Donner Laboratory: Fifty Years of Nuclear Medicine Innovation

For its annual meeting in San Francisco this June, the Society of Nuclear Medicine is returning to its hometown, for the suburb of Berkeley, California, is where cyclotrons were born. Here the first cyclotron was built in 1937 at what is now Donner Laboratory. It was less than a foot in diameter, and could boost a handful of protons to a mere 80,000 electron volts. Its builder was Ernest O. Lawrence, PhD, who by 1939 had presided over the construction of a much larger cyclotron with magnets nearly five feet across that could energize particles to 20 million electron volts.

But the cyclotron is only one of Donner's innovations in the field. Lawrence Berkeley Laboratory at the University of California, of which Donner is a division, has a long list of firsts in nuclear medicine: the first successful medical treatment with a radioisotope; the first discoveries of the major radioactive tracers still in use today; the first gamma camera; and the first family of nuclear medicine, Ernest Lawrence and his brother, John H. Lawrence, MD.

'Vicarious Pleasure'

In 1936, Dr. John Lawrence left Yale University with a carload of cancer-bearing white mice to join his brother. The summer before he had performed the first biological experiments with the neutron beam while visiting Berkeley, discovering that neutrons are much more lethal than x-rays. But while radiation was seen to cause tissue damage, it also seemed likely that radioactive isotopes and the beams of high-energy particles—protons, deuterons, alpha particles, neutrons—offered rich possibilities for biological and medical research.

"Later, John Lawrence headed a strong research team that investigated many phases of the new radiation medicine and biology," wrote Luis W. Alvarez, PhD, in a biographical memoir. "Ernest Lawrence, who had abandoned a medical career for one in physics, now had the vicarious pleasure of a 'second life' in medical physics. He gave the Laboratory's medical program his strongest support, often in the face of keen disappointment on the part of some of the physicists who worked so hard to keep the cyclotron in operating condition and whose research efforts had to be curtailed. In 1938 and 1939, all physics at the cyclotron was suspended for a full day each week, so that terminal cancer patients could be treated with neutrons from the 37-inch cyclotron."

"We weren't always popular with our physicist colleagues," Dr. John Lawrence conceded to a reporter in 1963. "My brother and others once spent the whole night repairing the cyclotron and had just got it running again when I walked by with a pair of pliers in my lab jacket. The powerful magnet jerked them out and sent them smashing into the vacuum chamber window, wrecking it. I still blush when I think of it."

William G. Myers, PhD, MD, a student of the history of the lab and historian emeritus of the Society of Nuclear Medicine, wrote in 1977, "Professor Ernest Orlando Lawrence initiated nuclear biomedicine with his prophetic statement in October, 1934: 'In the biological field, radiosodium has interesting possibilities that hardly need to be emphasized.' This projection stemmed from his estimation that millicurie amounts of sodium-24 could be generated readily with his cyclotron." Dr. Lawrence's comment was uttered within months of the discovery of artificial radioactivity in the

