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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 neuroendorine 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."

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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 1-128 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.

Barbara Hertz

Curator, Dr. Saul Hertz Archives and Saul Hertz MD.com

Address for correspondence: Barbara Hertz Med,
Curator, Dr. Saul Hertz Archives and Saul Hertz MD.com,
6 Buckthorne Lane, Greenwich - 06830, CT, USA.
E-mail: htziev@aol.com

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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

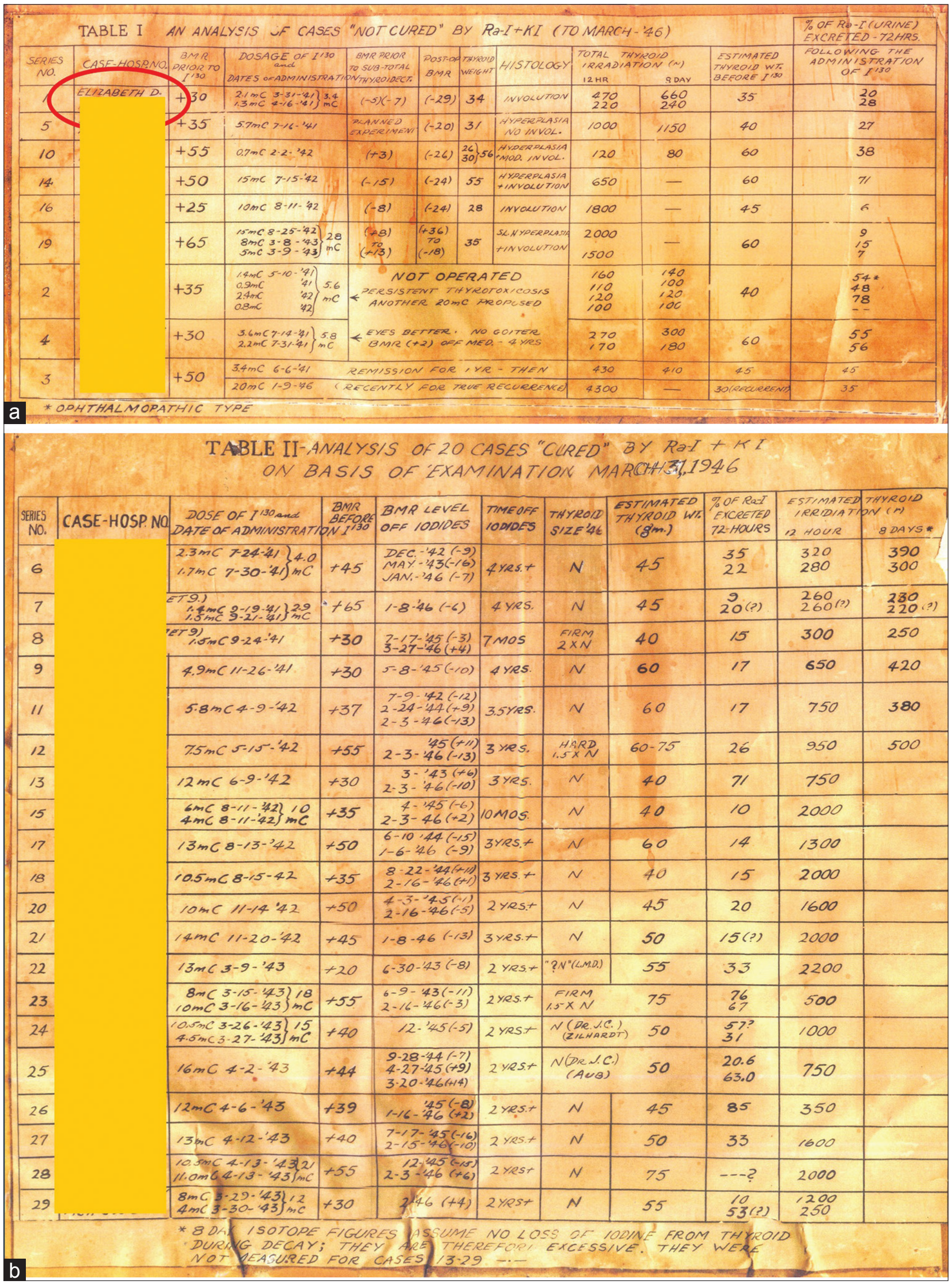

TABLE I AN ANALYSIS OF CASES "NOT CURED" BY Ra-I+KI (TO MARCH-'46)

