Ernest Orlando Lawrence (1901-1958), Cyclotron and Medicine

On August 8, 2001, Lawrence Berkeley National Laboratory celebrated the centennial of the birth of its founder (and namesake), Ernest Orlando Lawrence. For the occasion, many speeches were given and old speeches were remembered. We recall the words of the late Luis Alvarez, a Nobel Laureate and one of the Lawrence's closest colleagues: "Lawrence will always be remembered as the inventor of the cyclotron, but more importantly, he should be remembered as the inventor of the modern way of doing science." J. L. Heilbron and R. W. Seidel, in the introduction of their book, "Lawrence and His Laboratory"[1] stated, "The motives and mechanisms that shaped the growth of the Laboratory helped to force deep changes in the scientific estate and in the wider society. In the entrepreneurship of its founder, Ernest Orlando Lawrence, these motives, mechanisms, and changes came together in a tight focus. He mobilized great and small philanthropists, state and local governments, corporations, and plutocrats, volunteers and virtuosos. The work they supported, from astrophysics and atomic bombs, from radiochemistry to nuclear medicine, shaped the way we observe, control, and manipulate our environment." Indeed, all over the civilized world, the ways we do science changed forever after Lawrence built his famed Radiation Laboratory. In this editorial, we epitomize his legacy of changing the way we do medicine, thereby affecting the health and wellbeing of all humanity.

This year marks the 75$^{th}$ anniversary of the invention of the cyclotron by Ernest Orlando Lawrence at the University of California at Berkeley. Lawrence conceived the idea of the cyclotron early in 1929 after reading an article by Rolf Wideröe on high-energy accelerators. In the spring of 1930 one of his students, Nels Edlefsen, constructed two crude models of a cyclotron.[2] Later in the fall of the same year, another student, M. Stanley Livingston, constructed a 13-cm diameter model that had all the features of early cyclotrons, accelerating protons to 80,000 volts using less than 1,000 volts on a semi-circular accelerating electrode, now called the "dee."[3]

Following the discovery by J. D. Cockcroft and E. T. S. Walton of how to produce larger currents at higher voltages, Lawrence constructed the first two-dee 27-Inch (69-cm) Cyclotron, which produced protons and deuterons of 4.8 MeV. The 27-Inch Cyclotron was used extensively in early investigations of nuclear reactions involving neutrons and artificial radioactivity. In 1939, working with William Brobeck, Lawrence constructed the 60-Inch (150-cm) Cyclotron, which accelerated deuterons to 19 MeV. It was housed in the Crocker Laboratory, where scientists first made transmutations of some elements, discovered several transuranic elements, and created hundreds of radioisotopes of known elements. At the Crocker Laboratory the new medical modality called nuclear medicine was born, which used radioisotopes for diagnosis and treatment of human diseases. In 1939 Lawrence was awarded the Nobel Prize in Physics, and later element 103 was named "Lawrencium" in his honor.

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1 J. L. Heilbron and R. W. Seidel, "Lawrence and His Laboratory- A history of the Lawrence Berkeley Laboratory, Vol. 1, Univ. of Calif. Press, Berkeley, Los Angeles, Oxford (1989).

2 Lawrence, E.O. and Edlefsen, N.E., **Science**, **72**: 376 (1930).

3 Lawrence, E.O. and Livingstone M.S., **Phys. Rev 37**: 1707 (1931); and Livingston, M.S., "The Production of High-Velocity Hydrogen Ions Without the Use of High Voltages," PhD thesis, University of California, Berkeley (1931).

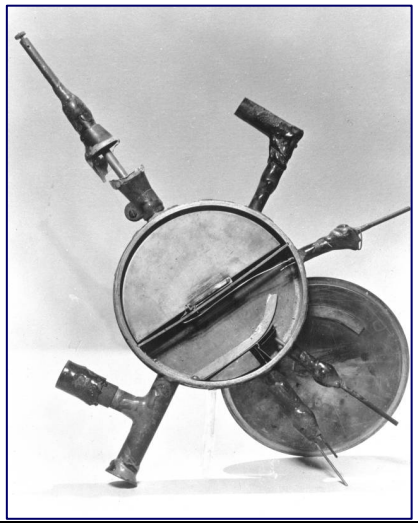

Fig. 1. The first cyclotron made by Lawrence and Livingston (1930).