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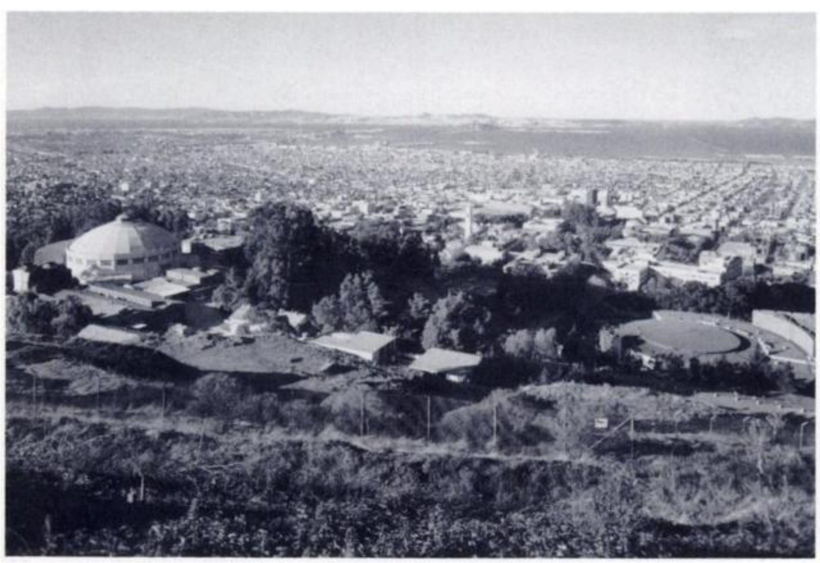
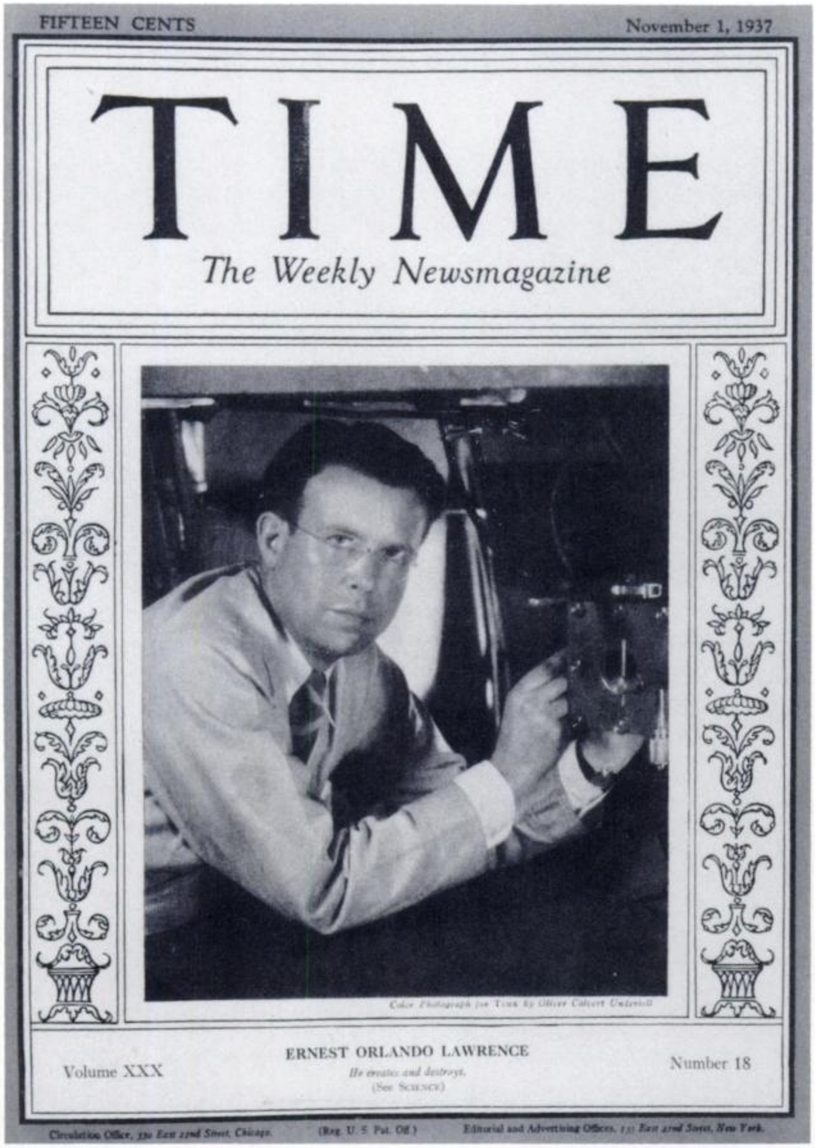


A view of the Lawrence Berkeley Laboratory shortly after the installation of the Bevatron synchrotron (the circular structure on the right) in 1954. The cyclotron is the domed building on the left.



Ernest O. Lawrence, who appeared on the cover of Time after winning the Comstock Prize of the National Academy of Sciences.

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same year, in Paris, by F. Joliot and Irene Curie. At the "Rad Lab," which Lawrence founded on the University of California at Berkeley campus, he created multidisciplinary scientific teams and pushed for the inclusion of engineers as full partners, as well as the integration of engineering concepts and designs into basic scientific research equipment.

