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Chapter 1

Dr. Saul Hertz (1905–1950) Discovers the Medical Uses of Radioactive Iodine: The First Targeted Cancer Therapy

Barbara Hertz

Additional information is available at the end of the chapter

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Abstract

Dr. Saul Hertz spontaneously posed the question “Could iodine be made radioactive artificially?” to the MIT President Karl Compton, on November 12, 1936. MGH’s Dr. Hertz and his MIT collaborator, Dr. Arthur Roberts, were the first and the foremost to develop the experimental data for the medical uses of radioiodine (RAI) and apply it in the clinical setting. Dr. Hertz expanded the successful use of RAI of treating hyperthyroidism, Graves’ disease, to the treatment of thyroid cancer in 1946. Dr. Saul Hertz established the Radioactive Isotope Research Institute to diagnose and treat thyroid cancer, which he believed held the key to the larger problem of cancer in general. RAI is the first and gold standard of targeted cancer therapies.

Keywords: radioiodine (RAI), Dr. Saul Hertz

1. Seminal question

Dr. Saul Hertz (Figure 1) attended a luncheon meeting at Harvard Medical School’s Vanderbilt Hall on November 12, 1936 (Figure 2). Karl T. Compton, the President of Massachusetts Institute of Technology (MIT), was speaking on the topic “What Physics Can Do for Biology and Medicine.”

Dr. Hertz, who was the director of the Thyroid Clinic (1931–1943) at Massachusetts General Hospital (MGH), asked President Compton the seminal question, “Could iodine be made radioactive artificially?” Hertz had been conducting studies on the use of iodine and its effect on thyroid function. Hertz’s question came spontaneously as documented in MGH’s Dr. James Means’s letter (Figure 3) to Archie Woods of the Mary and John Markle Foundation that
sponsored the building of the MIT Cyclotron. Dr. Arthur Roberts, Dr. Hertz’s MIT collaborator, wrote to Dr. John Stanbury, the author of *A Constant Ferment: A History of MGH Thyroid Clinic and Laboratory at The Massachusetts General Hospital: 1913–1990*, as Stanbury was developing his book. Dr. Roberts in his letter dated April 3, 1991, states “Your conjecture that it was the outcome of a group discussion has no basis in fact.” Stanbury’s book has been in publication for many decades and has been used as a citation with false information (Figure 4a–c).

Figure 1. Mallinckrodt, a $2.1 billion global pharmaceutical company honors Dr Saul Hertz’s discovery of the medical uses of radioidine (RAI).

Figure 2. Harvard Medical School’s Vanderbilt Hall the site of Dr Hertz spontaneously asking MIT’s President Karl Compton, “Could iodine be made radioactive artificially?”.
Dr. Saul Hertz (1905–1950) Discovers the Medical Uses of Radioactive Iodine: The First Targeted Cancer Therapy

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Figure 3. MGH’s Chief of Medicine’s letter to the Markle Foundation documenting Dr Hertz’s spontaneous seminal question that launched the RAI breakthrough research.

Dr. Hertz’s seminal question brought together the work established in 1896 of E. Bauman’s reporting the effect of iodine on the functioning of the thyroid. Bauman found high concentrations of iodine tightly bound to proteins in extracts of the thyroid gland, thyroid extracts were standardized to contain 0.2% iodine in order to maintain equal potency of different preparations. Additionally, in the field of radioactivity, in 1896 Henri Becquerel investigated the newly discovered X-rays that led to studies of how uranium salts are affected by light. Saul Hertz’s seminal question brought together the effect of iodine on the thyroid and radioactivity. Hertz’s question launched the radioactive iodine (RAI) research that established the cornerstone of Nuclear Medicine.
Thyroid Cancer - Advances in Diagnosis and Therapy

DUMAND—Deep Underwater Muon and Neutrino Detection

Hawaii Institute of Geophysics
University of Hawaii
DEE 25-7

Dr. John R. Starcher
400 St. Mary's Rd.
Charleston, IL 62901

Dear Dr. Starcher,

Miss Elsa D. Hart, has been on a leave of absence for five years, but I have heard it was never official. She was always very welcome in our library, and her presence was missed. She was a quiet, reserved woman, but her gentle manner made her a pleasant companion. She was always interested in the latest developments in geophysics, and her questions were always well thought out. She was a valuable member of our team, and her absence will be felt by all.

Elsa Hart was a devoted student of geophysics, and her contributions to the field were significant. She was one of the first women to pursue a career in this field, and her determination and perseverance set an example for others. Her work in deep underwater detection was groundbreaking, and her insights into the behavior of muons and neutrinos were invaluable.

I am pleased to hear that she has returned to her work, and I look forward to working with her again in the future. Her contributions to our field are always welcome.

Sincerely,
John R. Starcher

Dr. John R. Starcher
400 St. Mary's Rd.
Charleston, IL 62901
2. Rabbit studies

In early 1937, the collaboration was established between the Massachusetts Institute of Technology and Boston’s Massachusetts General Hospital. The young physicist Dr. Arthur Roberts was hired by MIT, and MGH’s Dr. Saul Hertz began the first studies on rabbits to evaluate the effects of a nuclear substance, radioactive iodine, on the thyroid. Dr. Roberts produced noncyclotron I-128 in small quantities based on 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 (Figure 5).

