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COMMENTARY

Leonidas D. Marinelli: Cold War Scientist

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Early in the Cold War that followed the secret Manhattan Project and first atomic bomb, Leonidas D. Marinelli pioneered the knowledge his adopted country urgently needed about long-term effects of radium in humans in order to protect against radiation toxicities from nuclear weapons and nuclear reactors.

To obtain a standard for estimates of radionuclides in the body, he studied individuals contaminated in the 1930s by medical radium injections at the Elgin Illinois State Hospital, and by radium paint used at an Illinois watch dial factory. He studied people contaminated in the 1940s and 1950s from weapons fallout, exposure at nuclear reactors, and radioactive materials used in industry and medicine. These studies elucidated internal dose recommendations made by the International and National Commissions of Radiation Protection (ICRP and NCRP) (1).

In 1956, Marinelli identified the isotope Radium 224 (Ra-224) as the cancer-inducing culprit in bone, and encouraged others to gather more data to confirm the findings (2).

University of Chicago physicist Ugo Fano described Marinelli's pioneering contributions. "His studies of physics dealt with electron diffusion from point sources in air and cosmic ray background. In radiology he pioneered in the detection of minimal burdens of radioactivity in humans, studying their distribution and variation in tissues and the epidemiology of chronic low levels of radiation. The center for Human Radiobiology, which now has the responsibility for all AEC-supported research on effects of internally deposited radioisotopes grew out of his effort" (Fig. 1) (3).

Columbia University Radiological Research Laboratory Director Harald H. Rossi wrote in 1975, Marinelli's greatest contributions "were to the complex subject of human radioactivity..." and the origination of scintillating crystals for whole body counting, "so patently superior to any other approach..." (Fig. 2).

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The Legacy of Leonidas D. Marinelli (Glenn D. Flux)

Leonidas D. Marinelli's legacy has proved to be far reaching. Cancer therapy with radioactive drugs (radiotherapeutics) offers the unique potential to image and measure the uptake and distribution within the patient over time. From these images the radiation doses delivered to areas of disease and to healthy organs can be calculated, as Leonidas Marinelli and other early investigators realized from the outset. Marinelli was the first to present the methodology needed to calculate the radiation doses, taking into account the amount of activity that was delivered to volumes of interest, the rate at which the radiation was emitted and the energies released from the radioactive decays. However, while radiation dosimetry has been an integral aspect of the development of external beam radiotherapy, dosimetry for radiotherapeutics has had a turbulent history, in part due to the wide therapeutic window of radioiodine, which enables a high success rate of treatments of benign and malignant thyroid disease without the procedures and calculations necessary to perform dosimetry.

Nonetheless, individual dosimetry is gradually being accepted as key to personalizing treatments to improve success rates further and to avoid unnecessary toxicities and has become of greater importance to newer radiotherapeutics in a field that is now expanding at an unprecedented rate.

The formalism that Marinelli developed to calculate the radiation doses delivered from therapeutic procedures is still used, following some reconfiguration by the Society of Nuclear Medicine & Molecular Imaging's committee on Medical Internal Radiation Dose (MIRD). Clinical trials have been performed to assess the impact of dosimetry and how this may be used to improve patient treatments for those at low risk, with just thyroid remnants after surgery, and for patients with metastatic disease that are at higher risk.

While modern technology has enabled detailed imaging of the distribution of radiotherapeutics after administration, the ability to measure retention of the drug in a patient, following Marinelli's development of the whole-body

The center for Human Radiobiology, which now has the responsibility for all AEC supported research on the effects of internally deposited radioisotopes, grew out of his effort.

FIG. 1. From Obituary by U. Fano, Leonidas D. Marinelli (1906–1974). *Radiat Res* 61, 538–539 (1975).

counter, is now used to deliver individualized treatments to children with neuroblastoma and is currently being investigated in a European clinical trial involving centers in many countries.

The issues surrounding radiation and its effects on patients and on the general population either from direct irradiation or from environmental contamination are still under investigation, with the EU funding a series of large-scale projects focused on the potential long-term effects of exposure to low doses. This has relevance for staff in nuclear medicine. Some important questions have been raised by epidemiological studies as was proposed by Leonidas Marinelli.