To date the Lab has produced nine Nobel laureates. The first Nobel went to Ernest Lawrence, who on November 9, 1939, was awarded the prize in physics "for the invention and development of the cyclotron and especially for the results attained by means of this device in the production of artificial radioactive elements." Like all highly productive research facilities, Donner succeeds because it provides two things: an atmosphere conducive to original thinking, and the equipment necessary to carry it out. "I am truly fortunate to have been at Donner, surrounded for seven years by brains, energy and the complete freedom to seek the truth," Myron Pollycove, MD, professor of laboratory medicine and radiology at the University of California at San Francisco, and director of nuclear medicine at San Francisco General Hospital, said during the 50th anniversary celebration at Donner last October. Louis Wasserman, MD, professor emeritus of medicine and distinguished service professor at Mount Sinai Hospital in New York City, added that he was glad at last "to give homage to my friend and teacher, John Lawrence, who is not only an investigator of note, always searching for answers to puzzling questions, but also a humane teacher, who respected the dignity of his colleagues. My years with John were full of interest, kindness, and opportunities for work and discoveries. I will always be grateful to him for opening Pandora's box to me."

Activity in Fingertips

The Laboratory fostered individual initiative. During the 50th anniversary celebration, Dr. Pollycove told of the time, seven months after his arrival at Donner in July, 1955, when Dr. John Lawrence called him into his office. "After discussing my work, he inquired as to where Roslyn and I were living," Dr. Pollycove said. "When told that we and our four children were comfortably settled into a house we had purchased in Walnut Creek, he gave a slight start. He then emphasized that my appointment was for one year only, with renewal dependent on productivity. He allowed freedom," Dr. Pollycove said with a laugh, "but he also guided and encouraged and stimulated the person."

Always, the Lawrence brothers remained involved in research. "I well recall," said Harvey White to Dr.

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Myers in a personal communication dated March 23, 1977, "that soon after the discovery of induced radioactivity by the Curie-Joliots, [Ernest] Lawrence bombarded sodium with 2-MeV deuterons from the Berkeley cyclotron and produced radioactive sodium-24 with a half-life of about 15 hours. Wishing to test the radioactive sodium as a tracer in the human body, Lawrence personally took some of the salt orally and several people around him saw the determination of the activity in his fingertips within a very few minutes."

Despite that somewhat impetuous experiment, the Laboratory has been a leader in radiation safety. Early on Dr. John Lawrence and a colleague placed a rat in a cylinder and then put it in the cyclotron beam for a two-minute run. "When we removed the rat," Dr. Lawrence told a reporter in 1963, "we were all horrified to find it dead. The fright had a salutary effect on our safety record. We have never had a serious radiation accident. Not until much later did those of us who autopsied that rat admit publicly that it had died of suffocation."

Named for Steel President

The laboratory is named for William H. Donner, once president of Donner Steel Corporation (later Republic Steel), who took an interest in cancer research because his eldest son had died from the disease. In 1940, a charitable trust created by Mr. Donner donated $165,000 to the University of California for the construction of laboratory space. The Lab, which provided a new home for the researchers already working at Berkeley, was built in 1942, and the foundation has provided additional funds since then.

For many years, the Berkeley cyclotron was the only important source of radioisotopes and intense beams of neutrons and high-energy particles, and it attracted many dedicated and able investigators. One of these is Glenn Seaborg, PhD, who, in collaboration with colleagues, is responsible for such important isotopes as cobalt-57, cobalt-58, cobalt-60, iodine-124, iodine-130, iodine-131, manganese-52, manganese-54, iron-52, iron-59, molybdenum-99, and technetium-99m. He won the Nobel Prize in chemistry in 1951.

"In the adventures I had as a chemist, I benefited from good timing," Dr. Seaborg said during Donner's 50th anniversary. "I just happened to be here at this time as a young chemist, and I made my acquaintance with a number of people at the radiation laboratory. I was able to apply the powerful methods of analytical chemistry to the identification of the transmutation products produced in the cyclotron."

Dr. Seaborg worked with John J. Livingood, PhD, from 1936 to 1941. Dr. Livingood left Berkeley for Harvard at the end of 1948, Dr. Seaborg said, but despite the distance, he continued collaborating with him. "I made the bombardments and chemical separations here at Berkeley, and then put the various radioactive isotope portions into envelopes and airmailed them to Jack at Harvard, a practice that I think would be totally impossible today," he said.

Basic Research

Dr. Seaborg and his colleagues were not looking for medical breakthroughs while doing their work. "Our motivation in searching for new isotopes was simply the fascination of exploring this exciting new frontier of science. Actually, we gave little thought to the possibility that any of our discoveries would have practical applications. However, we were in for some surprises. On two occasions, medical researchers expressed to us their hope that radioisotopes of specific elements with desirable half-lives would be found and we were lucky in hitting the jackpot on both of these occasions."

