

Review Article

A tribute to Dr. Saul Hertz: The discovery of the medical uses of radioiodine

ABSTRACT

Dr. Saul Hertz was Director of The Massachusetts General Hospital's Thyroid Unit, when he heard about the development of artificial radioactivity. He conceived and brought from bench to bedside the successful use of radioiodine (RAI) to diagnose and treat thyroid diseases. Thus was born the science of theragnostics used today for neuroendocrine tumors and prostate cancer. Dr. Hertz's work set the foundation of targeted precision medicine.

Keywords: Dr. Saul Hertz, nuclear medicine, radioiodine

INTRODUCTION

A eureka moment for Nuclear Medicine occurred on November 12, 1936, when Dr. Saul Hertz [Figure 1] spontaneously asked Karl Compton, the President of the Massachusetts Institute of Technology (MIT), "Could iodine be made radioactive artificially?" Dr. Hertz solely conceived of the question bringing together the work conducted in 1896 by E. Bauman, who discovered that iodine was taken up by the thyroid and the 1935 Nobel Prize-winning work of Pierre and Marie Joliot-Curie, for their creation of artificial radioactive elements.

Dr. Hertz served as the director of the Massachusetts General Hospital's (MGH) thyroid unit from 1931 to 1943. Hertz and his Chief of Medicine, Dr. James H. Means, who had established the MGH thyroid unit in 1920, attended a luncheon meeting at Harvard Medical School, held in Vanderbilt Hall. The speaker was Karl Compton, President of the MIT. Compton's topic was, "What Physics Could Do For Biology and Medicine."


Dr. Means wrote, "Our primary interest was in iodine metabolism and when it became apparent that there maybe radioactive isotopes of iodine, it at once occurred to Hertz that we might solve a problem we were already working on."

Initial funding was acquired from Harvard Medical School and a young physicist, Dr. Arthur Roberts, was hired to work at MIT. MIT physicist, Dr. Roberts, created noncyclotron I-128 based on the work of Enrico Fermi. Hertz and Roberts designed an animal study of 48 rabbits. The noncyclotron I-128 was administered to rabbits with altered thyroid gland function. Hertz and Roberts' qualitative analysis showed that hyperplastic glands retained more radioactive iodine (RAI) than normal glands [Figure 2]. These studies demonstrated the principle that tracer amounts of RAI could be used to investigate thyroid gland physiology. Hertz and Roberts wrote the paper and it was accepted for publication.^[1] When it was at the publishers, MIT's Robley Evans dictated a letter for Dr. Hertz to sign that his name, Evans, should be included. It was a condition of Arthur Roberts employment that the director of the laboratory, Evans, should be included on any papers that would be presented. It is to be noted that Hertz and Roberts designed the research, executed the work, analyzed the data, and wrote the paper.

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Figure 1: Dr. Saul Hertz 1905–1950 (published with permission of the Dr. Saul Hertz archive)

At the onset of the animal studies, experiments in 1937, Dr. Hertz thought that there would be equally promising therapeutic possibilities in the treatment of cancer of the thyroid with RAI.

Mayo Soley, a MGH colleague of Dr. Hertz, wrote to Hertz congratulating him on his RAI work. Dr. Soley was then at the University of California Berkeley (UCB), where Ernest Lawrence had built a cyclotron. Work was done at UCB that confirmed the Hertz/Roberts animal study findings. UCB's Glenn Seaborg and John Livingood developed cyclotron produced RAI.

FIRST THERAPY

A total of \$30,000 was funded by New York City's Markle Foundation to build a cyclotron at MIT to produce I-130 and I-131. On March 31, 1941, Dr. Hertz administered MIT cyclotron produced RAI to Elizabeth D. at the MGH. This was the first therapeutic use to of RAI. Dr. Saul Hertz was the first and the foremost to develop the experimental data on RAI and apply it in the clinical setting with the first clinical trial leading to a series of 29 patients. In 1942, Hertz conducted and reported to the Markle Foundation his limited clinical trials of RAI to treat thyroid carcinoma.

In 1943, this work was interrupted as Dr. Saul Hertz was commissioned into the United States Navy to serve his country during World War II.

CONTROVERSIES

During the war years, MGH's Dr. Earl Chapman took over Dr. Hertz's work and teamed up with MIT's Robley Evans. Before Dr. Hertz returned to Boston, Chapman and Evans

submitted a paper to the Journal of the American Medical Association (JAMA) of their (Chapman and Evans) work utilizing RAI without Dr. Hertz's name. In April 2016, MGH's Chairman Emeritus, Department of Radiology stated, "...Chapman and Evans had basically stolen his (Hertz's) work"... "the most flagrant, unethical, academically reprehensible behaviour...worst yet, Saul Hertz died... in 1950 and these two gentlemen (Chapman and Evans) spent a great deal of time and effort rewriting history."