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 (Figure 4a–c). When Roberts was hired Evans had included 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.

Figure 5. MIT’s Dr Arthur Roberts (left) MGH’s Dr Saul Hertz (right) administering non cyclotron produced I-128.
These studies demonstrated the principle of using a radioactive substance as a tracer.

Hertz and Roberts were hopeful that they could go from diagnosis to treatment; however, they
knew that 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, took the train from Boston
to New York City and secured a $30,000.00 check from the Mary and John Markel Foundation
for the building of MIT’s Cyclotron.

2.1. The first therapeutic use of RAI

The new Markel MIT Cyclotron, the first built exclusively for medical purposes, began
operations in late 1940. Most of the RAI produced by this cyclotron was I-130 that has a half-
life of 12 hours. Another 10% of the cyclotron product was I-131. Dr. Hertz administered the
first therapeutic treatment of RAI on March 31, 1941 to Elizabeth D. at the Massachusetts
General Hospital. Noted on Hertz’s Data Charts (Figure 6a and b) was that this first patient
received 2.1 mCi (77.7 MBq) of I-130 because its radiation was delivered rapidly to the thyroid
cells over a day or two.
Dr. Saul Hertz (1905–1950) Discovers the Medical Uses of Radioactive Iodine: The First Targeted Cancer Therapy

Dr. Hertz and his MIT collaborator Dr. Arthur Roberts continued to treat about one new patient per month for the rest of 1941. The total estimated RAI given to each of the eight patients ranged from 55 to 230 MBq with an average of 144 MBq. RAI was taken up by the patient’s thyroid glands, and the patients did in fact get better. Hertz gave each patient a stable iodine beginning 1–3 days after the radioiodine at the insistence of his chief Dr. James Means. Means wanted to protect the patients against thyroid storm in case the RAI therapy was not effective. At the American Society for Clinical Investigation Meeting in May, 1942, Hertz presented a series of eight patients treated with RAI he had followed for at least 3 months; according to the abstract there were both “failures and successes.”
Hertz continued to treat hyperthyroid patients with I-131 throughout 1942. In January 1943, Dr. Hertz joined the United States Navy to serve his country during World War II. MGH’s Dr. Earl Chapman was four “F” and was ineligible for service. Chapman, a private practice doctor who treated Boston’s Beacon Hill-style affluent patients managed to carry on clinical research and worked part-time at MGH. Hertz asked Chapman to take over his RAI cases, in that he felt he (Hertz) had firmly established the work. Dr. Leonard Wartofsky stated “Chapman was probably honored to get involved in some clinical research and take on these patients [1].” 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 tweaked the protocol and the letters between Hertz and Chapman during the war years produced tension. 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. Although there remained quotas at medical schools, “Jews” were being trained and needed a place to practice. 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 [2].” 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 (Figure 8a and b) [3, 4].

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 at 44 years old in 1950 and these two gentlemen (Chapman and Evans) spent a great deal of time and effort rewriting history [5].”
Hertz strongly encouraged 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 (Figure 7).
Thyroid Cancer - Advances in Diagnosis and Therapy

Figure 8. (a) JAMA: May 11, 1946 MGH's Saul Hertz/MIT's Arthur Roberts VII. The use of radioactive iodine therapy in hyperthyroidism and (b) JAMA: May 11, 1946 MGH's Earl Chapman/MIT's Robley Evans the treatment of hyperthyroidism with radioactive iodine. Documentation of unethical publishing practices...stolen intellectual property.
2.2. 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 to make note, “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.”

Figure 9. 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.”

The American Weekly, June 2, 1946, quoted Dr. Hertz as stating, “…demand is expected for radioactive iodine and as research develops in the field of cancer and leukemia for radioactive medicines” (Figure 9).

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 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 after his brother Saul’s death to win a Lasker Award. Dr. Eugene Nelson was the Physicist (Figure 10).
Figure 10. September 9, 1946 announcement of the world’s first Radioactive Isotope Institute. Dr Saul Hertz established the institute and served as the director.

Figure 11. The Harvard Crimson, May 24, 1949 Hertz To Use Nuclear Fission in Cure for Cancer “&he (Hertz)empha-
sized this example in therapeutic application as a beacon in utilizing the tracer methods employing radioactive sub-
stances in other organs than the thyroid.”.
Dr. Hertz while at The Beth Israel Hospital explored the use of RAI in treating thyroid cancer patients. In a radio broadcast on Boston’s WEEI’s Yankee Network, November 18, 1948, Hertz discussed extensively RAI treatment being used in treating thyroid cancer at The Beth Israel Hospital.

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... (Figure 11).

Figure 12. Boston Globe August 3, 1949 "atomic cocktail" cured cancer.

Figure 12 shows Boston Globe photo of a man drinking an “atomic cocktail.”

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.
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References


