes ours from all earlier generations is that we have seen our atoms."[24] PET specialists Henry Wagner and Peter Conti have this in mind when they point out that our bodies are made of combinations of atoms—molecules—which, with PET, can now be tracked. Cancer, they explain, has traditionally been seen as an invasion by something foreign into the body, to be destroyed or excised. Their view is that everyone is constantly in danger of developing cancer, but that normal control mechanisms keep it from happening. They define cancer as a failure of normal controls, and its treatment the restoration of these mechanisms. The real mission of PET, they believe, is to help physicians see the process of restoration as it takes place.[25]



42. Serial PET studies (1992) in patients with high-grade brain tumors being treated with high doses of tamoxifen on an experimental therapeutic protocol. Note reduction in metabolic activity in response to treatment. Contrast-enhancing lesions noted on MRI examination (not shown) were unchanged through therapy. Courtesy of Dr. Peter Conti.

PET in Court

All eyes in the courtroom look to Charles Reese. The jury has convicted him of six counts of premeditated murder. Grasping at the only straw left to save his client's life, his lawyer asks for a PET scan before the jury passes sentence. A computer-generated skull revolves behind a computer monitor, and as the skin peels effortlessly away, the ivory bones dissolve, leaving a naked brain rotating in red and green. A second brain, a "control," appears beside the first. Anyone can see that the two brains are different. A doctor explains why.

Pointing to the first, he says, "These are abnormal patterns without a doubt. . . . What you are seeing is a computer-enhanced image of the chemistry of [Reese's] brain. And what it shows is a picture of madness."

Convinced, the jury sends Reese to a mental hospital instead of the gas chamber. The picture has done what words could not. It has convinced the jury that an abnormal brain scan indicates an abnormal brain in an abnormal person, who is not responsible for his actions.[26] This is the finale of *Rampage*, a 1989 movie that was filmed, in part, at the PET laboratory at the University of California at Irvine, a lab that had made a specialty of forensic PET scans.

Because California law requires a second trial after a guilty verdict when the death penalty is involved, and because the PET facility at this campus is not part of the federal network, its entrepreneurial leaders established amicable relations with high-profile lawyers in the neighborhood. The PET program at the Irvine campus began when the psychiatry department bought a scanner with bank loans, which it repaid, not by leasing its lab as a movie set—that was just a one-time gig—but by fees from providing expert testimony.

By 1993 the vast majority of Irvine's clinical referrals came from lawyers, many of whom sought testimony about the brains and the head injuries of convicted felons for the penalty phase of their trials.[27] Responding to demand, the Irvine physicians began lecturing to lawyers and judges about how PET works until PET became the community standard in Orange County. This dovetailed neatly with the interests of the laboratory's head at the time, Monte Buchsbaum, whose research focused on schizophrenia, and especially the psychiatry of violence. These cases provided him with the data on the brains of forty-four people who, like the fictional Charles Reese, had been convicted of brutal crimes.

The idea of explaining violence by finding evidence of neural malfunctions builds on a 1987 study of four convicted criminals with histories of repetitive, purposeless, violent behavior. Studies of these men with CT, EEG (electroencephalograph, which shows surface electrical activity and comes out of a printer looking like a squiggly line), and PET uncovered curious discrepancies. Two of the men had normal CT scans, but their PET examinations revealed widespread defects in cerebral functioning. There was no instance of a normal PET scan coupled with an abnormal anatomical scan. The authors were tentative in their conclusions, suggesting that PET did seem able to find something awry in the brains of three out of the four men, something that had been overlooked by CT. But whether the findings were indicative, much less predictive, of violence, they could not know. The only claim the authors made is that PET might confirm brain derangement in people who had already behaved violently.[28]

PET has a curious history in American courts in that it stands the Frye rule on its head. The Frye rule calls for the acknowledgment by experts that the technology in question is accurate and measures up to some community standard. PET has measured up to the Frye test many times in its use in Orange County courts, long before it received the blessing of the FDA. Even as it was accepted for use before juries, it was still officially experimental in the medical world. Its history is in some ways analogous to DNA identification, which is challenged in many localities each time it is offered in evidence, but which has long since become a standard tool in medical and biological research.