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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

http://dx.doi.org/10.5772/64609

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

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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**).

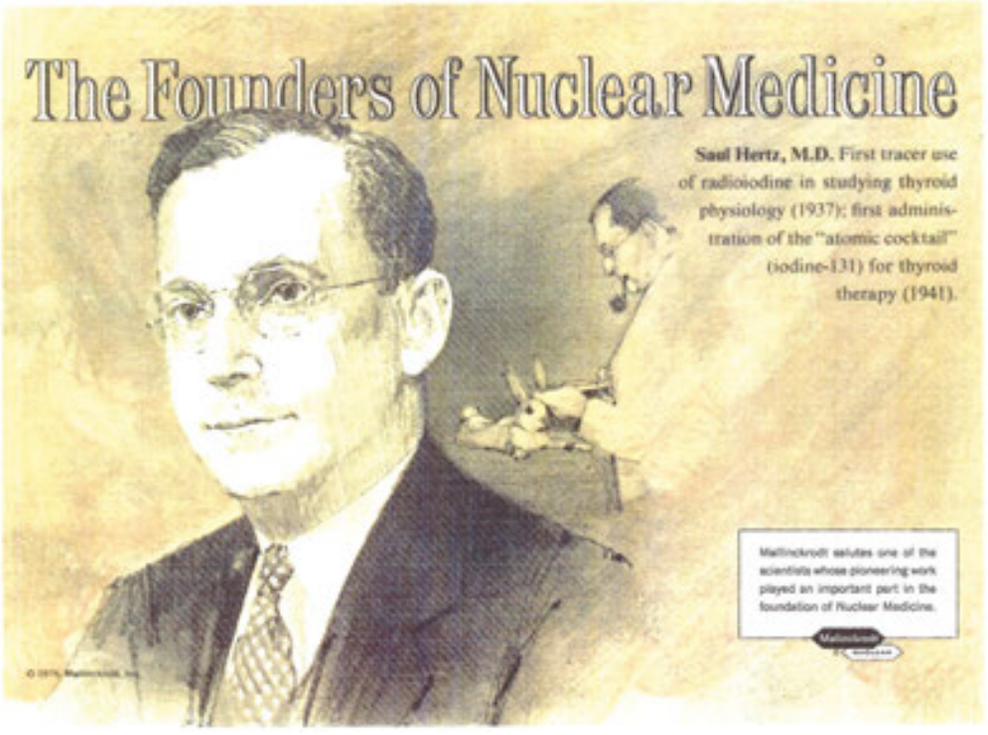


Figure 1. Mallinckrodt, a $2.1 billion global pharmaceutical company honors Dr Saul Hertz's discovery of the medical uses of radioiodine (RAI).

