A historic review of the discovery of the medical uses of radioiodine

Barbara Hertz[1*], Pushan Bharadwaj[2], Bennett Greenspan[3]

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contact@psnmed.com
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Correspondence to: Barbara Hertz
*Dr. Saul Hertz Archives Greenwich, CT.
Email: htziev@aol.com
Full list of author information is available at the end of the article.

Dr. Saul Hertz (1905–1950) discovers the medical uses of radioiodine.

How many times have you prescribed Iodine-131 for thyrotoxicosis or differentiated thyroid cancer? Probably too many to count. For nearly 80 years, radioiodine (RAI) has been the mainstay of nuclear medicine therapy. One pivotal question began it all. This enduring paradigm change was sparked on November 12, 1936, when Dr. Saul Hertz, director of the Massachusetts General Hospital's (MGH) Thyroid Unit went to a lecture presented by the president of the Massachusetts Institute of Technology (MIT), Karl Compton, Ph.D. Dr. Hertz conceived and spontaneously asked the question to President Compton, "Could iodine be made radioactive artificially?"[1]

MIT's President Compton responded and wrote about the qualities of radioactive iodine. Hertz replied, "that iodine is selectively taken up by the thyroid" and "that he hopes that it will be a useful method of therapy."[1] Quickly thereafter, a unique collaboration was established between MGH and MIT, when physicist Arthur Roberts was hired by MIT's lab's director, Robley Evans.

Hertz and Roberts-Animal Studies 1937: 1st Therapeutic Use 1941

In 1937, Harvard Medical School funded the Hertz/Roberts first series of experiments with 48 rabbits and Iodine-128. MIT physicist Arthur Roberts, Ph.D. made I-128 without a cyclotron. I-128, with a half-life of only 25 minutes, was given to the rabbits with altered thyroid gland function. The data showed that hyperplastic glands held more I-128 than normal glands. These studies confirmed the tracer quality of a radioactive substance, bringing to light the tracer principle that RAI could be used to study thyroid physiology; a giant step for what was to become Nuclear Medicine.

MIT's Robley Evans, the lab director, insisted that his name be added to the author list at the time the Hertz/Roberts rabbit study paper was accepted for publication. Evans had taken no part in the research or writing of the paper. This event foreshadowed other unethical practices that Dr. Hertz needed to overcome to bring his lifesaving research to fruition.

After the publication of the Hertz/Roberts rabbit studies, Dr. Joseph Hamilton, a neurologist in a medical practice near Berkeley, CA, became interested in their research. Hamilton measured the differential absorption ratio of various radionuclides produced by the Berkeley cyclotron. Hertz's former Boston colleague, Dr. Mayo Soley, wrote to Hertz about copying the Hertz/Roberts rabbit study. Hertz wrote back, "Welcome aboard!" The Soley/Hamilton group in Berkeley was motivated by the animal work of Hertz and Roberts and sent Hamilton to Boston. Hamilton went back to California to join Mayo Soley in the thyroid clinic. Hamilton complained to Berkeley's Glenn Seaborg about the short half-life of I-128. In June, 1938, Glenn Seaborg and John Livingood made a cyclotron mixture of I-130 (t1/2 12 hours) and I-131, with a physical half-life of about 8 days.

Hertz and Roberts needed a cyclotron to produce RAI to start clinical trials. MGH's Chief of Medicine and founder of MGH's Thyroid Unit, Dr. James Means, received $30,000 from the Markle Foundation to establish MIT's first cyclotron. Means reported to the Markle Foundation, "My former house officer, Mayo Soley, is working on radioactive iodine. Hertz and Roberts deserve a great deal of credit in getting the pioneering work done without a cyclotron, as soon as the cyclotron here is available, we can progress rapidly."