The first occasion concerned iron.

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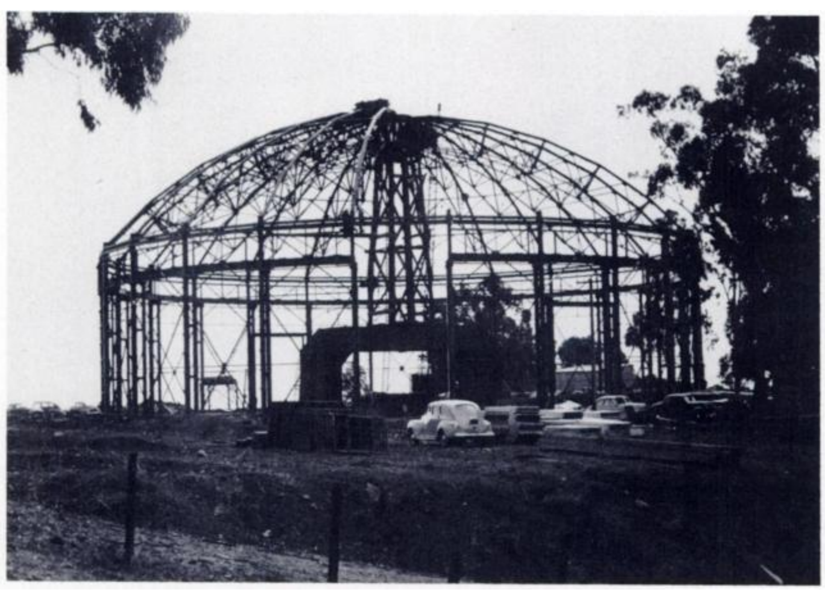

The magnetic yoke of the 184-inch cyclotron is visible inside the skeleton of the structure in this photo from the 1940s. In 1975 the cyclotron was dedicated exclusively to medical use.

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"George Whipple [MD, Nobel Prize in Medicine, 1934] of the University of Rochester was looking for radioisotopes of iron for use in human blood studies. In 1937, the year I finished my PhD degree, I started working on this problem," Dr. Seaborg said.

Soon he set about preparing the samples. "I resolved on this occasion to make a very complete separation. This meant separating iron from the element just above it, cobalt, and the element just below it, manganese, so I worked all night using the crude methods of separation that were available at that time. And then at about daylight, Jack Livingood came into the laboratory and took the samples, iron, manganese, and cobalt fractions, and brought them down to his electroscope in the basement.

"We found that the iron fraction that contained the isotope iron-59, which had a half-life of about 45 days, suited the purpose very well. Ernest Lawrence sent samples of iron-59 to Dr. Whipple, who performed the first tracer experiments on blood, which opened a new area of our understanding of iron metabolism," said Dr. Seaborg.

Drs. Glenn Seaborg and Jack Livingood at the University of California at Berkeley campus Sather Gate in 1938, on their way to the branch post office to mail their manuscript on iodine-131, "Radioactive Isotopes of Iodine," to Physical Review. The 50th anniversary of their discovery, and the discovery of Tc-99m in the same year, will be commemorated during SNM's annual meeting in June.

Iodine-131

At times the researchers did tackle a specific medical problem. "Perhaps the most interesting of all my collaborations with Jack Livingood, and one that had a special personal meaning to me, was the discovery of what is now the workhorse of medical tracers and therapy activity, iodine-131," Dr. Seaborg said. "One day in the spring of 1938, Joe Hamilton [PhD] met me on the steps of LeConte Hall. He was doing work on thyroid metabolism using iodine-128, which had a half-life of 25 minutes, and he complained bitterly that this really cramped his style, and that he needed an isotope with a longer half-life. I asked Joe, 'What kind of half-life would you like?' And Joe said, 'Oh, about a week.' Most of you know we succeeded in identifying iodine-131 with neutron bombardment of thorium and found that it had a half-life of eight days. So we came pretty close in this case. . . . And I have the additional satisfaction that my mother had her life extended many years as a result of treatment with iodine-131."

Working conditions at the Laboratory were not the best, however, according to Dr. Seaborg. "I had cramped headquarters on the second floor, just a corner of a physics lab in which they had installed a sink and a really decrepit hood and a source of tap water for me to carry on my separations," he said. "All of my work with Jack Livingood was sort

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of moonlighting from my regular duties, and I carried on after the regular work hours I spent as a graduate student and as a research assistant."