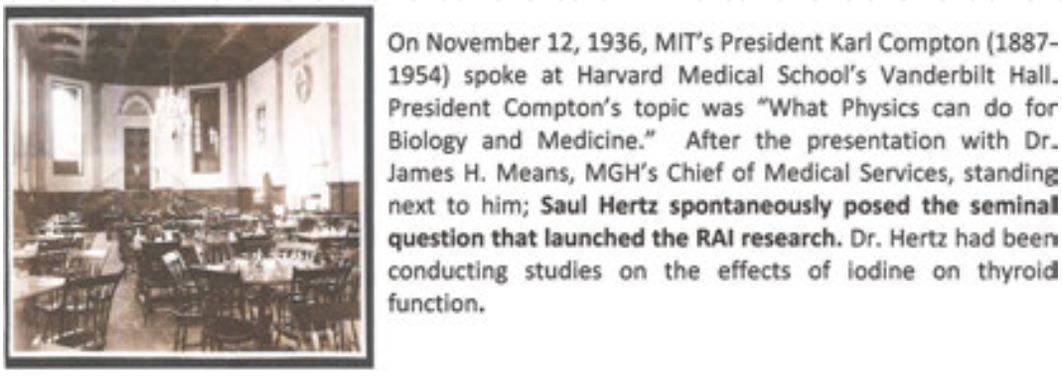
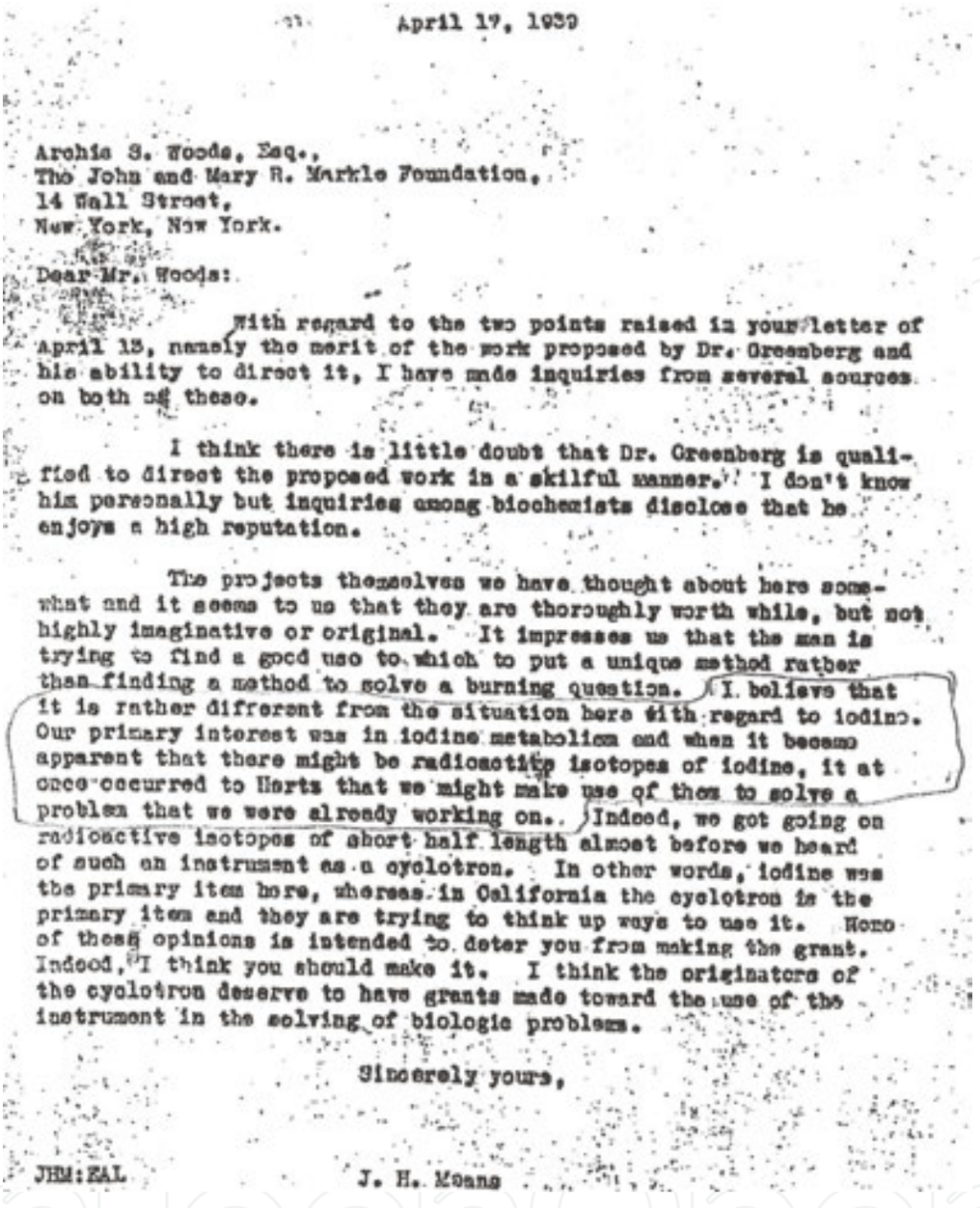


Figure 2. Harvard Medical School's Vanderbilt Hall the site of Dr Hertz spontaneously asking MIT's President Karl Compton, "Could iodine be made radioactive artificially?".

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April 17, 1939

Archie S. Woods, Esq.,
The John and Mary R. Markle Foundation,
14 Wall Street,
New York, New York.

Dear Mr. Woods:

With regard to the two points raised in your letter of April 13, namely the merit of the work proposed by Dr. Greenberg and his ability to direct it, I have made inquiries from several sources on both of these.

I think there is little doubt that Dr. Greenberg is qualified to direct the proposed work in a skilful manner. I don't know him personally but inquiries among biochemists disclose that he enjoys a high reputation.

The projects themselves we have thought about here somewhat and it seems to us that they are thoroughly worth while, but not highly imaginative or original. It impresses us that the man is trying to find a good use to which to put a unique method rather than finding a method to solve a burning question. I believe that it is rather different from the situation here with regard to iodine. Our primary interest was in iodine metabolism and when it became apparent that there might be radioactive isotopes of iodine, it at once occurred to Hertz that we might make use of them to solve a problem that we were already working on. Indeed, we got going on radioactive isotopes of short half length almost before we heard of such an instrument as a cyclotron. In other words, iodine was the primary item here, whereas in California the cyclotron is the primary item and they are trying to think up ways to use it. None of these opinions is intended to deter you from making the grant. Indeed, I think you should make it. I think the originators of the cyclotron deserve to have grants made toward the use of the instrument in the solving of biologic problems.