The importance of calculating the radiation doses delivered and the potential benefit for cancer patients or the long-term risks for people receiving low doses of radiation was recognized by Leonidas Marinelli 80 years ago. The astonishing breadth of the work he undertook throughout his career provided the foundations on which medical practice and radiation protection is continuing to advance. The medical community and the public at large owe a great debt of gratitude to this visionary physicist.

A Daughter's Story (Judith Marinelli Godfrey)

My father Leonidas D. Marinelli was a patriot. "America has been very good to me," he would say.

He was born in Buenos Aires, Argentina, November 28, 1906, to parents in a family of bell-makers in Agnone, Italy (Molise), since the year 1100. Leonidas emigrated to New York City immediately after graduating in electrical studies from the Alessandro Volta Royal Institute, Naples, Italy. The school awarded him the first gold medal in its history, engraved "3-10-1925."

In New York City, he was attending the Cooper Union Engineering College when he became initiated into experimental radium studies at the Memorial Cancer Hospital in 1929 by Dr. Gioacchino Failla, student of Marie Curie (the discoverer of radium), and originator of the concept of relative biological effectiveness (RBE). Hardly a year later, young Leo Marinelli adapted the X-ray roentgen unit to quantify intensities of gamma rays from 4 grams of radium, enabling the first scientific comparison of X rays and gamma rays (4). He published his first paper in 1933, obtained his M.A. degree from Columbia University in 1936, and published five more papers and completed all course requirements for the Ph.D. degree in Columbia's

Perhaps his greatest single contributions were to the complex subject of human radioactivity. He clearly originated the combination of massive scintillating crystals, multi-channel analysis and steel shielded rooms which was so patently superior to any other approach. It was almost immediately copied in many laboratories throughout the world and has yielded many insights into the human metabolisms of many elements and their compounds.

FIG. 2. Harald H. Rossi, Essay on Marinelli, April 25, 1975.

Division of Mathematics and Physics by 1938. He became Assistant Professor of Radiology at Cornell University in 1944, and Head of Biophysics at Sloan-Kettering Institute in New York City in 1945.

In the 1930s and 1940s, Marinelli advanced radiobiological physics. He traced metabolisms of laboratory animals in vivo in 1941 (5), laid out the principles to determine dosage of internally deposited radioisotopes in 1942 (expressing dosage in equivalent roentgens), (6) played a decisive role in the first treatment of metastatic thyroid cancer with radioactive iodine in 1946, administering doses calculated to the patient's thigh, spine, lung, and brain (7). He measured radioactive liquids rapidly in the Marinelli Beaker. In 1947 his comparative histopathologic and radioautographic studies of thyroid carcinomas kept tissue intact (8). He developed breakthrough cancer treatments at the Memorial Sloan Kettering hospital which the *Time Magazine* cover story featured December 14, 1949.

Pioneering Radium Effect in Humans

The University of Chicago called Marinelli to pioneer information America urgently needed about long-term effect of radium in humans. He taught biophysics at the University of Chicago in 1947 and moved his family to Chicago in 1948 (Fig. 3).

On the University of Chicago campus, Marinelli prepared an "Iron Room" for his pioneering studies. At the new Argonne National Laboratory, 30 miles west of the University, he set up the divisions of Radiological Physics and Medical and Biological Research with John E. Rose and Austin M. Brues for the scientific studies he designed and directed for the "radium-in-humans" project. He played a key role in obtaining the Argonne Cancer Hospital's participation for the clinical part of the studies. He became Associate Professor of Radiology at the University of Chicago Medical School. Deeply concerned about the growing risks of cancer and the need for radiation protection, Marinelli committed himself to investigate basic science for new knowledge.

Radium in Humans and Whole-Body Counter

Marinelli prohibited human experimentation at Argonne National Laboratory. Studies were exclusively of individuals previously exposed to atomic explosions, or the radiations used in industry and medicine. In 1950,



FIG. 3. The Marinelli Family in Yonkers, New York, 1947.