Collaboration with Emilio Segrè

In the summer of 1938, Emilio Segrè, PhD, met Dr. Seaborg soon after moving to California from Italy. Dr. Segrè had participated in the discovery of technetium, element number 43, and did further study of the element with Dr. Seaborg. "To our delight we discovered an isotope of great scientific interest, because it decayed by means of an isomeric transition from an upper state to a lower state in the same element," Dr. Seaborg recalled.

But the story did not end there. "We sent this in to *Physical Review*, but when Ernest Lawrence and [J.] Robert Oppenheimer learned about this, and read our little publication, they called us in, because Robert Oppenheimer felt that it was impossible for the gamma ray emitted in an isomeric transition to be practically 100% converted to electron emission," Dr. Seaborg recalled. "And so we were asked to send a telegram to *Physical Review* withdrawing our publication." But this professional concern was not the only thing Dr. Seaborg remembers about that day. "I recall on that occasion, when I went into Lawrence's office, that he had a newly acquired secretary named Helen Griggs, and as I dictated this telegram to Helen, I was very much attracted to this attractive young girl. Well, you know, I didn't have enough sense to pursue this at the time, but a couple of years later I began to date her, which resulted in our marriage in 1942."

Despite the telegram, in 1938 the brief article was published in *Physical Review* (see box, p. 435) because an analogous discovery in another ele-

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Discovery of Technetium-99m

(the most commonly used isotope in medicine)

Nuclear Isomerism in Element 43

We wish to report briefly an interesting case of isomerism which has appeared during an investigation of the short-lived radioactive isotopes of element 43. The irradiation of molybdenum with deuterons or slow neutrons produces a radioactive molybdenum isotope with a half-life of 65 hours which emits electrons with an upper energy limit of approximately 1 Mev. (This molybdenum activity has also been reported recently by Sagane, Kojima, Miyamoto and Ikawa.)[1] This molybdenum decays into a second activity which has a half-life of 6 hours and which emits only a line spectrum of electrons. Since the molybdenum emits electrons, the daughter activity must be ascribed to element 43; chemical identification has been carried out and has confirmed this identification of the 6-hour activity. Absorption measurements in aluminum and measurements with a magnetic spectrograph[2] indicate an energy for the electrons of about 110 kev. This line spectrum must be due to the conversion electrons of a gamma-ray of about 130 kev energy. The 6-hour activity also emits x-radiation and γ-radiation. The absorption of the x-rays in molybdenum, columbium and zirconium shows a discontinuity that is consistent with the $K\alpha$ line of element 43, which is to be expected on the basis of the interpretation given below.

The simplest and most reasonable explanation for these facts is the existence of an excited state in this isotope of element 43 which reverts to the ground state by the emission of conversion electrons and gamma-rays with a half-life of 6 hours. A line of conversion electrons corresponding to a similar transition seems to have been detected by Pontecorvo[3] during a study of the nuclear isomerism in rhodium. A more complete discussion and a description of the experiments will be published later in the *Physical Review*.

We wish to thank Professor E. O. Lawrence for the privilege of working with the cyclotron and for his interest in this problem.

We wish also to express our appreciation to Mr. D. C. Kalbfell for the photographing of the line spectrum of electrons. This research has been aided by grants from the Research Corporation.