Sincerely yours,

JHM:ZAL

J. H. Means

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.

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Honolulu, HI 96817
Apr. 3, 1991

Dr. John B. Stanbury
43 Circuit Rd
Chestnut Hill, MA 02167

Dear Dr. Stanbury,

Mrs. Vitta Hertz has sent me a copy of Chapter V from the book I understand you will soon publish on the history of the MGH Thyroid Clinic. I have read it with great interest, since I was closely involved with the earliest history of the use of radioactive iodine in connection with thyroid physiology and therapy.

You will no doubt remember telephoning me in regard to a minor point concerning references to M.I.T. in the first paper on the use of radioiodine in rabbits. At that time I gave you a detailed description of the work at M.I.T. and of the degree of Evans' scientific participation in it – namely zero. I was unpleasantly surprised to see how completely you have ignored it.

I understood it somewhat better as I read the false and distorted picture you have given of the early work on radioiodine. I began to understand even more when I read your description of Evans: I quote "an exceptionally engaging, modest, and brilliant colleague whose contributions to the Thyroid unit were incomparable." That literally turned my stomach. Evans may have been engaging when he wanted to be, but brilliant? The great contribution to the thyroid unit was not his, but Saul Hertz's. It was Hertz who first conceived the idea of using radioactive iodine for both research and therapy in thyroid work; it was Hertz who asked the question at Comptons' lecture – though Chapman and Evans tried their best to cast doubt on this after he died. Your conjecture that it was the outcome of a group discussion has no basis in fact. Not only did Saul tell me that the idea was his alone, but Evans in an written record as confirming it; Mrs. Hertz and I have copies of his letter. There cannot be the slightest doubt on that subject.

More important, it was Hertz who conceived and carried out, with my help, all the ground-breaking work in the next seven years. The notion that you advance that it was Evans who led the "team" because he headed the laboratory in which the work was done is simply naive and absurd. He wasn't even on the "team", much less its leader. He was the owner, back in the clubhouse.

Furthermore, that was the way he wanted it. He had every opportunity, and certainly the authority, to have taken an active part in the work; but he chose not to do so. I do not know why; but it may well be, in view of his known anti-Semitism, that he could not stomach the notion of working with two Jews.

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. (See Hertz's letter to him on this subject.) It was Hertz – with some suggestions from me – who designed the animal experiments we carried out, and the therapeutic tests on patients with Graves' disease. Evans took no part in any of this work in the five years I was connected with it. He was not excluded; he simply had no interest in doing anything other than managerial work.

You seem to attach great significance to the fact that Evans' name appears on the first few publications (as does Means's). If you think that necessarily implies scientific contribution to the work, you don't understand how authorship on academic papers is obtained. In Evans' case, we omitted his name from the first draft of the first paper because he had made not the slightest contribution to the work, other than that involved in managing the laboratory in which we worked.

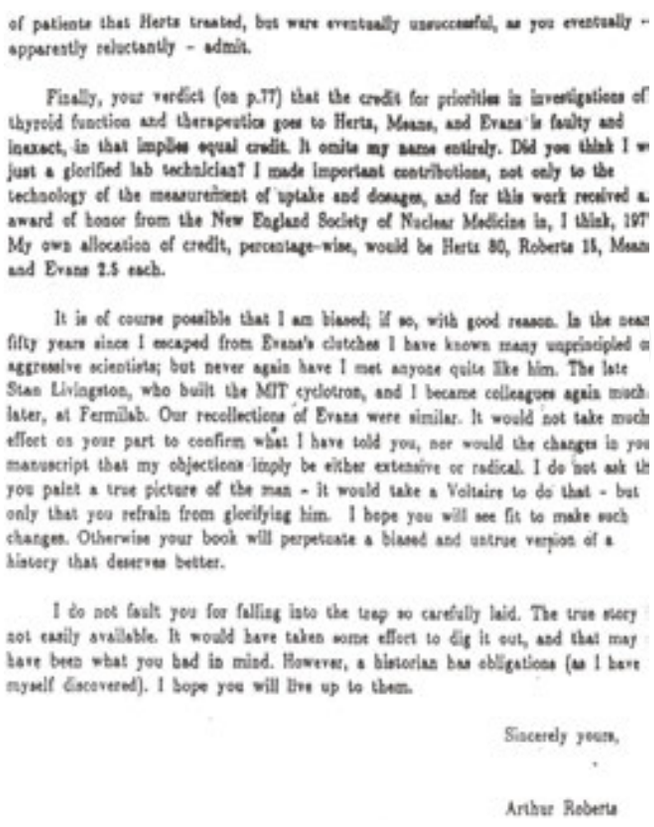
An example of his managerial contribution was providing the neutron source we used to produce the radio-iodine. Later, with the help of Means, he secured the funds with which the M.I.T. Markle cyclotron was constructed, and which provided the much more intense therapeutic quantities of radio-iodine.