SERIES NO.	CASE-HOSP.NO.	BMR PRIOR TO I^{130}	DOSAGE OF I^{130} and DATES of ADMINISTRATION	BMR PRIOR TO SUB-TOTAL THYROIDECT.	POST-OP BMR	THYROID WEIGHT	HISTOLOGY	TOTAL THYROID IRRADIATION (r) 12 HR	8 DAY	ESTIMATED THYROID WT. BEFORE I^{130}	% OF Ra-I (URINE) EXCRETED - 72HRS. FOLLOWING THE ADMINISTRATION OF I^{130}
1	ELIZABETH D.	+30	2.1mC 3-31-'41 1.3mC 4-16-'41 } 3.4 mC	(-5)(-7)	(-29)	34	INVOLUTION	470 220	660 240	35	20 28
5		+35	5.7mC 7-16-'41	PLANNED EXPERIMENT	(-20)	31	HYPERPLASIA NO INVOL.	1000	1150	40	27
10		+55	0.7mC 2-2-'42	(+3)	(-26)	26 30 } 56	HYPERPLASIA +MOD. INVOL.	120	80	60	38
14		+50	15mC 7-15-'42	(-15)	(-24)	55	HYPERPLASIA +INVOLUTION	650	—	60	71
16		+25	10mC 8-11-'42	(-8)	(-24)	28	INVOLUTION	1800	—	45	6
19		+65	15mC 8-25-'42 8mC 3-8-'43 5mC 3-9-'43 } 28 mC	(+8) TO (+13)	(+36) TO (-18)	35	SL.HYPERPLASIA +INVOLUTION	2000 1500	—	60	9 15 7
2		+35	1.4mC 5-10-'41 0.9mC '41 2.4mC '42 0.8mC '42 } 5.6 mC	← NOT OPERATED PERSISTENT THYROTOXICOSIS ANOTHER 20mC PROPOSED				160 110 120 100	140 100 120 100	40	54* 48 78 --
4		+30	3.6mC 7-14-'41 2.2mC 7-31-'41 } 5.8 mC	← EYES BETTER. NO GOITER. BMR (+2) OFF MED. - 4 YRS				270 170	300 180	60	55 56
3		+50	3.4mC 6-6-'41	REMISSION FOR 1 YR - THEN				430	410	45	45
			20mC 1-9-'46	(RECENTLY FOR TRUE RECURRENCE)				4300	—	30(RECURRENT)	35

* OPHTHALMOPATHIC TYPE

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

SERIES NO.	CASE-HOSP NO.	DOSE OF I^{130} and DATE OF ADMINISTRATION	BMR BEFORE I^{130}	BMR LEVEL OFF IODIDES	TIME OFF IODIDES	THYROID SIZE '46	ESTIMATED THYROID WT. (gm.)	% OF Ra-I EXCRETED 72-HOURS	ESTIMATED THYROID IRRADIATION (r) 12 HOUR	8 DAYS*
6		2.3mC 7-24-'41 1.7mC 7-30-'41 } 4.0 mC	+45	DEC.-'42 (-9) MAY-'43(-16) JAN.-'46 (-7)	4 YRS.+	N	45	35 22	320 280	390 300
7		(ET 9.) 1.4mC 9-19-'41 1.5mC 9-21-'41 } 2.9 mC	+65	1-8-'46 (-6)	4 YRS.	N	45	9 20(?)	260 260(?)	230 220(?)
8		(ET 9) 1.5mC 9-24-'41	+30	7-17-'45 (-3) 3-27-'46 (+4)	7 MOS	FIRM 2XN	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		7.5mC 5-15-'42	+55	'45 (+11) 2-3-'46 (-13)	3 YRS.	HARD 1.5XN	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		6mC 8-11-'42 4mC 8-11-'42 } 10 mC	+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 (+11) 2-16-'46 (+1)	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.+	"?N" (L.M.D.)	55	33	2200	
23		8mC 3-15-'43 10mC 3-16-'43 } 18 mC	+55	6-9-'43 (-11) 2-16-'46 (-3)	2 YRS.+	FIRM 1.5XN	75	76 67	500	
24		10.5mC 3-26-'43 4.5mC 3-27-'43 } 15 mC	+40	12-'45 (-5)	2 YRS.+	N (DR. J.C.) (ZILHARDT)	50	57? 31	1000	
25		16mC 4-2-'43	+44	9-28-'44 (-7) 4-27-'45 (+9) 3-20-'46 (+14)	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		10.5mC 4-13-'43 11.0mC 4-13-'43 } 21 mC	+55	12-'45 (-15) 2-3-'46 (+6)	2 YRS.+	N	75	---?	2000	
29		8mC 3-29-'43 4mC 3-30-'43 } 12 mC	+30	2-'46 (+4)	2 YRS.+	N	55	10 53(?)	1200 250	

* 8 DAY 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 form 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

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THE JEWISH ADVOCATE

Dedicated to Americanism, Judaism, Social Service

Title Registered in the United States Patent Office

Vol. 97, No. 17 — THURSDAY, MAY 23, 1946 — Twenty-Four Pages — Seven Cents the Copy