Just before WWII, Lawrence and Brobeck designed the 184-inch cyclotron, but the war prevented the building of this machine. Immediately after the war ended, the Veksler-McMillan principle of phase stability was put forward, which enabled the transformation of conventional cyclotrons to successful synchrocyclotrons. When completed, the 184-Inch Synchrocyclotron produced 340-MeV protons. Soon after, more modern synchrocyclotrons were built around the globe, notably at Columbia University, Carnegie Institute of Technology, and University of Chicago in the United States, and another in Uppsala, Sweden. The synchrocyclotrons in Berkeley and Uppsala, together with the Harvard cyclotron, would perform pioneering work in treatment of human cancer using accelerated hadrons.

In the 1950s larger synchrotrons were built in the GeV region at Brookhaven (3-GeV Cosmotron) and at Berkeley (6-GeV Bevatron), which produced antiprotons and antineutrons, many of the transuranic nuclei, and many excited states of hadrons. Today most of the world's largest accelerators are synchrotrons, such as the 1-TeV Tevatron at Fermilab near Chicago and the 450-GeV Super Proton Synchrotron (SPS) at CERN in Switzerland, and all are direct descendents of Lawrence's cyclotron invented 75 years ago.

Lawrence's interest in building accelerators centered, of course, on nuclear physics; but from the onset he was keenly aware of their important applications in medicine. To study radiation in medicine, Lawrence brought to Berkeley his physician brother, John Hundale Lawrence, M.D., from Yale School of Medicine, who soon demonstrated the isotope-making cyclotron's worth in disease research. John Lawrence became Director of the Division of Medical Physics at the University of California at Berkeley. Starting in 1936, John Lawrence operated a clinic to treat leukemia and polycythemia patients with radioactive phosphorus produced at Crocker Laboratory, then the site of the 60-Inch Cyclotron. These were the first therapeutic applications anywhere of artificially produced radioisotopes on human patients. Thus John Lawrence became the "Father of Nuclear Medicine." In this vein, we could call Ernest Lawrence the "Uncle of Nuclear Medicine," as he was the brother of John. Ernest Lawrence constantly collaborated with his brother to study medical and biological applications of the cyclotron, and himself became a consultant to the Institute of Cancer Research at Columbia. We can trace the interest of Ernest

Lawrence in medicine to his college years when he studied to become a physician, and later in 1932 when he married Mary Kimberly Blumer, daughter of the Emeritus Dean of Yale Medical School.

Fig. 2. E.O. Lawrence (seated) placed strong emphasis on medical uses of his cyclotrons. His brother J. H. Lawrence, M.D., became known as the "Father of Nuclear Medicine."

One of the earliest biomedical uses of radioactive elements was research conducted during WWII by John Lawrence and Cornelius Tobias, another student of Ernest Lawrence. They used radioactive nitrogen, argon, krypton, and xenon gases, which were produced at the 60-Inch Cyclotron. Their research discovered the nature of decompression sickness, known as the "the bends," that many military aviators suffered when flying at high altitudes without pressurized suits.[4] It is interesting to note that after more than a half century later, $^{81m}$Kr gas is still used at hospitals to yield functional images of pulmonary ventilation. Now it became routine for nuclear medicine procedures that use radioisotopes to provide diagnostic information about the functioning of a person's specific organs, or to treat diseases. The thyroid, bones, heart, liver and many other organs can be readily imaged, and disorders in their function revealed. It is estimated that 15 to 20 million nuclear medicine imaging and therapeutic procedures are performed every year around the world, and demand for radioisotopes is increasing rapidly. In developed countries (about a quarter of world population) the frequency of diagnostic nuclear medicine procedures performed is approximately two per 100 persons per year, and the frequency of therapy with radioisotopes is about one tenth of this.

[4] C.A. Tobias, H.B. Jones, J.H. Lawrence, and J.G. Hamilton, Journal of Clinical Investigation. **28**: 1375-1385 (1949).

A radioisotope used in Single Photon Emission Computed Tomography (SPECT) must emit gamma rays of sufficient energy to escape from the body yet it must have a halflife short enough for most of it to decay away soon after imaging is completed. A positron emitter with a similarly short halflife is needed in Positron Emission Tomography (PET). PET's most important clinical role is in oncology, where fluorodeoxy glucose (FDG) is used (incorporating $^{18}$F as the tracer), due to its accuracy in detecting and evaluating most cancers in a non-invasive way. It is also used in cardiac and brain imaging. Positioning of the radiation source within the body is the fundamental difference between nuclear medicine imaging and other imaging techniques such as x-rays. Gamma imaging by either SPECT or PET provides a view of the position and concentration of the radioisotope within the body. Organ malfunction can be indicated if the isotope is either partially taken up in the organ (a cold spot), or taken up in excess (a hot spot). If a series of images is taken over a period of time, an unusual pattern or rate of isotope movement could indicate malfunction in the organ. Nuclear fission reactors produce the bulk of medical radioisotopes[5], but isotopes of very short halflives, especially those for PET, are produced by cyclotrons located near PET machines in hospitals. Around the world, there are about 100 isotope-producing cyclotrons (accelerating protons, and much less frequently deuterons, to energies in the range of 15-20 MeV). The typical beam power of such a cyclotron is of the order of 15 kW. In the foreseeable future, >100-MeV cyclotrons, and linacs, with beam power ten times greater, will be required to produce isotopes for newer nuclear medicine procedures.