The customary and proper way of crediting this sort of contribution is as an acknowledgment of assistance, such as the one you will find in the paper of Hertz and Roberts in Endocrinology, July 1941. It most emphatically is not to include the person in question among the authors, which implies participation in the scientific work.

Evans made it a condition of my employment – I wish I still had the letter – that his name was to appear on all publications. Even at that time, this was unusual, and occasioned much comment. It led to the contretemps concerning the late addition of his name to our first paper. It was also on the second paper; but after that Saul and I felt sufficiently secure that we ignored him in our subsequent publications. Had he actually participated in the work, there would have been no problem in including him.

Evans was the first boss I worked under after receiving my degree at N.Y.U. I was puzzled and unhappy at the way I was treated; but at the time I had no basis for comparisons. (An example: he constantly assured me my work was highly satisfactory; but in five years I never received any salary raise. As a consequence, when I joined the MIT Radiation Lab in 1943, I found my salary suddenly doubled. He also made it clear that I could look for no advancement at M.I.T., and for no recommendations from him to any subsequent employer. Luckily the war made this immaterial.

It was only later that I fully realized what a thoroughly unprincipled racist manipulator he was. Have you ever taken the trouble to find out what other young people who had the misfortune to work under him thought of him? His particular talent was taking all the credit for the work others had done. In the case of the radioiodine field, he had a clear field for operations after I left, and Hertz and Means died. He was abetted in this by Chapman, and between them they concocted the preposterous story that you repeat. They did their best to denigrate the initial ser



of patients that Hertz treated, but were eventually unsuccessful, as you eventually – apparently reluctantly – admit.

Finally, your verdict (on p.77) that the credit for priorities in investigations of thyroid function and therapeutics goes to Hertz, Means, and Evans is faulty and inexact, in that implies equal credit. It omits my name entirely. Did you think I w just a glorified lab technician? I made important contributions, not only to the technology of the measurement of uptake and dosages, and for this work received a award of honor from the New England Society of Nuclear Medicine in, I think, 197 My own allocation of credit, percentage-wise, would be Hertz 80, Roberts 15, Mean and Evans 2.5 each.

It is of course possible that I am biased; if so, with good reason. In the near fifty years since I escaped from Evans's clutches I have known many unprincipled a aggressive scientists; but never again have I met anyone quite like him. The late Stan Livingston, who built the MIT cyclotron, and I became colleagues again much later, at Fermilab. Our recollections of Evans were similar. It would not take much effort on your part to confirm what I have told you, nor would the changes in you manuscript that my objections imply be either extensive or radical. I do not ask th you paint a true picture of the man – it would take a Voltaire to do that – but only that you refrain from glorifying him. I hope you will see fit to make such changes. Otherwise your book will perpetuate a biased and untrue version of a history that deserves better.

I do not fault you for falling into the trap so carefully laid. The true story not easily available. It would have taken some effort to dig it out, and that may have been what you had in mind. However, a historian has obligations (as I have myself discovered). I hope you will live up to them.

Sincerely yours,

Arthur Roberts

Figure 4. (a–c) Pivitol letter from MIT's Dr Arthur Roberts to the author of *A Constant Ferment*, of which the author, Dr John Stanbury, chose to ignore.

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.