In May 11, 1946, two articles appeared side by side in the JAMA both from the same institutions [Figure 3]. One article authored by Hertz and Roberts and the other from Chapman and Evans demonstrated the successful use of RAI in the treatment of Graves' Disease (hyperthyroidism).

LOOKING AT CANCER

After the war, Dr. Hertz wrote in his correspondence to MGH, "My new research is in Cancer of the Thyroid which I believe holds the key to the larger problem of Cancer in general." Hertz was quoted in *The American Weekly Magazine*, June 2, 1946, as saying, ".demand is expected in the fields of cancer and leukaemia for other radioactive medicines."

In March 1946, in a letter to MIT, Hertz wrote, "I have proposed... a course in Physical application to Biology and Medicine. There are already ten doctors... who desire indoctrination in Nuclear Physics and its application." He also writes to MGH, "...with the rapid development of the field of Nuclear Physics and its application to the problems of medical research and treatment, it might be desirable for the hospital to build up a new class of specialists. I suppose an appropriate name for them might be 'Atomizers', 'isotopers' or 'Atomic Specialists'."^[2]

In the spring of 1946, Saul Hertz joined the staff of Boston's Beth Israel's Hospital. He is able to gain funding from the Navy, to refine the use of RAI in treating thyroid cancer. The Navy grant also provided for Dr. Hertz to explore with Dr. Herman Blumgart, the use of RAI to disable the thyroid in an effort to treat angina. Dr. Hertz directed his colleagues at Boston's Beth Israel Hospital in the use of RAI to diagnose and treat thyroid carcinoma successfully. Essential was the development and use of the multiscaler. Dr. Hertz designed and helped to create, the multiscaler at MIT where Dr. Hertz was teaching [Figure 4]. The multiscaler provided uptake testing so that dosimetry could be utilized to determine the appropriate amount of RAI for each patient. In September 1946, with Hertz family money, the Radioisotope Research Institute with facilities in Boston and New York City was

TABLE I AN ANALYSIS OF CASES "NOT CURED" BY R_aI + KI (TO MARCH 1946)

SERIES NO.	CASE HOSP NO.	BMR PRIOR TO I ¹³¹ DOSAGE OF I ¹³¹ DATES OF ADMINISTRATION	BMR PRIOR TO SUB-TOTAL THYROIDECTOMY	POSTOP THYROID BMR	THYROID WEIGHT	HISTOLOGY	TOTAL THYROID IRRADIATION (M) 12HR 8 DAY	ESTIMATED THYROID WK BEFORE I ¹³¹	% OF R _a -I (URINE) EXCRETED - 72 HRS FOLLOWING THE ADMINISTRATION OF I ¹³¹
	ELIZABETH D.	+30 21mc 9-21-41 13mc 9-6-41	(-3)(-7)	(-29)	34	INVOLUTION	470 220 690	35	20 28
5		+35 57mc 7-16-41	MARKED ENLARGEMENT	(-20)	31	HYPERTROPHIA NO INVOL.	1000 1150	40	27
10		+55 07mc 2-2-42	(+3)	(-26)	26 30 56	HYPERTROPHIA MOD. INVOL.	120 80	60	38
14		+50 15mc 7-15-42	(-15)	(-24)	55	HYPERTROPHIA + INVOLUTION	650	60	71
16		+25 10mc 8-11-42	(-8)	(-24)	28	INVOLUTION	1800	45	6
19		+65 14mc 8-25-42 8mc 3-8-43 3mc 3-9-43	(+8) (+36) TO (+18)	(-35)	35	SLIGHT HYPERTROPHIA INVOLUTION	2000 1500	60	9 15 7
2		+35 14mc 3-10-41 03mc 24mc 08mc 42	3.6 5.6	NOT OPERATED PERSISTENT THYROTOXICOSIS ANOTHER 20mc PROPOSED			160 140 110 100 120 130 100	40	54 48 78
4		+30 3.6mc 7-12-41 2.2mc 7-31-41	5.8	EYES BETTER. NO GOITER. BMR (+2) OFF MED. 4 WKS.			270 300 170 180	60	55 56
3		+50 34mc 6-6-41 20mc 1-3-46	REMISSION FOR 1 YR - THEN RECENTLY FOR TRUE RECURRENCE				430 410 4300	45	45 35