Marinelli developed a whole-body counter for the specific purpose of studying patients injected with medical radium in 1930 at the Elgin Illinois State Hospital, whom he perceived would provide a standard for estimates of radionuclides in the body (9). He studied Marshall Islanders and other previously contaminated individuals: radium dial painters at an Illinois watch factory; uranium miners from St. Joachimsthal, Germany; workers in accidents at nuclear reactors and laboratories; and radium-treated ankylosing spondylitis (10). In 1951, his closely protected toxicity studies received awards from the Radiological Society of North America and, in 1952, from the Society of Orthopaedic Surgeons.³

In the 1956 *British Journal of Radiology*, Marinelli summarized developments at Argonne Laboratory from 1950 to 1956 of spectrometers with sodium iodide crystals (NaI-Tl) and their uses to study gamma-ray activity in vivo (9) The gamma-ray energy emitted by an exposed person was quantified and sources identified. The entire setup was placed underground in a basement to reduce atmospheric radiations. He applied the versatile counter to also survey soils, drinking water, and dusts in the vicinities around Argonne Laboratory. Marinelli's whole-body counter, considered patently superior to any other in 1975, was used more than twenty years later for counting individuals by Argonne physicists in 1999 and 2011.⁴

K-40 In Vivo Measurement

In 1954, Marinelli decided to check the unexposed human body. He developed a "twin" scintillation low-level

³ The Leonidas D. Marinelli Collection, curated by Judith Marinelli Godfrey. (www.leonidasdmarinelli.com)

⁴ Private conversation between Dr. Irshad Ahmad, Argonne National Laboratory Physics Division, and Judith Marinelli Godfrey, September 2, 2011.



FIG. 4. Georg de Hevesy, Titus Evans, and Leo Marinelli in Copenhagen, 1953.

gamma-ray crystal spectrometer for this purpose (11). The check resulted in the in vivo measurement that established beyond doubt the total naturally radioactive K-40 potassium content in the normal human body (12, 13). The new spectrometry "had introduced a totally new order of spectrometry...the most sensitive in the world...." the *Argonne News* reported (14).

1953 - Copenhagen, Gamma-Rays in Living Persons

The "Atoms for Peace," spirit was new when Marinelli went to the Seventh International Congress of Radiology, in Copenhagen, Denmark, July 1953. President Eisenhower encouraged the exchange of scientific ideas. Marinelli shared methods he used to investigate the gamma-ray activities of workers exposed in an accident at a nuclear reactor and inhaled radium sulfate (15, 16). Accident cases differ "radically" from cases of chronic human radium poisoning, he concluded.

International conferences were an opportunity for Marinelli to interact with his European colleagues, as George de Hevesy, Nobel Prize laureate, and Val Mayneord, his Great Britain friend from the Chalk River conferences, as well as his American friend Titus C. Evans, University of Iowa, and others (Fig. 4).



FIG. 5. Leonidas Marinelli and Mrs. Helen Marinelli admire the Janeway Medal presented by the American Radium Society, November 1958.

1953 - Maximum Permissible Body Burden of Radium

Cancer was the feared but scientifically unproven long-term effect of radium and nuclear fallout. As late as 1956, harm from radioactive fallout was denied by the AEC chairman (17).

How much radium can the human body stand? people wondered. Marinelli sought the “maximum permissible burden of radioactivity” by measuring relatively healthy individuals who had been contaminated many years ago. Laboratories around the nation measured hundreds of mice to obtain the maximum permissible level. Repeatedly, Marinelli stated, differences in scale between mice and men

are too great to extrapolate from mice accurate safe numbers for humans (18).⁵

“The most expedient method of measuring X-radiation doses for radiological purposes is by measurement of ionization in gases...considering that the X-rays, like all photons, transfer energy mostly to the electrons in matter...,” Marinelli stated at a symposium on Physical Measurement in Radiobiology presented at the 1953 meeting of the Radiation Research Society (19). University of Chicago physicist Ugo Fano noted Marinelli’s method of beta measurement in the 1954 *Annual Review of Science* (20).

1955 - Geneva, Atoms for Peace

At the International Conference on the Peaceful Uses of Atomic Energy, Geneva, 1955, Marinelli followed up on the reactor-accident workers’ physical dosimetry and clinical observations (21). The skeleton, he concluded, is the “seat of the retained radon.” He introduced a spectrometric method for the partition of radon gas in animal lungs (22).