On March 31,1941, Dr. Hertz gave 2.1 mCi of MIT cyclotron-produced RAI, the first therapeutic treatment of radioiodine to a patient, Elizabeth D, with a chasing dose of stable iodine in the form of Lugol Solution to prevent a possible thyroid storm. Gradually, the first series of 29 patients was developed. Hertz and Roberts continued to treat hyperthyroid patients in 1942. Of importance, also in 1942, are the first limited clinical trials to treat thyroid cancer patients with RAI that Hertz administered and reported to the Markle Foundation. (Figure 1)

In early 1943, Dr. Hertz joined the Navy during World War II. Hertz felt that his cases had been well established and that the protocol was in place, having used uptake testing and dosimetry in making an effective therapy. Dr. Earle Chapman, who treated wealthy patients, worked part time at MGH. Hertz asked Chapman to take over his

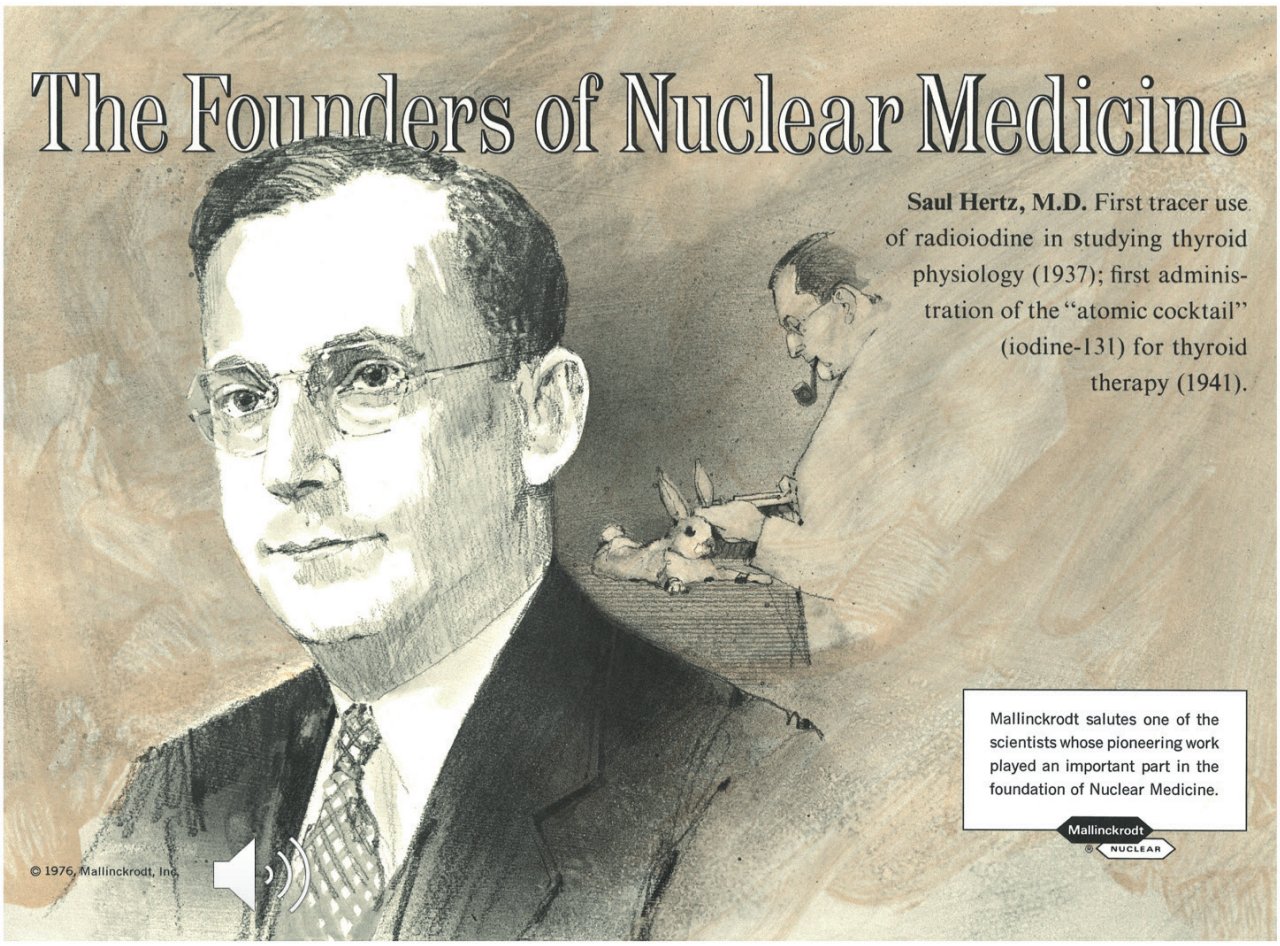

Figure 1. *Mallinckrodt Commemorative Poster. Courtesy: Dr. Saul Hertz Archives Greenwich, CT USA..*

cases during his absence. Hertz had firmly established the work. Arthur Roberts, wrote, "I would believe nothing on this subject from Chapman, who bungled the follow-up on Hertz's original series when Hertz joined the Navy."[2] Yes, Chapman changed the protocol, making little use of dosimetry, used a standard large dose and stopped giving the chasing dose of stable iodine.