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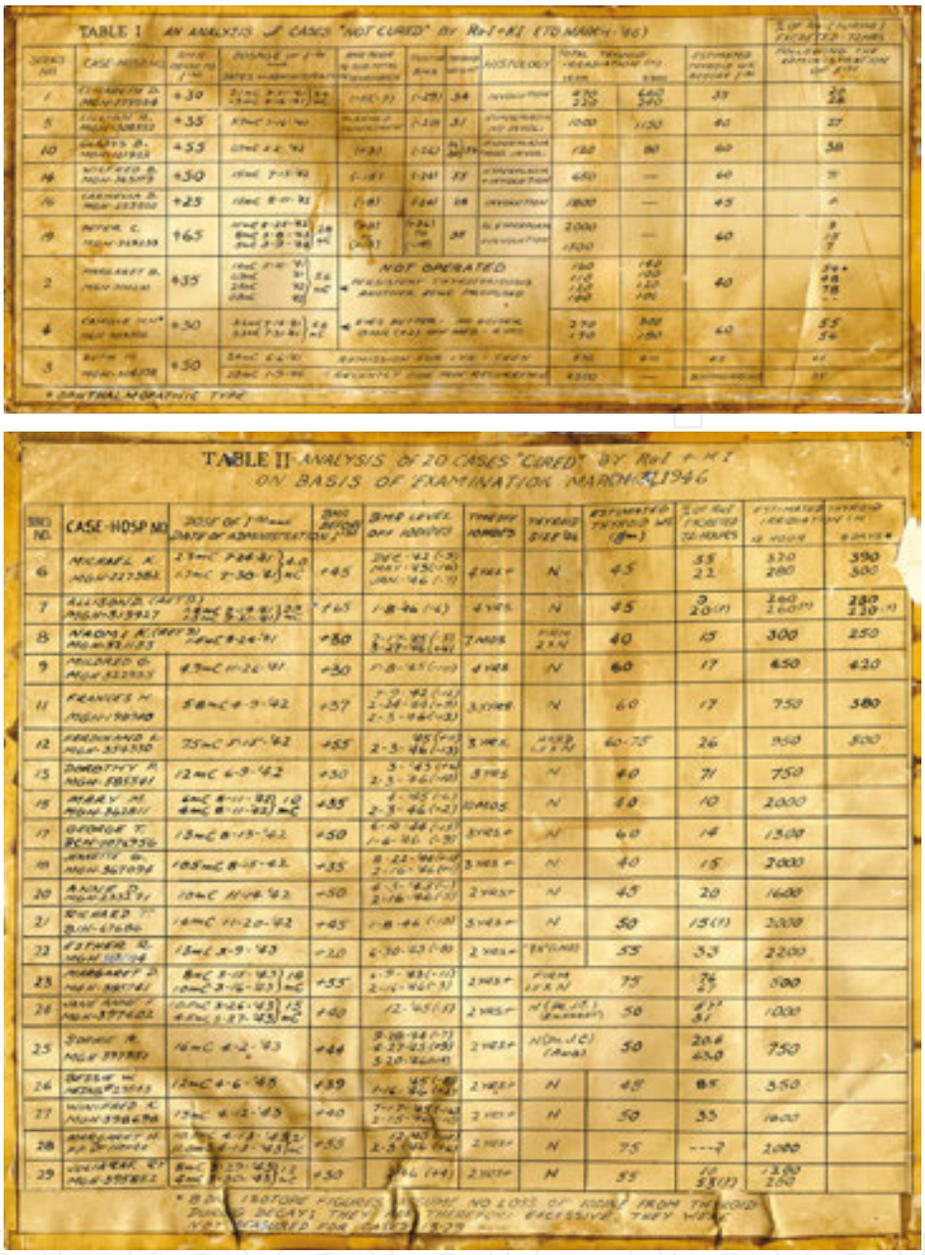


Figure 6. (a and b) Dr Hertz's handwritten Data Charts (1941–1946) of the very first series of patients treated successfully with a radioactive substance, RAI.

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."


The Cleveland Press

"As Newspaper That Serves Its Readers"

HOME EDITION

Former Clevelander Develops First Atomic Medical Cure

Figure 7. Cleveland Press Newspaper headline. Dr Hertz was born and grew up in Cleveland, Ohio.

Hertz continued to treat hyperthyroid patients with I-130 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 theses two gentlemen (Chapman and Evans) spent a great deal of time and effort rewriting history [5]."

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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**).



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RADIOACTIVE IODINE IN THE STUDY OF THYROID PHYSIOLOGY

VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism

SAUL HERTZ, M.D.
Boston
and
ARTHUR ROBERTS, Ph.D.
Cambridge, Mass.

In previously published experiments of this series [1] radioactive iodine was used as an indicator in the study of animal and human thyroid physiology and iodine metabolism. Much of this preliminary work was done with a view to the discovery of the conditions under which radioactive iodine might be administered with maximum radiational effect in the pathologic thyroid of patients ill with hyperthyroidism. The present paper is a progress report on our early experiences (1941-1946) with such "internal irradiation" in the treatment of 29 cases of hyperthyroidism. It is, indeed, a three to five year follow-up report on these cases.

PROCEDURE

Patients were selected who had had no previous iodine treatment and who were judged clinically to have hyperthyroidism. The usual clinical tests were made and the patients were presented to the Thyroid Clinic of the Massachusetts General Hospital for discussion and determination of their suitability for this type of treatment. In each instance a dose of radioactive iodine, which had been made by the cyclotron at the Massachusetts Institute of Technology or by the Harvard University cyclotron, and separated chemically as sodium iodide, was then orally administered.

