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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

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 radiiodine (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: radiiodine (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 radioiodine (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?”.
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.
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.

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).
profession, this form of treatment may well prove itself not only highly effective, safe and inexpensive but also cheap and of least inconvenience to the patient who may receive it while continuing at his normal pursuits. After a short period of hospitalization for the usual preliminary clinical studies and the administration of radioiodine, the patient may be fully iodinized and released, to be followed as an ambulatory case.

**SUMMARY**

On the basis of a series of animal and clinical experiments using radioactive isopoles of iodine as a tracer in the study of thyroid physiology and iodide metabolism, the treatment of 29 cases of hyperthyroidism with internal irradiation of radioactive iodine was instituted. By careful excretion studies, external counter measurements over the thyroid gland, and by planned operations in 2 cases, data were obtained which allowed us to construct a formula for a procedure in treatment.

The addition of ordinary iodine therapy after the administration of radioiodine offers many advantages in the clinical care of these patients and in the economy and safety of the procedure.

By an analysis, over a long period, of both the failures and successes in this series of 20 cases, it is shown that radioactive iodine when given in the dosage range of 5 to 25 millirads to iodinized patients with hyperthyroidism possessing goiter of 60 to 75 cm. A highly effective as a cure of the disease in about 50 per cent of cases. When appreciable activity has been administered and sub-total thyroidectomy is resorted to, myxodema or hypothyroidism may be expected to develop in a large fraction of the cases (100 per cent in 5 cases in this series).

**THE TREATMENT OF HYPER THYROIDISM WITH RADIOACTIVE IODINE**

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Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Meunoz and Holmes pointed out that in this form of treatment about one in two cases are cured, another third improved and another third not affected. Since 1923, the treatment in the form of a treatment by means of a protective measure of quieting the hyperactive thyroid in preparation for surgery, under iodine alone occasionally the patient and the doctor have been agreed to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that some day a more effective, non-invasive agent would be found. In 1939, MacKenzie and Antwood discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated, and until now thioalas has been found to be most useful in the treatment of hyperthyroidism.

Induced radioactivity was discovered in 1934, and that same year Ferrini and his co-workers in Italy prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine radiated radioactive would have a greater radiation effect than that derived from roentgen rays delivered through the skin and overlying tissues. The use of radioactive iodine in the study of thyroid physiology was soon undertaken and reported first in 1936 by Hertz, Roberts and Evans. Subsequently these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function and it was found that in untreated hyperthyroidism the thyroid may take up as much as 80 per cent of a small dose (less than 2 mg.) of iodine within a few hours after oral administration. This established the basis for therapeutic trials of radioactive iodine, and in 1942 Hertz and Roberts published a preliminary report of the treatment in this manner of 10 patients. In this series the procedure was to give the radioactive iodine and follow this with ordinary iodine by mouth for a period of several months. However, our review is the clinic of these 10 cases of Hertz and Roberts, and an additional 18 is treated under the direction of Hertz, has led to the conclusion that it is difficult to decide whether those patients who improved were responding to the ordinary iodine, to the radioactive iodine or to their combination. The dosage of radioactive iodine given to these 25 patients averaged 3 millirads in 1941, 10 millirads in 1942 and 14.5 millirads in 1943, the largest single dose being 21 millirads. The current April Dr. Hertz, who worked on active duty in the Navy and asked us to continue this work. The present report is on a series of 22 patients with hyperthyroidism treated only with radioactive iodine and with considerably higher doses. Although both Hertz and Roberts and Hamilton and Lawrence were encouraged by their therapeutic trials, the details of their findings have not yet been published.

**METHODS AND DOSE**

Selection and Care of Patients

The patients selected in the Thyroid Clinic of the Massachusetts General Hospital for radioactive iodine therapy were judged by several physicians to be non-toxic on the basis of classic disease pattern accompanied by symptoms and after 10 months in those. All but 3 were kept free from all forms of treatment especially iodides, for at least four weeks prior to giving radioactive iodine. For the administration of the dose they were usually kept under bed rest for a time adequate to obtain levels of their blood metabolic rate, then given radioactive iodine by mouth—simply a drinik of what tastes like rather bitter water.


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 fields 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