1956 - Thorotrast and Ra-224

In 1956, radium was found present in Thorotrast patients at Danish hospitals who were never exposed to radium. Marinelli determined that their internal doses of Ra-224 had come from the decay of thorium inside the body and the translocation of its “daughters” to the skeleton (2). He perceived the Ra-224 dose in the Thorotrast patients and the Ra-224 dose in the Elgin patients and Illinois radium dial painters had produced the cancer-damaged bones in all cases (23). The Ra-224 culprit was caught at last. More data were needed, however.

As Marinelli was studying the K-40 in healthy volunteers from countries around the world, he discovered they were all contaminated with Cs-137 fallout by year end. The Joint Commission on Atomic Energy summoned him to testify at the 85th U.S. Congress in Washington D.C. on the day of my 18th birthday (24).

1957 - Turin, Italy, Spectrometry for Nuclear Medicine

In Turin, Italy, Marinelli announced the use of low-level gamma-ray spectrometry in nuclear medicine at the opening of the European International Congress of Nuclear Medicine, June 5, 1957 (25). He invited researchers to replicate the spectrometry to study Thorotrast patients and gather data worldwide on radium-damaged bone (26). The Italian Society for Radiobiology and Nuclear Medicine elected Marinelli a member of the Board of Collaborators of the *Minerva Nucleare* Journal. Scientists invited him to their

⁵ Marinelli LD. Estimates of Bone Pathology to be Expected from Sr-90, mailed with cover letter to fifty-seven AEC Advisory and network associates (April 22, 1957). The pre-print for ANL-5716 is unpublished. (www.leonidasdmarinelli.com)

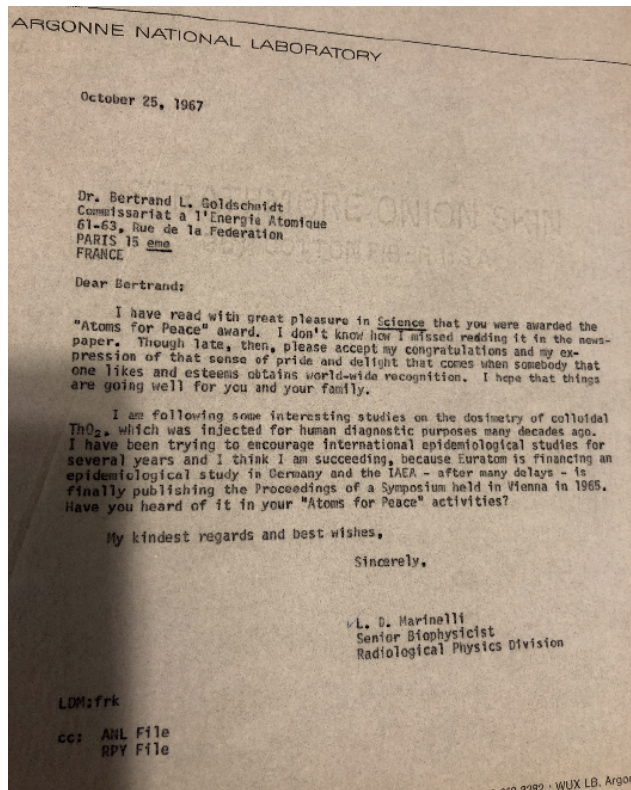


FIG. 6. Letter to Bertrand Goldschmidt, Oct. 25, 1967.

laboratories to calibrate their replications of his spectrometer (27).

1958 - The Janeway Medal

In 1958, the American Radium Society awarded Leonidas D. Marinelli the prestigious Janeway Medal. "Radioactivity and the Human Skeleton," the Janeway Lecture, proposed epidemiological studies of human populations to estimate future cancer risk. He invited others to carry out studies of Thorotrast patients (28).

International Influence

Marinelli influenced many scientists and organizations as he shared advances in radiobiology and spectrometry at international conferences. At the 2nd International Conference on Peaceful Uses of Atomic Energy, Geneva, 1958, he presented the spectrometry for gamma emission in humans (29). At the Health Physics Symposium in Riso, Denmark, 1959, he presented his evaluation of radioactive contamination in humans (30, 31). At the 9th International Congress of Radiology, in Munich, Germany, 1959, he lectured on effects of low-level irradiation in humans and on the contribution of epidemiological studies. I was present at his standing-room-only lectures (32).