E. Segrè
G. T. Seaborg

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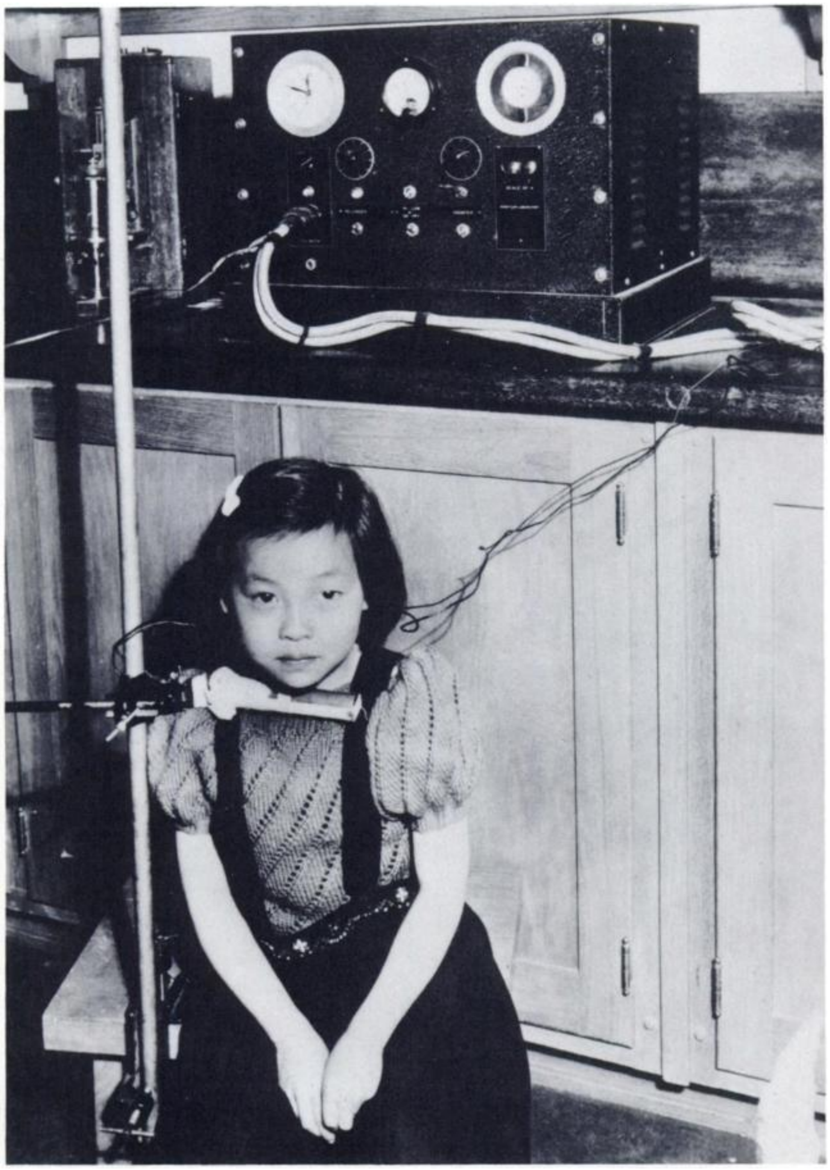
Berkeley, California,
October 14, 1938.

[1] Sagane, Kojima, Mijamoto and Ikawa, Phys. Rev. 54, 542 (1938).
[2] Kalbfell, Phys. Rev. 54, 543 (1938).
[3] Pontecorvo, Phys. Rev. 54, 542 (1938).

Physical Review 54, 772, 1938



This famous photo shows what is believed to be the first kinetic study on the function of the human thyroid using iodine-131 and a Geiger-Müller counter.

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ment helped pave the way. "In the meantime, Segrè's former Italian colleague, while working in Paris, observed and published a description of an identical isomeric transition that had been observed in an isotope of rhodium. This was a form of radioactive decay that had never been observed before this time. It was a moderately important discovery, but we were scooped. Segrè and I were able to show that this radioactive isotope of the element with the atomic number 43, which as we know was later given the name technetium, came with a half-life of about six hours, and most importantly, that it was the daughter of a 67-hour molybdenum parent radioactivity. This chain of decay was later shown to have the mass number 99, and after the convention of designating isomeric states of measurable half-life with the symbol m, meaning metastable, it was established that the six-hour activity should be given the designation technetium-99m, and that's how we know it today."

List of Innovations

The list of nuclear medicine developments at Berkeley and, later, at Donner is a substantial one, and includes the following:

- 1935—The first use of artificially radioactive tracers in animals and humans. Sodium-24 was first traced by Drs. Hamilton of Berkeley and Robert S. Stone of the University of California Medical Center in San Francisco.
- 1935—Dr. John Lawrence performed the first biological experiments with neutrons, determining that they are five times as lethal as x-rays.
- 1935—The first safety regulations to protect against radioisotopes and beams of particles were introduced.
- 1937—The first use of a radioisotope in the treatment of human disease was carried out by Dr. John Lawrence. On Christmas Eve he administered phosphorus-32 to a patient with leukemia.
- 1938—Neutrons were used for the first time in the treatment of disease by Drs. Stone, John Lawrence and John Larkin.
- 1939—The first known successful treatment of disease with a radioactive isotope was Dr. John Lawrence's treatment of polycythemia vera. One or two doses of radioactive phosphorus at monthly intervals were found to return the red blood cell count to normal and relieve symptoms, giving patients a near-normal life expectancy.
- 1940–1941—The first use of radioiodine in the diagnosis and treatment of hyperthyroidism was made by Drs. Hamilton and Mayo Soley.
- 1940—The concept of therapy of

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cancer by neutron capture was tried initially at Berkeley in animals. Boron, localized in cancer tissue in animals, was bombarded by neutrons.

