Dr. Saul Hertz Discovers The Medical Uses of Radioiodine (RAI) to Treat Graves' Disease and Cancer: A Daughter's Tribute as Presented "Autoimmunity in 2017; Where Are We Now?"

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A patient emailed this in March, 2016, "Treatment with radioactive iodine knocked the thyroid cancer (metastatic to a little bit of bone and lung) right out of me, exceeding my doctor's expectations… 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."

I had learned a great deal about my dad and his groundbreaking research in the last few years with the help of many eminent thyroid specialists, nuclear medicine professionals and archivists. Saul Hertz passed in 1950 from a sudden death heart attack when I was a small child. My mother carefully stored all of his original research, photos, newspaper articles, correspondence and much more for some sixty years in our family home outside of Boston, Massachusetts.

The history unfolds as such:

Saul Hertz was born on April 20, 1905 in Cleveland, Ohio, to Aaron Daniel and Bertha Hertz. His parents had emigrated from Europe to avoid persecution in the late 1800's. They raised their seven boys as Jews. Saul attended public school and went on to The University of Michigan graduating Phi Beta Kappa. He graduated from Harvard Medical School in 1929, at a time of strict quotas for outsiders. He fulfilled his internship and residency in Cleveland at The Mt. Sinai Hospital. In 1931, he returned to Boston to The Massachusetts General Hospital where he was appointed director of their newly formed Thyroid Clinic (1931-1943).

SEMINAL QUESTION

On November 12, 1936, Dr. Saul Hertz spontaneously asked MIT's President Karl Compton, "Could iodine be made radioactive artificially?" This eureka moment for medicine brought together the effect of iodine on the thyroid and artificial radioactivity discovered in 1934. Hertz's seminal question launched his research that led to the development of the field of nuclear medicine.

RABBIT STUDIES

In early 1937, a collaboration was established between the Massachusetts Institute of Technology and Boston's Massachusetts General Hospital. A young physicist, Dr. Arthur Roberts, was hired by MIT to work with MGH's Dr. Hertz. Hertz and Roberts began the first rabbit studies to evaluate the effect of a nuclear substance, radioactive iodine (RAI), on the thyroid. Dr. Roberts produced noncyclotron I-128 in small quantities based on Enrico Fermi's work. The experiment involved 48 rabbits. The RAI was administered to rabbits with altered thyroid function. Quantitative analysis showed that hyperplastic thyroid glands retained more RAI than normal thyroid glands. The studies demonstrated the principle that tracer amounts of radioactive iodine could be used to investigate thyroid gland physiology demonstrating the tracer capabilities of RAI and its effects on the thyroid gland.

The original draft of the article describing their rabbit study findings had Hertz and Roberts as the coauthors, as they had done the work and written the paper. MIT's Robley Evans, who was the administrator of the lab at MIT and who had hired the physicist Arthur Roberts, insisted that his name be added to the paper while it was at the publishers. Robley Evans had done no work in the construction of the experiment, analysis of the data or writing the paper. When Roberts was hired, Evans had included as a condition of his employment that his (Evans) name be added to any papers that might be forthcoming. Evans dictated a letter to the editor for Hertz to sign that Robley Evans's name be added although Evans made no contribution.

Hertz and Roberts were hopeful that they could go from diagnosis to treatment; however, they knew that

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they would need a larger quantity of RAI with a longer half-life. Cyclotron produced RAI was needed. MGH's Chief of Medicine, Dr. James H. Means, secured a $30,000 check from the Mary and John Markle Foundation for the building of MIT's cyclotron.

THE FIRST THERAPEUTIC USE OF RAI

The new Markle MIT cyclotron began operations in late 1940. Dr. Hertz administered the first therapeutic treatment of RAI in early 1941 to Elizabeth D. at the Massachusetts General Hospital. Hertz's Data Charts indicated that this first patient received 2.1 mCi (77.7 MBq) of I-130. The radiation was delivered rapidly to the thyroid cells over a day or two. A follow up Lugol Solution was administered to prevent the patient from having a thyroid storm.