The samples of radioactive iodine used were obtained by deuteron bombardment of tellurium and at the time of administration consisted of a mixture of different radioactive isotopes of iodine. Over 90 per cent of the activity at this time consisted of the 12.6 hour isotope I^{130} and most of the remainder of the 8 day isotope I^{131}. The total activity administered varied between 0.7 and 28 millicuries. In 19 cases the total dose was administered to the individual patients as one dose; in 10 cases divided dosages were employed.

From the data already obtained from tracer studies it was considered desirable to keep the total amount of iodide administered below 2 mg. of iodine in order to insure maximum collection by the thyroid.

Urinary iodine excretion was determined during the first seventy-two hours after the administration of radio-iodine. An indirect estimate of the thyroid retention of radioactive iodine was thereby obtained, since an approximate balance exists between administered iodine on the one hand and the sum of thyroid iodine retention and urinary excretion on the other.

Urinary studies were carried out on aliquot portions of carefully collected twenty-four hour specimens, which were kept iced and corked during the collection periods.

It was early found [2] that significant amounts of the original dose were to be found only in the first three days' specimens. Fecal excretion was tested and was found to be so low as to be negligible for the purpose of these experiments.

In a few cases external gamma ray counter measurements were made of the activity of the thyroid of patients following the administration of radioactive iodine. Such measurements are difficult, for obvious reasons, to evaluate quantitatively. However, day to day measurements of this type can give good data on the variation of thyroid iodine content. They were performed in order to follow the loss of iodine from the thyroid following the initial uptake and to evaluate the effect of routine iodinization following the administration of radioactive iodine.

External counter measurements were roughly calibrated against actual direct measurements on the thyroid glands at operation and after chemical separation [3] in 2 patients, previously scheduled for surgery, who received therapeutic amounts of radioactive iodine.

Following the administration of radioactive iodine, routine iodine (nonradioactive) in the usual dosage of saturated solution of potassium iodide 5 minims (0.3 cc.) twice a day was begun at periods varying from one day to several weeks after the radioactive iodine dose.

The basal metabolic rate of the patients treated was tested frequently both before and after the radioactive iodine administration. Basal metabolic levels were taken prior to treatment to establish a measure of the degree of thyrotoxicosis present. In addition to the basal metabolic rate, weights, pulse rates and physical findings were recorded and the total clinical picture was used to evaluate the effects of treatment. No adverse effects, such as fever, nausea or irradiation sickness, were noted in this series of patients. No complaints were recorded regarding the taste of the medicament (since it is tasteless), nor were any local effects, either in the oral cavity or over the thyroid, encountered at the dosage levels used. No increase in the degree of thyrotoxicosis following the radioactive iodine treatment, per se, was recorded, although several test patients were kept uniodinized for three to four weeks prior to routine iodinization.

In most cases, after a period of two to four months following the radio-iodine administration, routine iodine therapy was stopped when an essentially normal basal metabolic rate had been maintained on iodine for a few weeks or months. Such basal metabolic rate response was taken to be indicative of good control of

A report to March 15, 1946.
From the Thyroid Clinic and Metabolism Laboratory of the Massachusetts General Hospital and the Radioactivity Center, Massachusetts Institute of Technology. This material was presented in part to the American Society for Clinical Investigation in May 1942 (see abstract of proceedings, Physiol. Rev. 22:6, 1942). The work was aided by a grant from the John and Mary R. Markle Fund in the names of Professors J. H. Means and Robley D. Evans and was accomplished by close cooperation of the Radioactivity Center of the Massachusetts Institute of Technology, Cambridge, Mass., and the members of the medical staff of the Massachusetts General Hospital, Boston.
This work was performed at the Massachusetts General Hospital and the Massachusetts Institute of Technology under a grant from the John and Mary R. Markle Fund. Cooperation and assistance in this work were given by Professor J. H. Means, Professor J. W. Irvine, Dr. Wendell C. Peacock, Professor M. Stanley Livingston, Professor Robley D. Evans, Drs. R. W. Rawson and Jacob Lerman, the technical assistants Mrs. Phyllis Brown Shattuck, Miss Ann Gourdo and Miss Mary Lennon as well as the nursing, surgical and medical staffs of the Massachusetts General Hospital. The speech of President Karl T. Compton of the Massachusetts Institute of Technology before a Harvard Medical School colloquium in the fall of 1936 served to inspire the senior author in the initiation of this investigative program.

1. Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as an Indicator in the Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. 38:510 (May) 1938. Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology: II. Iodine Collection by Normal and Hyperplastic Thyroids in Rabbits, Am. J. Physiol. 128:565 (Feb.) 1940; Tr. Am. A. Study Goiter, 1939, p. 260. Hertz, S.: Radioactive Iodine as an Indicator in Thyroid Physiology: III. Observations on Rabbits and on Goiter Patients, Am. J. Roentgenol. 46:467 (Oct.) 1941. Hertz, S., and Roberts, A.: Radioactive Iodine as an Indicator in Thyroid Physiology: VI. Application of Radioactive Iodine in Therapy of Graves' Disease, J. Clin. Investigation 21:624 (Sept.) 1942. Hertz, Roberts and Salter.[2] Hertz and Roberts.[3]

2. Hertz, S.; Roberts, A., and Salter, W. T.: Radioactive Iodine as an Indicator in Thyroid Physiology: IV. The Metabolism of Iodine in Graves' Disease, J. Clin. Investigation 21:25 (Jan.) 1942.

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profession, this form of treatment may well prove itself not only highly effective, safe and noninjurious 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 radio-iodine, 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 isotopes of iodine as a tracer in the study of thyroid physiology and iodine metabolism, the treatment of 29 cases of hyperthyroidism with internal irradiation by 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 allow us to construct a formula for a procedure in treatment.

The addition of ordinary iodine therapy after the administration of radio-iodine 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 29 cases, it is shown that radioactive iodine when given in the dosage range of 5 to 25 millicuries to uniodinized patients with hyperthyroidism possessing goiters of 60 to 75 Gm. is highly effective as a cure of the disease in about 80 per cent of cases. When appreciable activity has been administered and subtotal thyroidectomy is resorted to, myxedema or hypometabolism may be expected to develop in a large fraction of the cases (100 per cent in 5 cases in this series).

THE TREATMENT OF HYPERTHYROIDISM WITH RADIOACTIVE IODINE

EARLE M. CHAPMAN, M.D.
and
ROBLEY D. EVANS, Ph.D.
Cambridge, Mass.

Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes [1] pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised 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, nonsurgical agent would be found. Then the MacKenzies [2] and Astwood [3] 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 thiouracil has been found to be most useful in the treatment of thyrotoxicosis.

Induced radioactivity was discovered in 1934, and that same year Fermi and his co-workers [4] in Italy prepared radioactive isotopes of iodine. Because the thyroid absorbs iodine selectively, it seemed likely that beta rays from iodine rendered 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 1938 by Hertz, Roberts and Evans.[5] Subsequently these and other investigators used various isotopes of radioactive iodine as tracers for the study of thyroid function [6] 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 iodide within a few hours after oral administration.[7] This established the basis for therapeutic trials of radioactive iodine, and in 1942 Hertz and Roberts [8] 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 in the clinic of these 10 cases of Hertz and Roberts, and an additional 18 so 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 28 patients averaged 5 millicuries in 1941, 10 millicuries in 1942 and 14.5 millicuries in 1943, the largest single dose being 21 millicuries. In April 1943 Dr. Hertz went on active duty in the Navy and asked us to continue with this study. 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 [8] and Hamilton and Lawrence [9] were encouraged by their therapeutic trials, the details of their findings have not yet been published.

METHODS AND DOSAGE

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 thyrotoxic on the basis of classic disease pattern accompanied with constantly elevated basal metabolic rates. All patients had thyroids estimated to be at least two to three times normal in size. All but 3 were kept free from all forms of treatment, especially iodine, for at least four weeks prior to giving radioactive iodine. For the administration of the drug they were usually hospitalized for a time adequate to obtain levels of their basal metabolic rate, then given radioactive iodine by mouth—simply a drink of what tastes like rather stale water.

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From the Thyroid Clinic of the Massachusetts General Hospital (Dr. Chapman) and the Radioactivity Center of the Department of Physics of the Massachusetts Institute of Technology (Dr. Evans).

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Downloaded from jama.ama-assn.org at Harvard University on January 19, 2012

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.

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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."