At meetings of the International Atomic Energy Agency in Vienna, he presented, in 1961, on sodium-iodide systems and on the retention of radium in humans 20 to 29 years



FIG. 7. Marinelli at Euratom in 1966.

after intravenous administration (33–35). In Vienna, 1965, he presented the status, prospects and implications of doses from Thorotrast migrated descendants, and proposed to the WHO and IAEA that they coordinate the Thorotrast toxicity cases internationally (36).⁶ In Houston, Texas, 1963, he presented advances of his spectrometry at the Rice University Natural Radiation Environment Symposia (37, 38). In Italy, 1965, he explained problems with the "maximum permissible" determination (39). In 1967, he addressed the New York Academy of Sciences on the in vivo counting of the Thorotrast patients (40). At the International Guidelines meetings in Montreal Canada, 1967, he presented on leukemias and carcinomas in Thorotrast patients (41).

1960 - Dr. Failla Joins Marinelli and the Argonne Staff

The plan Marinelli and Dr. Failla discussed in Munich was realized the next year when Dr. Failla retired from Columbia University and joined Marinelli's Radiological Physics division at Argonne, July 1, 1960. Failla and his wife Dr. Patricia McClement Failla chose their new residence nearby Helen and Leo Marinelli in Hinsdale, Illinois. Failla's choice to spend the rest of his scientific life with Leo at Argonne was perhaps the greatest of all tributes to Marinelli. On November 6, 1960, they reviewed Marinelli's scientific contributions to radiobiology and spectrometry from 1930 to 1960.⁷ They were about to undertake the arduous task of analyzing the worldwide data on Thorotrast and bone that scientists were gathering, when the car carrying Dr. Failla in the passenger seat was struck

⁶ Foreign travel trip report: to the WHO and IAEA, Vienna. LD Marinelli to ME Gahlon, DDO, ANL. Oct. 4–7, 1965. (Marinelli reading file, p. 8)

⁷ The single-page chart references the original published papers. In the Leonidas D. Marinelli Collection, curated by Judith Marinelli Godfrey. (www.leonidasmarinelli.com)

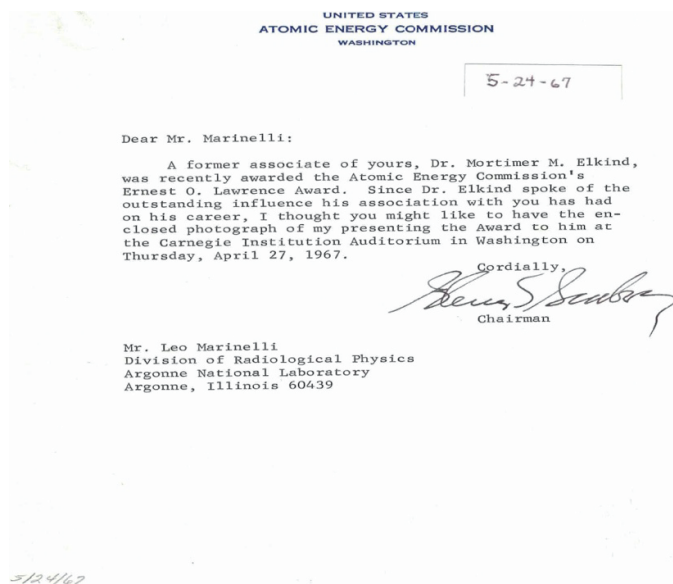


FIG. 8. Letter from Glenn Seaborg, May 24, 1967.

by a truck at the Argonne highway exit, killing him instantly.

Radiation Protection Studies

Marinelli analyzed and interpreted the data alone. In 1967, he wrote Bertrand Goldschmidt, future Chairman of the International Atomic Energy Agency (IAEA), his

To Dr. Leo D. Marinelli, Director
Radiological Physics Division
Argonne National Laboratory
9700 S Cass Ave, Argonne, IL 60439

“Dear Leo:

Thanks for your good letter as I relinquish the job of Director of the Division of Biology and Medicine.

In 1949 just as I was going with the AEC I heard about you as a special steal from New York—a feather in Rose and Brues’ collective cap. I was shown in some awe what seemed to have been a part of the bait [—] an aluminum, or was it a stainless, shack.

Simply as a knowledgeable scientist and also a trusted adviser to our Advisory Committee for Biology and Medicine and on ad hoc jobs you made our work in radiologic physics and biological studies with a variety of internal emitters much easier, more productive and scientifically sound. I shall always be grateful for your help.