Stolen Intellectual Property

Chapman together with MIT's Robley Evans went to publish the work as their own in JAMA without Dr. Hertz's name and before Dr. Hertz returned from WWII. The editor of JAMA asked Hertz and Roberts for their paper on the topic, so two papers from the same institutions were published side by side in JAMA on May 11, 1946.

During the war many professional meetings were postponed. Chapman and Evans state in their paper, "Although Hertz and Roberts were encouraged by their therapeutic trials, the details of their findings have not been published." They also used the follow up Lugol solution to justify their ownership of the RAI discovery.

The truth was revealed and explained in April, 2016 by MGH's Chairman Emeritus of the Department of Radiology, Dr. James Thrall, who stated, "Chapman and Evans had basically stolen Hertz's work...the most flagrant, unethical, academically reprehensible behavior, worst yet, ...Chapman and Evans spent a great deal of time and effort rewriting history."

Use of Radionuclides to Diagnose and Treat Cancer: Precision Targeted Oncology

With courage and tenacity, Saul Hertz moved forward. He used newspapers and magazines. There was a great interest in using atoms for peace. Hertz stated in the June 2, 1946 *American Weekly Magazine*, "...demand is expected for radioactive iodine and as research develops in the field of cancer and leukemia, for other radioactive medicines." [2]

To be noted, a limited number of outsiders were being trained at medical schools however, they were not allowed on the staffs of most hospitals. At that time, there was a significant lack of diversity at medical schools and on the staff of most hospitals. In fact, Hertz had come to MGH in 1931 as a volunteer and was not paid. Catholics and Jews built their own hospitals. After World War II, Hertz joined Boston's newly expanded Beth Israel Hospital.

It's at the Beth Israel Hospital that Dr. Hertz continued to develop and refine the use of RAI to diagnose and

treat thyroid cancer. He had funding from the Navy to use radioiodine for the treatment of thyroid carcinoma and to research disabling the thyroid to explore its possible benefits for patients with angina. Hertz used radionuclides with the tracer targeted method. This upset Dr. Hermann Blumgart, a cardiologist and the director of the hospital, who used Radium-C (Bismuth-214) to determine the velocity of blood flow in the 1920's. Blumgart blocked Hertz and his research. Hertz's work was an economic threat. The cost of the RAI treatment was $3.40. Surgery to remove the thyroid was much more expensive, costing hundreds of dollars. Many patients wrote to Dr. Hertz with the same themes, "How can we get it?" and "I can't afford an operation." There was no medical insurance and patients were desperate to have the RAI treatment. Additionally, Blumgart resented Hertz's success and his international reputation.

Hertz wrote, "..my new research project is in Cancer of the Thyroid which I believe holds the key to the larger problem of Cancer in general."[2] In September, 1946, The Radioactive Isotope Research Institute was established with the mission of applying nuclear physics to medical investigation, diagnosis, and treatment. There were clinical and laboratory facilities in Boston and New York. Dr. Hertz was the founder and director. New York Montefiore Hospital's Dr. Samuel Seidlin was the associate director who managed the New York offices.

By happenstance, Dr. Seidlin used RAI to treat cancer, when a patient known as "BB" came to Montefiore Hospital with thyrotoxicosis due to metastasized thyroid cancer. Years earlier, patient BB's thyroid had been surgically removed. After consulting with Hertz, Seidlin treated the cancer patient with RAI, in 1943. BB's metastases responded to the RAI. No new lesions appeared and some had completely disappeared. However, in 1952, BB died from anaplastic carcinoma.

Dosimetry became essential in preparing a personalized treatment plan. Dosimetry expert Glenn Flux writes, "To calculate patient-specific dosimetry showed an early understanding of the medical use of radionuclides that is now being investigated on a large scale to personalize treatments. Hertz and Roberts were truly visionaries."[1] Dr. Hertz developed a Multiscaler, equipment that facilitated uptake testing, to determine with precision an effective dose of RAI for each patient.