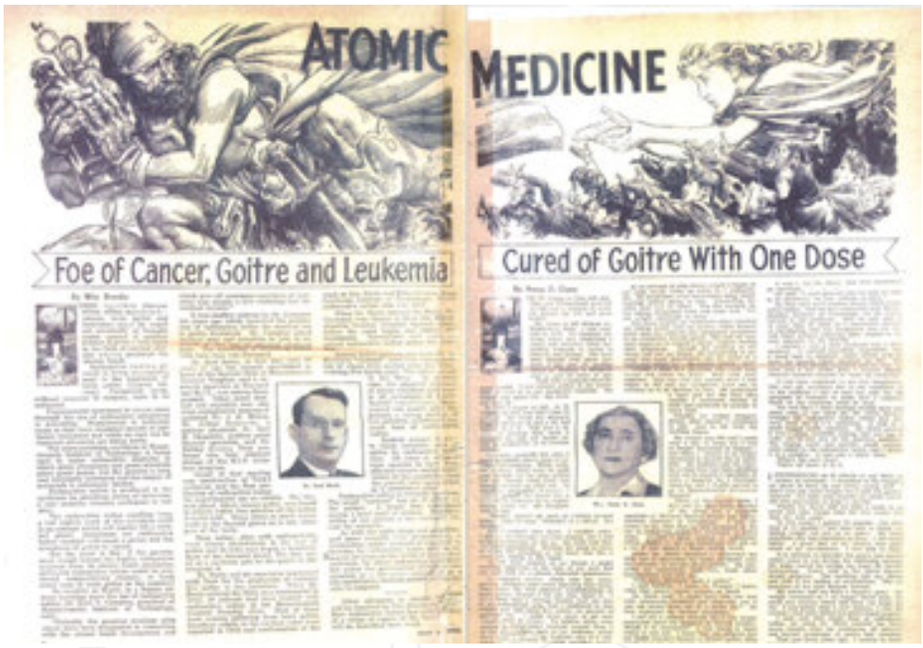
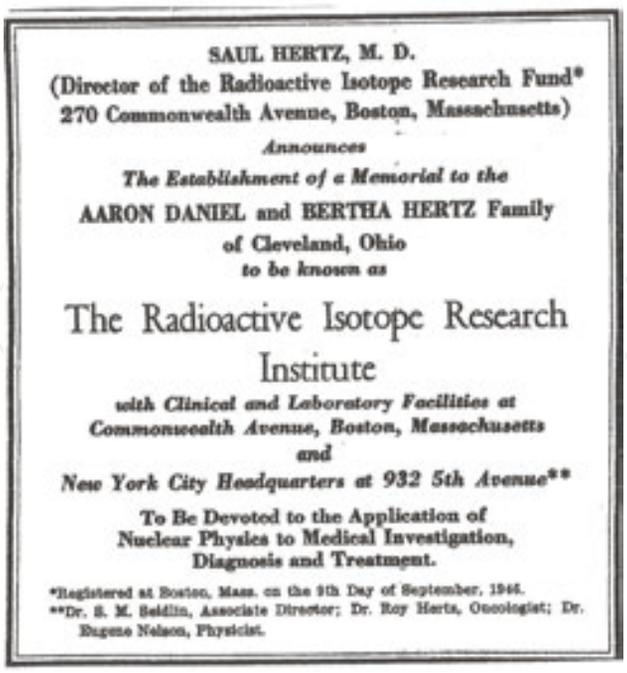


Figure 9. The *American Weekly* June 2, 1946 Dr Hertz states, "…demand is expected for radioactive iodine and as research develops in the field of cancer and leukemia for other radioactive medicines.".

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**).



SAUL HERTZ, M. D.
(Director of the Radioactive Isotope Research Fund*
270 Commonwealth Avenue, Boston, Massachusetts)
Announces
The Establishment of a Memorial to the
AARON DANIEL and BERTHA HERTZ Family
of Cleveland, Ohio
to be known as

The Radioactive Isotope Research Institute

*with Clinical and Laboratory Facilities at Commonwealth Avenue, Boston, Massachusetts and New York City Headquarters at 932 5th Avenue***

To Be Devoted to the Application of Nuclear Physics to Medical Investigation, Diagnosis and Treatment.

*Registered at Boston, Mass. on the 9th Day of September, 1946.
**Dr. S. M. Seidlin, Associate Director; Dr. Roy Herts, Oncologist; Dr. Eugene Nelson, Physicist.

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.



Hertz to Use Nuclear Fission in Cure for Cancer

SMITH HOUSE

HOTEL Continental

SHERIN MOTORS

Figure 11. *The Harvard Crimson*, May 24, 1949 Hertz To Use Nuclear Fission in Cure for Cancer "&he (Hertz)emphasized this example in therapeutic application as a beacon in utilizing the tracer methods employing radioactive substances in other organs than the thyroid.".

http://dx.doi.org/10.5772/64609

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.*

Author details

Barbara Hertz

Address all correspondence to: htziev@aol.com

Dr. Saul Hertz Archives, Greenwich, CT, USA

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