U.S. Government Officially Endorses Inquiry Committee Recommendation To Admit 100,000 Jews Into Palestine

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Local Researchist Discovers Cure for Goitre Through A-Bomb By-Product

By SHIRLEY I. CIBLEY

In 1936, the field of radioactive isotopes and their possible uses to extend and test medical theories and biochemical processes was just coming to the forefront of medical research. In that same year, Dr. Saul Hertz, of Brookline, attended a Harvard Medical School conference and was particularly inspired by a speech delivered by Dr. Karl T. Compton, in which the President of Massachusetts Institute of Technology made a plea for medical men to become interested in the application of the newer physical methods which were then becoming available through technological studies.

Thus was born the germ of an idea with which Dr. Hertz has worked, studied and experimented, and which today has resulted in his revolutionary discovery of a new treatment for Graves' disease (popularly referred to as pop-eyed goitre) through the application of radioactive iodine.

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DR. SAUL HERTZ
Commander (MC) USNR

Spotting the News

(World News Services Feature)

By ABRAHAM J. ARNOLD

HAGANA WARNING—The transfer of British military bases from Syria, Lebanon and Egypt to Palestine wil' not be tolerated, warned the Voice of Israel, underground radio of the Hagana resistance movement. Having agreed to remove their troops from Egypt and other countries in the Middle East, Britain is interested in maintaining the mandate at all costs and later taking over the trusteeship of Palestine. She wants this not in the interests of the Jewish people but to maintain her own power in the Middle East, the undrground radio pointed out.

THE "HOLY WAR" IS OFF—Latest statements by Arab League leaders and spokesmen for the Arab Higher Committee in Palestine finally reveal that the call for a "Holy War" in Palestine was nothing but a first-class hoax. Dr. Izzat Tannous, spokesman for the Arab Higher Committee, said this week that the use of force was not being considered and they were not prepared for a clash. It is also reported that the Arab attitude towards Russia has cooled off considerably. This shows quite clearly that the Arabs were bluffing in their war threats and leads us to believe that the Arab League has not got the full support among the Arab masses in Palestine to which they lay claim, . . . nor, as events show have they the alleged support of the Russians. This bears out the opinion of a highly placed Zionist leader, voiced to this writer, that the Russians would not support Arab demands at this time despite efforts to extend their influence and power in the Middle East.

Zionists Hold Special Meet In Washington

N. E. Emergency Council Plans Fund Dinner to Implement Decisions

A large delegation, representing leaders of the New England Zionist Region, Hadassah, Poale Zion and Mizrachi, as well as local Zionist Emergency Councils, is attending the all-day Conference called by Dr. Abba Hillel Silver and Rabbi Stephen S. Wise in Washington, D. C., today. The delegation, led by Ralph F. Bass, chairman of the New England Zionist Emergency Council, Mrs. Lewis Goldberg, representing the New England Hadassah Region, and Rabbi Isadore D. Passow, executive director of New England Zionist Emergency Council, will meet with leaders from all parts of the country to decide on a course of action "to fight the present policy of evasion and equivocation" on the Anglo-American Inquiry Committee's recommendation to admit 100,000 Jews into Palestine immediately.

The course of action on the Zionist political front to be decided at today's national conference will be implemented in

(Continued on Page 11)

State Dept.'s Request for More Views Doesn't Halt Urging Speedy Transfer

WASHINGTON, May 23 (Special Dispatch)—The State Department announced last night that the United States Government has officially endorsed the Palestine Inquiry Committee's recommendation for the immediate admission of 100,000 Jewish refugees into Palestine and that it was determined to press for speedy transfer of the immigrants.

The statement was issued to clear up misunderstandings created by a State Department memorandum issued this week requesting further views from Jews and Arabs on the Anglo-U. S. Report.

President Truman had endorsed the provision calling for the admission of the 100,000 when the Report was made public on April 30, and urged then that the immigration be carried out "with the greatest dispatch."

"It must be clear that the President's statements are controlling upon all the departments of government,"

(Continued on Page 7)

UN Commission In Report on Human Rights

NEW YORK (JTA)—The early writing of an International Bill of Rights under the provisions of the United Nations Charter, pledging world-wide promotion of human rights by all states which are members of the United Nations, is urged in a report which the U.N. Commission on Human Rights completed this week under the chairmanship of Mrs. Eleanor Roosevelt.

B'nai Brith To Convene Here This Week-End

B'nai Brith leaders from every part of New England, New York State and Eastern Canada, will gather in Boston this week-end, at the 94th annual convention of District No. 1, which will open Friday evening with special services at Temple Sinai, Brookline.