Hertz wrote, "I have certain ideas in the field of Cancer. Only recently a group of workers in England have reported the regular production of cancer of the thyroid in animals by a series of steps which are subject to analysis and close study by means of Radioactive Iodine as a tracer."[3] Hertz thought of using RAI to treat thyroid cancer in 1937, at the time of the pre-human studies, as well as conducting limited clinical trials in 1942 that were reported to The Markle Foundation. [4]

The headline from The Harvard Crimson, read, "Hertz to Use Nuclear Fission in Cure for Cancer." He supported the production of I-131 off the atomic piles that lowered the cost and increased the RAI distribution. Hertz stated, "The goiter treatment by means of radioactive iodine represents a 'first' in hopefully a long series of definitive treatments." [3]

Dr. Hertz established the first Nuclear Medicine Department in 1949 at The Massachusetts Women's Hospital. It was reported as, "Opening a new division where radioactive isotopes will be used to study and treat disease." (Figure 2)

In the 1980's, building on Dr. Hertz's work, the first radioimmunotherapy using monoclonal antibodies was developed. Hertz's teaching at both Harvard Medical School and MIT was the beginning of today's dual degree programs. Currently, we are internally targeting other tumors with radionuclides, such as, Yttrium-90 and Lutetium-177. In addition to thyroid, targeted therapies are being used for neuroendocrine tumors, lymphoma, prostate cancer, metastatic bone cancers, and neuroblastoma in children and there are many more to follow.

Saul Hertz's prediction that radionuclides, "...would hold the key to the larger problem of Cancer in general," may just be the best hope for diagnosing and treating cancer. Using the power of radionuclides as a weapon to fight cancer has extended the lives of countless generations of patients. A cancer survivor wrote, "Treatment with radioactive iodine knocked the thyroid cancer (metastatic to a little bit of bone and lung) right out of me, I am now 81. We have a large family. Many were praying for me. The cure delivered on the wings of prayer was Dr. Saul Hertz's discovery, the miracle of radioactive iodine. Few can equal such a powerful and precious gift." [3]

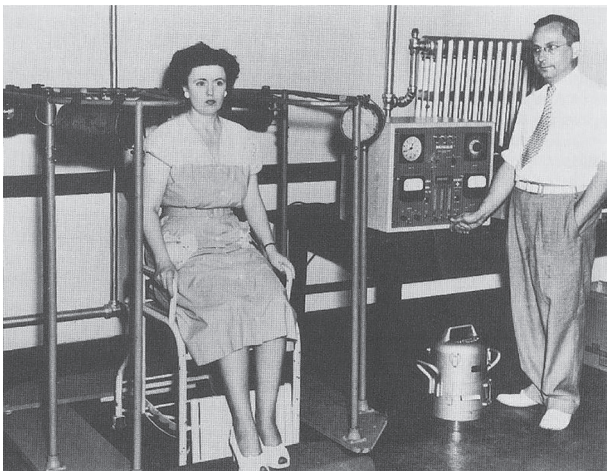

Figure 2. *Dr. Saul Hertz (circa 1940's) Multiscaler-Uptake Testing-Dosimetry-PrecisionOncology. Courtesy: Dr. Saul Hertz Archives Greenwich, CT USA.*

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Author details
Barbara Hertz[1], Pushan Bharadwaj[2], Bennett Greenspan[3]

1. Dr. Saul Hertz Archives Greenwich, CT
2. Consultant in Nuclear Medicine and PET, Singapore General Hospital, Singapore
3. B.G. Consulting North Augusta, SC

References

1. Fahey FH, Grant FD, Thrall JH. Saul Hertz, MD, and The Birth of Radionuclide Therapy. EJNMMI Phys. 2017;4(1):15. https://doi.org/10.1186/s40658-017-0182-7
2. Braverman L. I-131 Iodine therapy: a brief history. Presented at the AACE 2016 annual meeting Orlando, FL, May, 2016
3. Hertz B. A tribute to Dr. Saul Hertz: the discovery of the medical uses of radioiodine. World J Nucl Med. 2019;18:8–12. https://doi.org/10.4103/wjnm.WJNM_107_18
4. Hertz S. A plan for analysis of the biological factors involved in experimental carcinogenesis of the thyroid by means of radioactive isotopes. West J Surg Obstet Gynecol. 1946;54(12):487–9.