Radioisotopes produced at cyclotron facilities for varied nuclear medicine applications include: Positron emitters $^{11}$C, $^{13}$N, $^{15}$O, and $^{18}$F, which are used in PET to study brain physiology and pathology, in particular to localize epileptic focus, and in dementia, psychiatry and neuropharmacology studies. They also have a significant role in cardiology. $^{18}$F in FDG has become very important in detection of cancers and monitoring of treatment progress. Other radioisotopes are: $^{57}$Co (a marker to estimate organ size), $^{67}$Ga (for cancer diagnosis), $^{111}$In (for diagnostic brain studies), $^{123}$I (for diagnosis of thyroid function; it is a gamma emitter without the beta radiation of $^{131}$I), $^{81m}$Kr (produced from $^{81}$Rb; $^{81m}$Kr gas is used for functional images of pulmonary ventilation), $^{82}$Rb (produced from $^{92}$Sr; $^{82}$Rb is used in myocardial perfusion imaging with PET), $^{195m}$Hg (for studies of the blood flow rate), $^{201}$Tl (for myocardial scintigraphy).

When the 184-Inch Synchrocyclotron was built, Ernest Lawrence asked Robert Wilson, one of his graduate students, to look into the shielding requirements for of the new accelerator. Wilson soon realized that the 184-Inch would produce copious protons and other heavier ions that had enough energy to penetrate human body, which could be used for treatment of deep-seated diseases. Realizing the advantages of delivering a larger dose in the Bragg peak when placed inside deep-seated tumors (today we call it “conformal” treatment), he published a seminal paper on his rationale to use accelerated hadrons for treatment of human cancer.[6] Soon after the 184-Inch Synchrocyclotron was operating, Lawrence very generously partitioned the limited space on the experimental floor for treating patients. In 1954 Cornelius Tobias and John Lawrence performed the pioneering first therapeutic exposure of human patients to hadron (deuteron and

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5 Almost nine-tenths of all nuclear medicine procedures utilize $^{99m}$Tc, whose precursor $^{99}$Mo is produced in nuclear fission reactors. Also, $^{125}$I and $^{192}$Ir for cancer therapy are produced through neutron capture in reactors. Many of these aging nuclear reactors must be replaced either with spallation neutron sources or 150-MeV cyclotrons (or linacs) with high-power proton beams.

6 R. R. Wilson, *Radiology* **47**: 487 (1946).

helium ion) beams[7]. Very active clinical trials to treat human cancer using helium ions took place at the 184-Inch until 1986, when it was demolished to make room for the Advanced Light Source. The helium ion trials continued at the Bevalac, where trials using heavier ions including carbon, neon, silicon and argon ions were carried out to exploit their biological advantages over proton beams. It is worth noting that in the early 1970s when the aging Bevatron was converted to accelerate heavier ions, the main push came from biomedical users who wanted to use high-LET radiation for treating human cancer.

The hallmark of charged particle therapy with protons and helium ions is precise dose localization with tight margins to spare normal tissues. The clinical implementation of proper techniques at Berkeley Lab led to outstanding success in treating skull base and juxtaspinal tumors with an unparalleled control and higher rates survival. These trials clearly demonstrated that the use of protons and helium ions is of value in the treatment of unresectable or partially resectable neoplasms in critical locations such as the orbit, eye, skull base, head and neck, juxtaspinal area, retroperitoneum, biliary tract and pelvis. The Berkeley results formed a model for future implementation of hadron therapy facilities.

When both accelerators were closed in Berkeley, 2,054 cancer patients had been treated with helium ions and 433 patients with neon ions. Aside from these, many other clinical trials have been conducted at accelerators originally built for physics research, such as at the Gustaf Werner Institute (now Theodore Svedberg Laboratory in Uppsala), Harvard Cyclotron Laboratory (Cambridge), Institute of Theoretical and Experimental Physics (ITEP in Moscow), Joint Institute of Nuclear Research (JINR in Dubna), B. P. Konstantinov Institute of Nuclear Physics (in Gatchina near St. Petersburg), National Institute of Radiological Sciences (NIRS in Chiba), Proton Medical Research Center (PMRC in Tsukuba), Paul Scherrer Institute (PSI in Villigen), Clatterbridge Hospital (UK), University of Louvain (Belgium), iThemba Laboratory for Accelerator-Based Sciences (originally NAC in Faure, S. Africa), Centre Protontherapie d'Orsay (CPO in Orsay), Crocker Nuclear Laboratory at University of California in Davis, and Indiana University Cyclotron Facility (IUCF in Bloomington).