a * OPHTHALMOPATHIC TYPE

TABLE II - ANALYSIS OF 20 CASES "CURED" BY R_aI + KI ON BASIS OF EXAMINATION MARCH 31, 1946

SERIES NO.	CASE-HOSP NO.	DOSE OF I ¹³¹ AND DATE OF ADMINISTRATION	BMR BEFORE I ¹³¹	BMR LEVEL OFF IODIDES	TIME OFF IODIDES	THYROID SIZE 46	ESTIMATED THYROID WK (8m)	% OF R _a I EXCRETED 72 HOURS	ESTIMATED THYROID IRRADIATION (M) 12 HOUR 8 DAYS*
6		23mc 7-24-41 17mc 7-30-41	+45	DEC. 42 (-9) MAY 43 (-14) JAN. 46 (-7)	4 YRS. +	N	45	35 22	320 280 390 300
7		ET 9) 14mc 9-19-41 13mc 3-27-41	+65	1-8-46 (-6)	4 YRS.	N	45	9 20 (?)	260 260 (?) 280 210 (?)
8		ET 9) 10mc 9-24-41	+30	7-17-45 (-3) 3-27-46 (+4)	7 MOS	FIRM 2 X N	40	15	300 250
9		4.9mc 11-26-41	+30	5-8-45 (-10)	4 YRS.	N	60	17	650 420
11		5.8mc 4-9-42	+37	7-9-42 (-12) 2-24-44 (+9) 2-3-46 (-13)	3.5 YRS.	N	60	17	750 380
12		75mc 5-15-42	+55	45 (+11) 2-3-46 (-13)	3 YRS.	HARD 1.5 X N	60-75	26	950 500
13		12mc 6-9-42	+30	3-43 (+6) 2-3-46 (-10)	3 YRS.	N	40	71	750
15		4mc 8-11-42 10 4mc 8-11-42	+35	4-45 (-6) 2-3-46 (+2)	10 MOS.	N	40	10	2000
17		13mc 8-13-42	+50	6-10-44 (-15) 1-6-46 (-9)	3 YRS. +	N	60	14	1300
18		10.5mc 8-15-42	+35	8-22-44 (+10) 2-16-46 (+5)	3 YRS. +	N	40	15	2000
20		10mc 11-14-42	+50	4-3-45 (+1) 2-16-46 (+5)	2 YRS. +	N	45	20	1600
21		14mc 11-20-42	+45	1-8-46 (-13)	3 YRS. +	N	50	15 (?)	2000
22		13mc 3-9-43	+20	6-30-43 (-8)	2 YRS. +	"9" (UMR)	55	33	2200
23		8mc 3-15-43 18 10mc 3-16-43	+55	6-9-43 (-11) 2-16-46 (-3)	2 YRS. +	FIRM 1.5 X N	75	76 67	500
24		10.5mc 3-26-43 15 4.5mc 3-27-43	+40	12-45 (-5)	2 YRS. +	N (Dr. J.C. ZILHARDT)	50	57 51	1000
25		16mc 4-2-43	+44	9-28-44 (-7) 4-27-45 (+9) 3-20-46 (+4)	2 YRS. +	N (Dr. J.C. AUB)	50	20.6 63.0	750
26		12mc 4-6-43	+39	45 (-8) 1-16-46 (+2)	2 YRS. +	N	45	85	350
27		13mc 4-12-43	+40	7-17-45 (+16) 2-15-46 (-10)	2 YRS. +	N	50	33	1600
28		10.3mc 4-13-43 2 11.0mc 6-13-43	+55	12-45 (+6) 2-3-46 (+6)	2 YRS. +	N	75	---	2000
29		8mc 3-29-43 12 4mc 3-30-43	+30	2-46 (+4)	2 YRS. +	N	55	10 53 (?)	1200 250

b * B D. ISOTOPE FIGURES ASSUME NO LOSS OF IODINE FROM THYROID DURING DECAY; THEY ARE THEREFORE EXCESSIVE. THEY WERE NOT MEASURED FOR CASES 13-29. ---

Figure 2: The original workbook of Dr. Saul Hertz showing patients with unsuccessful treatment (2a) and successful treatment (2b) (published with permission of the Dr. Saul Hertz archive)

registered. The institute with clinical and laboratory facilities was devoted to the application of nuclear physics to medical investigation, diagnosis, and treatment. Hertz reached out to Dr. Samuel Seidlin of New York's Montefiore Hospital to be the associate director. By happenstance, Dr. Seidlin explored the use of RAI to treat carcinoma, when a ward patient known as BB appeared some years after his thyroid had been surgically removed. Dr. Seidlin consulted with Dr. Hertz and BB was treated with RAI. No new lesions appeared and some almost completely disappeared. Dr. Seidlin's patient BB died in 1952 from anaplastic carcinoma.