Thank you for the kind words. I shall try to live up to them

Sincerely yours,

Chuck
Charles L. Dunham, MD
Director, AEC Biology and Medicine.”

(1972)

FIG. 9. Letter from Charles L. Dunham, 1972.

chemist back in 1942 (Fig. 6) (42). He apprised his old friend of the Thorotrast studies spreading in Germany, of the achievement of the Argonne 20- to 29-year studies on the Elgin radium patients, and the epidemiological studies being financed by EURATOM, the new organization for European interests in atomic energy. Marinelli was resident consultant at EURATOM the previous year (Fig. 7).

Time-of-Flight Camera

The reductions of neutron background Marinelli made continuously in his spectrometry enabled him to extract measurements of small distributions of radium from the Thorotrast data (43, 44).

In 1968, he developed a “Time-of-Flight” camera useful to localize radioactivity in vivo, to monitor internal contamination in neutron radioactivation analysis, and to perform tasks of several gamma-ray cameras (45, 46). Mathematician Ika Abu-Shumays worked closely with him to reduce patients’ radiation exposure during medical imaging. “These were the most exciting years of my career,” Abu-Shumays said to me in 2003.

Cancer Risk

In 1968, Marinelli’s radium-in-humans studies were assimilated into Argonne’s new Center of Human Radiobiology (ANL-7760 II, RPY July 1969–June 1970). This “million-dollar center...had to be built just to house all your father’s studies,” boasted Director Robert E. Rowland