On Saturday afternoon, a tea and entertainment will be tendered visiting ladies at the Salle Moderne, Hotel Statler, and a special reception to visiting dele-

Marine Flasher Brings First Immigrants—4 Have Kin Here

Local Community Plans to Welcome Its Quota; Rabbi Shubow Accompanies Group from Germany

Dreams of freedom, sustained through the horror and degradation of the war years, became reality for 867 European immigrants aboard the "S. S. Marine Flasher" when the reconverted troopship docked this past Monday in New York harbor.

Passage for 444 of the displaced persons, who are the first to arrive here under President Truman's immigration directive,

Judge Pinanski Public Library Board Chairman

New Palestine Colony Honors Massachusetts

JERUSALEM (JTA) — The colony of Nachlath Massachusetts, named in honor of the

Governor Tobin To Sign Mass.

Sen. Barkley to Address Dinner

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

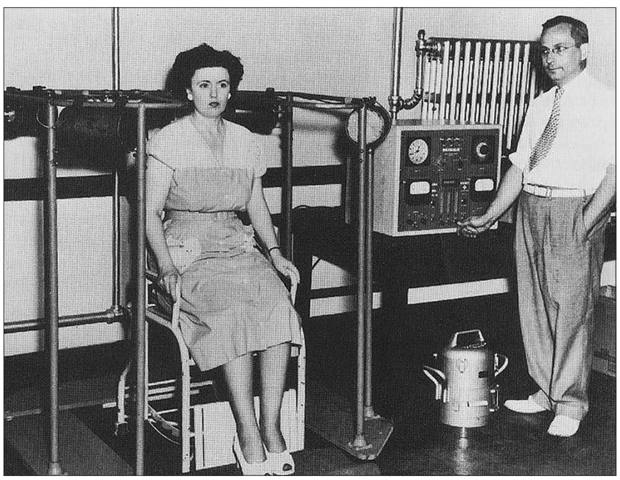


Figure 4: A volunteer shows how the multiscaler works, Dr. Saul Hertz stands next to the machine (published with permission of the Dr. Saul Hertz archive)

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.

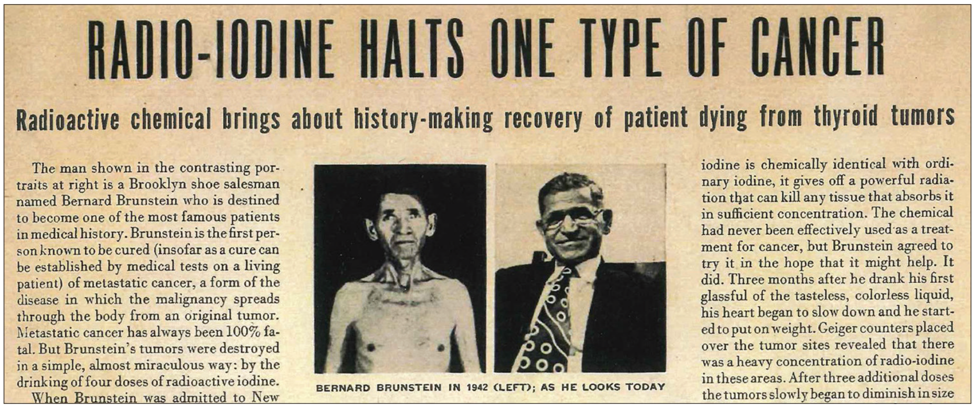
THE HERTZ LEGACY

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 therangnostic. 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



RADIO-IODINE HALTS ONE TYPE OF CANCER

Radioactive chemical brings about history-making recovery of patient dying from thyroid tumors

The man shown in the contrasting portraits at right is a Brooklyn shoe salesman named Bernard Brunstein who is destined to become one of the most famous patients in medical history. Brunstein is the first person known to be cured (insofar as a cure can be established by medical tests on a living patient) of metastatic cancer, a form of the disease in which the malignancy spreads through the body from an original tumor. Metastatic cancer has always been 100% fatal. But Brunstein's tumors were destroyed in a simple, almost miraculous way: by the drinking of four doses of radioactive iodine.

When Brunstein was admitted to New

BERNARD BRUNSTEIN IN 1942 (LEFT); AS HE LOOKS TODAY

iodine is chemically identical with ordinary iodine, it gives off a powerful radiation that can kill any tissue that absorbs it in sufficient concentration. The chemical had never been effectively used as a treatment for cancer, but Brunstein agreed to try it in the hope that it might help. It did. Three months after he drank his first glassful of the tasteless, colorless liquid, his heart began to slow down and he started to put on weight. Geiger counters placed over the tumor sites revealed that there was a heavy concentration of radio-iodine in these areas. After three additional doses the tumors slowly began to diminish in size

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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