NUCLEAR MEDICINE IS BORN

In May 24, 1949, in a *Harvard Crimson* article, Hertz, "...emphasized this example of therapeutic application as a beacon in utilizing the tracer methods employing radioactive substances for the analysis of cellular function, growth, metabolism and nutrition in the body in other organs than the thyroid." Dr. Hertz stressed the tracer, targeted approach. In correspondence, Hertz wrote, "I have certain ideas in the field of Cancer... that are more intriguing from a physician's point of view than the cure of Graves' Disease with radioactive



Figure 3: News of Dr. Saul Hertz's work reaches a wider audience (published with permission of the Dr. Saul Hertz archive)



Figure 4: A volunteer shows how the multiscaler works, Dr. Saul Hertz stands next to the machine (published with permission of the Dr. Saul Hertz archive)

iodine without operation... the cancer field is relatively virgin territory both from the standpoint of actual knowledge or prognostic attack [Figure 5]."

Dr. Hertz advocated to the Atomic Energy Commission, for the distribution of RAI off of the atomic pile. He was closely involved in setting government regulations. Nuclear medicine had come of age.

In 1949, Dr. Hertz established the first Nuclear Medicine Department at the Massachusetts's Women's Hospital. At the time of his passing in July of 1950, from a sudden death heart attack, Dr. Hertz had expanded his research to other areas of cancer research using radionuclides.

THE HERTZ LEGACY

Saul Hertz's legacy is profound and enduring.^[3,4] His work established the cornerstone of nuclear medicine. The collaboration developed between Boston's MGH and the MIT converged the sciences in the quest to conquer cancer. Precision medicine has its roots in Dr. Hertz's use of dosimetry. Utilization of RAI to trace the functioning of an organ as well as to treat disease is the first theragnostic. Dr. Hertz's teaching at Harvard Medical School and at MIT planted the seed of combined MD-PhD programs.

Now some 80 years later, since Dr. Hertz posed his pivotal question, we are internally targeting other tumors with radionuclides such as Y-90 and Lu-177 using peptide receptor radionuclide therapy. In addition to thyroid and neuroendocrine tumors, targeted therapies are being used for metastatic bone cancers, prostate cancer, and neuroblastoma.^[5-7]

Dr. Hertz with his physicist colleague, Dr. Roberts' use of dosimetry, is being investigated to personalize treatments. Precision medicine has expanded into the area of radioimmunotherapy.

The use of the sodium/Iodide symporter in the treatment of cancer holds promise. This key plasma membrane transporter that mediates active iodine in the thyroid is being used to make other tumors take up the I-131 like those of thyroid cancer cells. Dr. Hertz overcame many challenges to bring his work to fruition. Let us be grateful to the patients who take a leap of faith to participate in clinical trials, to all the

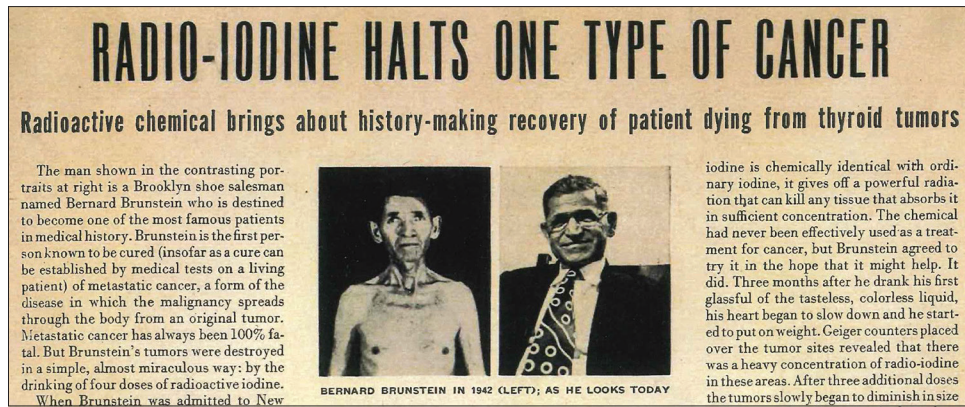


Figure 5: The use of radioiodine in treating cancer makes the press (published with permission of the Dr. Saul Hertz archive)

professionals and their support staffs, to the nuclear medicine industries, training, research and hospital centers worldwide, as well as to the professional organizations who propel Saul Hertz's dream forward.

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Conflicts of interest

There are no conflicts of interest.

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