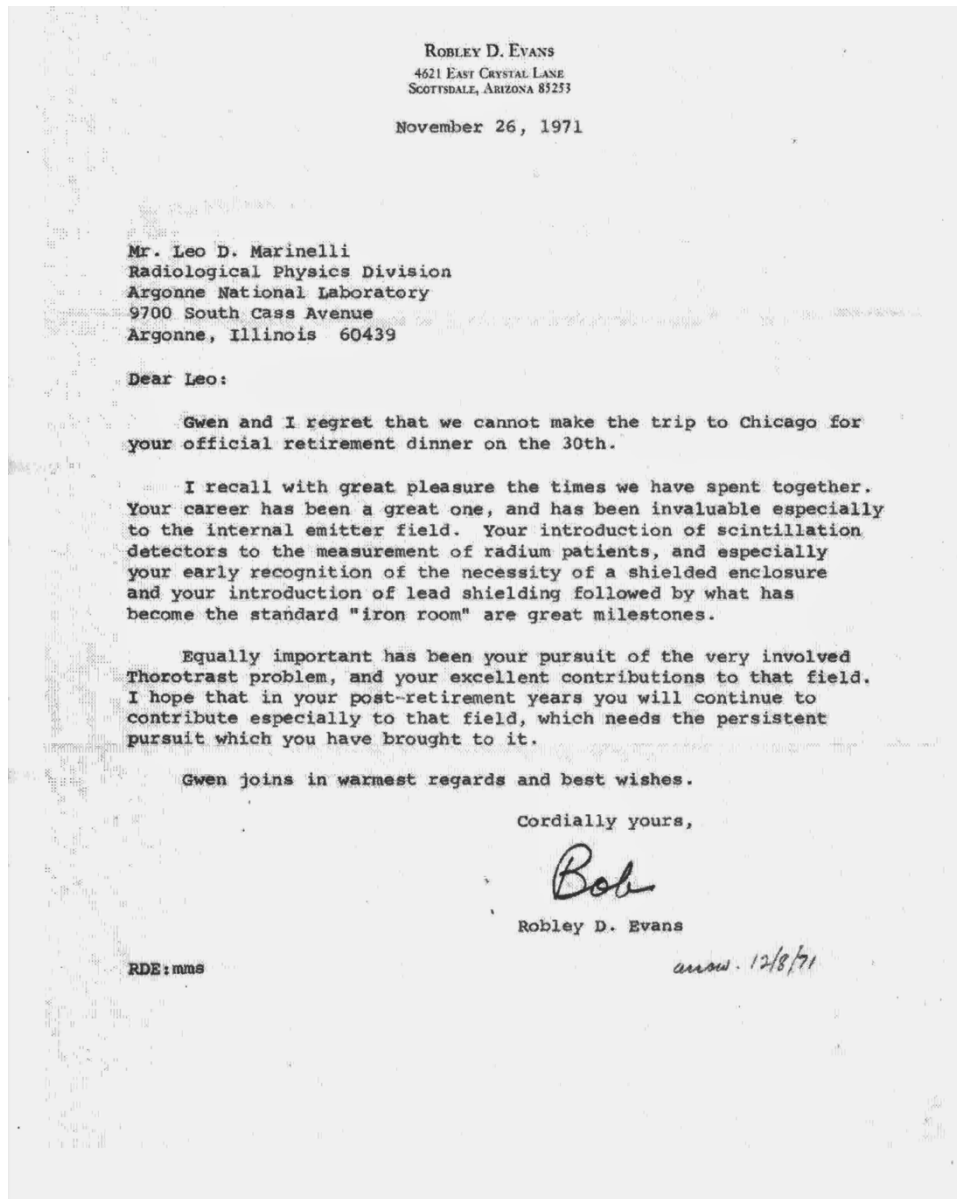


FIG. 10. Letter from Robley D. Evans, Nov. 26, 1971.

the second day in his new Center office, January 14, 1976. The name of the Radiological Physics (RPY) division was changed to the division of "Radiological and Environmental Research" (RER).⁸⁷

Marinelli directed his efforts to reduce leukemia and solid cancers in the United States, advising the Director of Radiological Health in the U.S. Public Health Service (47, 48). He revised his estimate of the Sr-90 maximum burden, and he wrote the "Dosimetry" chapter for the German Medical Encyclopedia (49, 50).

⁸ Private conversation between Judith and her father, Summer 1969.

His last paper, published in 1974 on leukemia risk, states that the risk induced by internal alpha-radiation "remains constant over time in contrast to the decline in risk over time induced by a dose of external x-rays." He concluded in accordance with general biological findings that "there is little or no recovery from effects produced by high LET radiation" (18).

Glenn Seaborg, Chairman of the AEC, wrote Marinelli about his influence on a prize-winning scientist (Fig. 8).

Charles L. Dunham, director of AEC Biology and Medicine, warmly expressed his appreciation for Marinelli's guidance and advice (Fig. 9).

Robley D. Evans, MIT Professor and Marinelli's AEC advisory colleague, wrote admiringly of several Marinelli accomplishments (Fig. 10).



FIG. 11. Poster for the 25th anniversary of Marinelli's death, at the 'Leonida Marinelli' Institute, Agnone, Italy, Oct. 13, 1999.

Proof of Radium-induced Cancer

At the first International Symposium on Biological Effects of Ra-224 and Thorotrast, July, 1974, scientists presented the worldwide data to make "intercomparisons of the skeletal effects in Thorotrast patients, the Elgin patients, and radium-dial painters" as Marinelli had done twenty years earlier (23).

On September 13, 1974, my father died of cardiac arrest. "Radiological physics has lost one of its brightest stars, which had shone uninterruptedly for over 40 years," wrote Argonne Physicist and University of Chicago professor John Rundo in the Memorial dedicating the Symposium to Leonidas D. Marinelli (23).

In 1975, I went with Dr. Brues to my father's office for the original reprints of his 100 published papers, kept in a glass bookcase. I had them bound into five blue hardcover volumes.

In Italy, 1999, a region-wide festival celebrated the 25th anniversary of Marinelli's death at the "Leonida Marinelli" Technical Institute in Agnone, October 13th, on the 50th anniversary of the founding of the Institute. Senators, scientists, professors, educators, family and friends came to the celebration from afar. Marinelli Bells rang out joyously (Fig. 11).

Marinelli Road to Radiation Protection

A "Marinelli Road" off the Rockville Pike, not far from Washington, D.C., leads to the front entrance of the Nuclear Regulatory Commission, Rockville, MD, which is responsible for radiation protection standards and practices in the

U.S.A. Radiation protection was always a high priority in Marinelli's work.

My father was a content and gentle man. His quick observations amused, surprised and inspired. He was faithful to science, to his wife, to his family in America and Italy, and to the Catholic principles that formed him. If you met him, you'd feel he appreciated you, the Earth, and the people on it, their culture and music, preferably Italian opera.

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