In 1991, the Loma Linda University Medical Center in California heralded in the age of *dedicated* medical accelerators when it commissioned its proton therapy facility with a 250-MeV synchrotron, which now treats more than 1,200 patients per year. Soon after, many proton therapy facilities were constructed worldwide. Synchrotrons, typically accelerating 200-250 MeV protons, are used in Japan at the Proton Medical Research Center (PMRC) of the University of Tsukuba, Wakasa-Wan Energy Research Center, and Shizuoka Cancer Center. A new 250-MeV synchrotron facility is under construction at the MD Anderson Cancer Center in Houston, and when completed they plan to treat more than 3,000 cancer patients per year at the new facility. Cyclotrons, accelerating 235 MeV protons, are used at the National Cancer Center Hospital East in Kashiwa, Tokyo and the Northeast Proton Therapy Center in Boston. Similar cyclotron facilities are under construction in Jacksonville (Florida), Zibo (China) and Ilsan (Korea). Superconducting cyclotrons accelerating 250 MeV protons are being installed at the Paul Scherrer Institute (PSI in Villigen, Switzerland), and the Rinecker Proton Therapy Center (Munich, Germany).

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[7] C.A. Tobias, J. H. Lawrence, *et al*., *Cancer Research*, **18**: 121 (1958).

In 1994 the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, commissioned its Heavy Ion Medical Accelerator in Chiba (HIMAC), which has two synchrotrons that accelerates ions as heavy as argon nuclei to energy per nucleon of 800 MeV. Currently, their clinical trials use carbon ions, and they have successfully treated more than 1,000 patients. The Hyogo Ion Beam Medical Center (HIBMC) in Hyogo is another hospital-based charged particle treatment facility in Japan that utilizes both protons of maximum energy of 230 MeV and carbon nuclei of maximum energy per nucleon of 320 MeV. A synchrotron accelerating carbon ions is under construction at the University Clinic in Heidelberg, and similar carbon-ion accelerator facilities are planned by the TERA Project to build the National Centre for Oncological Hadrontherapy (CNAO) in Milan and also by Karolinska Institute in Stockholm. At HIMAC they have observed very promising clinical results with carbon-ion treatment of lung and liver cancers. Clinical trials at GSI, Darmstadt, have irradiated relatively radioresistant tumors such as chordomas and low-grade chondrosarcomas of the skull base, adenoid cystic carcinomas and malignant meningiomas. Early clinical results are excellent; local control rates achieved were comparable to neutron therapy but with less toxicity.

So what do we learn from Ernest Lawrence as a man? Born in Canton, South Dakota of Norwegian stock, the son of a superintendent of schools, he was a radio tinkerer in high school, and worked his way through local Midwestern colleges aspiring to become a physician. His interest in radio led him to a Ph.D. in physics at Yale (1925), and at 27 he was made an Associate Professor at the University of California. Two years later he became a full Professor, making him the youngest professor at Berkeley. “You don't have to have genius to be a scientist – just character. All you have to do is work hard and figure things out." So said Lawrence in what amounted to a telling self-portrait. Hard work and hard figuring ultimately led him to develop the cyclotron and win the Nobel Prize in 1939. His hard work led to the creation of the University of California Radiation Laboratory (now Lawrence Berkeley National Laboratory), the world’s oldest multidisciplinary research laboratory. It has been said that working his way through college selling kitchenware door-to-door made him into a good salesman who could “sell” his ideas to philanthropists and government funding agencies and support his bigger and bigger accelerators.

Ernest and John Lawrence made original and direct contributions that led to founding of nuclear medicine. Nuclear medicine has become an indispensable clinical modality that helps maintain our healthy society. Two Lawrence brothers, Wilson and Tobias, pioneered the development of accelerated hadron therapy. This novel modality is, 50 years after from its invention, being recognized by the healthcare community, and new hadron therapy facilities are burgeoning at medical centers worldwide. Because of the life of Ernest Orlando Lawrence, the world is a better place. His contributions to medicine appear almost greater than any one human could make. On the occasion of the 75$^{th}$ anniversary of invention of the cyclotron, we remember the words Louis Alvarez said in his memoirs, "For those who had the good fortune to be close to Lawrence both personally and scientifically, he will always seem a giant among men."

–William T. Chu, San Clemente, California, U.S.A.