Hertz continued to treat hyperthyroid patients with I-130 throughout 1942. In 1943, Dr. Hertz joined the United States Navy to serve his country during World War II. MGH's Dr. Earl Chapman was ineligible for service. Chapman, a private practice doctor who treated Boston's Beacon Hill affluent patients, managed to carry on clinical research and worked part-time at MGH. Hertz asked Chapman to take over his RAI cases, as Hertz had firmly established the work as a successful therapy. Hertz made use of uptake testing and dosimetry to determine an effective therapy. Hertz and Roberts initiated what today is called personalized precision medicine. Chapman saw an opportunity. Dr. Arthur Roberts, Hertz's MIT collaborator, writes "I would believe nothing on this subject from Chapman, whose self-interest is obvious and who bungled—whether deliberately or not—the follow-up on Hertz's original series when Hertz joined the Navy." Yes, Chapman changed Hertz's carefully designed protocol. Chapman and Evans used one standard large dose. In March of 1946, at the end of World War II, Hertz received a cold reception at MGH. His service to his country was not honored. In Boston, The Beth Israel Hospital was emerging and welcoming "outsiders" to the establishment to be on staff. Dr. Hertz joined the staff of The Beth Israel Hospital.

Meanwhile, Chapman had established 22 patients of his own along with MIT's Robley Evans. Chapman and Evans wrote up their first paper on the subject and sent it to the *Journal of The American Medical Association* (*JAMA*). Morris Fishbein, the editor of *JAMA*, contacted Dr. Hertz sharing with him that "I have a paper here from Chapman and Evans and they are saying they have propriety of the discovery of radioiodine and your name is not even on the paper." Fishbein asked Hertz and Roberts to write up their seventh paper on the medical uses of RAI. And so there appeared side by side in *JAMA* May 11, 1946, two articles from the same hospital using RAI describing the successful treatment of hyperthyroidism.

Dr. James Thrall, Chairman Emeritus MGH Department of Radiologist, stated on April 5, 2016, that "Chapman and Evans had basically stolen his (Hertz's) work … the most flagrant, I think, unethical academically reprehensible behavior…worst yet, Saul Hertz died in 1950 and these two gentlemen (Chapman and Evans) spent a great deal of time and effort rewriting history."

Hertz worked with The U.S. Atomic Energy Commission to distribute RAI off of the atomic pile. In August 1946, this service began and I-131 was used exclusively because it was much less expensive. Going forward RAI became the preferred method of treating Graves' disease worldwide.

RAI: THE FIRST AND GOLD STANDARD OF TARGETED CANCER THERAPY

Dr. Hertz responded to MGH's Director, Dr. Paxton's letter on March 12, 1946, "It is a coincidence that my new research project is in Cancer of the Thyroid which I believe holds the key to the larger problem of Cancer in general." The next day March 13, 1946, Hertz writes to MIT President Compton, "I have certain ideas in the field of Cancer of the Thyroid which are even more intriguing from a physician's point of view than the cure of Graves' disease with Radioactive Iodine without operation….the cancer field is relatively virgin territory both from the standpoint of actual knowledge or prognostic attack." Hertz goes on in the same correspondence explaining, "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 by means of RAI as a tracer. The relationship of this project to the one on Graves' disease will be evident to you."

In the *American Weekly* June 2, 1946, Dr. Hertz states, "…demand is expected for radioactive iodine and as research develops in the field of cancer and leukemia for other radioactive medicines.".

It should be noted that at the onset of the rabbit experiments in 1937, Dr. Hertz thought that there might be equally promising therapeutic possibilities in the

treatment of carcinoma of the thyroid. Hertz reported these clinical trials to treat thyroid cancer in 1942 to the Markle Foundation who had funded the intitial RAI research.

On September 9, 1946, The Radioactive Isotope Research Fund was registered in Boston, Massachusetts. The Fund established The Radioactive Isotope Research Institute with clinical and laboratory facilities on Commonwealth Avenue in Boston and on 5th Avenue in New York City. Dr. Hertz reached out to New York City Montefiore Hospital's Dr. S.M. Seidlin to be the associative director. His brother, Dr. Roy Hertz, was the oncologist. Roy Hertz went on to The National Institutes of Health to share an Albert Lasker Award with Dr. Min Chu Li for their breakthrough work in treating choriocarcinoma, a cancer of the placenta.

Dr. Hertz, while at The Beth Israel Hospital, refined the use of RAI in treating effectively thyroid cancer patients. The headline of *The Harvard Crimson* May 24, 1949, reads "Hertz to Use Fission in Cure for Cancer." In the text of the article is "Dr. Hertz feels that the application of isotope research to the cancer problem will be along the 'tracer' lines, since it has been demonstrated that the majority of cancerous thyroids do not take up the radioactive iodine in the manner in which do the glands of patients suffering from Graves' disease…he (Hertz) emphasized this example in therapeutic application as a beacon in utilizing the tracer methods." In conclusion, we owe Dr. Saul Hertz a debt of gratitude for prolonging the lives of countless generations of patients and establishing the cornerstone of Nuclear Medicine. After seasons of challenges, Dr. Hertz's research generated an eternity of success.

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