- 1941—The first radioactive colloid, chromic phosphate, was prepared by Hardin Jones, PhD, and used in the treatment of disease. Other radiocolloids first prepared at Donner include radiogold (1943, Dr. Jones) and radioyttrium (1944, John Gofman).
- 1942—Studies of the metabolism and toxicity of transuranium elements and fission products were initiated by Dr. Hamilton.
- 1942—The Donner Laboratory, the first center of research and training in atomic biology and medicine, was established.
- 1947—Neutron activation analysis in biology was introduced by C.A. Tobias, PhD, as a tool to measure trace elements in biological materials. Some of the first biological compounds containing radioactive tracer elements were synthesized by a Donner group headed by Melvin Calvin, PhD.
- 1935-1962—The first deep well scintillation counter, the first multiple port *in vivo* counter, the first multiple-channel, whole-body scanner (Dr. Tobias and Hal Anger), the first gamma ray camera (1957, Mr. Anger), the first positron camera (Mr. Anger), and the first use of a mass spectrometer to measure radioactive carbon in the breath (William Siri) were developed.

The Laboratory Today

Over the years, Lawrence Berkeley Laboratory has continued to be actively involved in nuclear medicine research. Perhaps one of the most interesting developments coming out of the Lab today is the Donner 600 Crystal PET (positron emission tomography) System, which has an in-plane spatial resolution of 2.5 mm, about twice as good as that of the best commercially available systems. Physicists Stephen Derenzo, PhD, and Ronald Huesman, PhD, built the device, which can register up to 1 million coincidence counts per second. Early images from this instrument were shown at the Society of Nuclear Medicine's meeting last June (see *Newsline*, August 1987, p. 1241). Peter E. Valk, MD, a researcher at the lab, said the device was completed last year, although software developments are continuing.

The device's high resolution capabilities allow the user to see details that are too small to be picked up by conventional PET scanners. "You can see things that you've never seen before," Dr. Valk said, and the images sometimes send scientists scurrying to anatomy atlases to identify structures.

Researchers at Donner are also studying heart perfusion imaging with a whole-body scanner, a 270-crystal PET system with 8.0 mm in-plane spatial resolution, which, when used with rubidium-82, provides higher resolution images than are possible with thallium single-photon emission computed tomography (SPECT) studies. The advantage, Dr. Valk said, is that one can see small, localized areas of abnormality with PET that are too small to be resolved by SPECT.

Rubidium-82, the daughter product of strontium-82, also offers special advantages. Dr. Valk said that it has a half-life of 75 seconds and can be administered to a patient every 10 minutes if needed. This means that a patient's progress during drug therapy can be monitored as it happens—i.e., drugs that dissolve blood clots can be watched as they work.

In brain studies, PET with rubidium-82 used together with fluorodeoxyglucose (FDG) helps physicians to distinguish between damage caused by irradiation of malignant tumors and that caused by the progress of the disease itself. Dr. Valk said this is the only technique he knows that can make this distinction, as biopsies are not reliable in all situations.

"You can see things that you've never seen before."

The lab is also using PET and nuclear magnetic resonance (NMR) to study dementia. One five-year study seeks to discover whether patients with non-specific cerebral white matter lesions on NMR imaging have a higher than normal chance of developing dementia, and whether this is associated with other evidence of cardiovascular disease. For this work, subjects older than 55 undergo NMR and PET studies and extensive testing of cognitive function to ferret out any early signs of dementia, and are divided into normal and demented groups accordingly. They will be tested again three years later to see what relationships among variables exist.

The lab has also been superimposing NMR, PET and computed tomography (CT) images by using a computer system that corrects for spatial distortions among the three modalities. The mapping of NMR and PET data on the CT images allows these data to be used for radiation therapy planning. This is particularly important for areas such as the base of the skull, where critical structures are separated by small distances.

Karla Harby

The author would like to thank the Public Information Department of the Lawrence Berkeley Laboratory.