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Radioiodine and the Treatment of Hyperthyroidism: The Early History*

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ABSTRACT

Little was known about iodine metabolism in the mid-1930s, but when Saul Hertz and his chief, J. Howard Means, at the Massachusetts General Hospital (MGH) realized in 1936 that radioiodine could be made and used as a tracer, they arranged with physicists Robley Evans and Arthur Roberts at the Massachusetts Institute of Technology (MIT) to make the short-lived ^{128}I and study its physiology in rabbits. By 1938, they showed that the rabbit's thyroid gland rapidly took up ^{128}I, especially when there was only a little non-radioactive iodine present. There was, however, no hope of using ^{128}I as a treatment because of its brief half-life (25 minutes).

In 1939, Joseph Hamilton and Mayo Soley, working with Ernest Lawrence's cyclotron in Berkeley, California, were able to make several other radioiodines; one was ^{130}I (12-hour half-life) and another ^{131}I (8-day half-life). They were the first to give these radioiodines to humans to study iodine physiology. The MGH-MIT group also built a cyclotron and by 1940 had generated these two new radioiodines.

One of the goals of both groups was the treament of hyperthyroidism. Hertz and Roberts were the first to do so on March 31, 1941; Hamilton and John Lawrence, Ernest's brother, began on October 12, 1941. By 1942, the United States was actively fighting in World War II. That year both the Boston and Berkeley groups gave preliminary data on the treatment of hyperthyroidism in Atlantic City; both showed that it was effective and went on to treat more patients. In Berkeley the therapy was viewed cautiously, and, in any case, the physicists were mainly occupied with work for the Manhattan District. In Boston Hertz used the therapy as often as he could, emphasizing the use of ^{130}I, until he joined the U.S. Navy in 1943.

Earle Chapman, a clinician on the voluntary staff of the MGH, took over Hertz's practice in 1943; their later differences over the precise treatment and who was in charge led to their falling out. After Hertz's release from the Navy he was not permitted to return to the MGH and became quite bitter; Chapman stayed on at the MGH. After the war was over, both had acquired a sufficient number of patients—there was then no such thing as a controlled trial—and wrote up the results for publication. Each wrote with a different physicist, Hertz with Roberts and Chapman with Evans. When Hertz learned that Chapman's paper was being considered by the *Journal of the American Medical Associations*, he quickly sent his manuscript to *JAMA* as well. Although the editor of *JAMA* was puzzled by two papers on the same topic from the same institution, both papers appeared in the same issue of *JAMA* on May 11, 1964, and announced the new therapy as effective treatment for hyperthyroidism.

INTRODUCTION

THERE WERE TWO PAPERS on a new treatment, radioactive iodine, for the hyperthyroidism of Graves' disease in the weekly issue of the *Journal of the American Medical Association* (*JAMA*) of May 11, 1946 (1,2). The thousands of readers who got that issue saw that the two papers were oddly similar: the papers reported patients from the same unit, the Thyroid Clinic at Boston's MGH who were given the same radioiostope of iodine, ^{130}I. Further, the radioiodine came from the same source, the MIT cyclotron, and both papers acknowledged the same mentor,

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J. Howard Means (1885–1967), then the chief of the Medical Service at MGH, a professor of medicine at Harvard's medical school, and a leading American thyroidologist although he was not a coauthor of either paper. Despite these similarities, and even more oddly, the two papers were written by two completely different physician-physicist teams; one was by the physician Saul Hertz (1905–1950) and the physicist Arthur Roberts (1912–) and the other by the physician Earle Chapman (1903–1990) and the physicist Robley Evans (1907–1995).

One well might wonder how two papers so similar could be written by two different sets of authors. Behind the two papers is the story of an innovative collaboration that not only melded physics and medicine to develop a successful therapy, now the most common treatment for hyperthyroidism in the United States, but also led to personality clashes, wounded egos, and a claim of academic theft.

BACKGROUND

The two 1946 papers on the radioiodine treatment of hyperthyroidism appeared 10 years after the Boston investigators first thought in 1936 that radioiodine might lead to such a treatment. The idea itself, however, did not spring from their minds *de novo* but was rooted in several antecedents in the science and medicine of the day. These were [1] the knowledge that the thyroid gland concentrates iodine, [2] the idea that tracer substances could be used to analyze biologic functions, [3] the discovery of artificial radioactivity, and [4] the knowledge that external x-irradiation could benefit hyperthyroidism.

Iodine and the thyroid gland

By the mid-1930s, any scientist or physician interested in the thyroid gland knew that it contained iodine, that it took up and concentrated iodine, and that its hormone (they only knew of one) was made up mostly of iodine. They knew, for example, that a German biochemist, Eugen Baumann (1846–1896), had found iodine in the thyroid gland in 1895, more or less by informed accident (3); that Edward Kendall (1886–1972) had isolated "the" thyroid hormone at the Mayo Clinic in 1914 by using iodine as a marker for the hormone (4) (unfortunately for Kendall, he proposed the wrong chemical structure, which was correctly determined by Charles Harington (1897–1972) in 1926 [5]); and that David Marine (1880–1976) in 1915, then in Cleveland, showed that the thyroid gland took up stable iodine from a perfusate when studied *in vitro* (6).

Clearly iodine metabolism was a dynamic key to how and why the thyroid gland functioned, but in the 1930s this knowledge nevertheless was frustrating to both the physiologist and the physician; there were then no suitable techniques to study the gland in detail and perhaps turn this knowledge to clinical use. For example, Marine was forced to give large, unphysiologic amounts of iodine and to remove a good part of the gland to measure its iodine content. No physiologist would be happy with an experiment as far removed from the normal, and no physician would remove routinely part of the gland to diagnose hyperthyroidism. At the time, the only way to diagnose hyperthyroidism with reasonable accuracy was by examining the patient and showing that there was a high oxygen consumption by measuring the time-honored basal metabolic rate (BMR), then the only useful laboratory test.

The concept of biologic tracers

György Hevesy (1885–1966) established the idea of using a "marker" or a tracer substance to assess biologic function a decade before the 1930s. Hevesy came to this idea because of his work with radioactive lead in 1911–1912. Charged then with the task of separating "radium D" from lead so that the radium D could be used for radiation studies, he was unable to separate the two. Eventually the reason became clear: radium D was in fact radioactive lead. So, rather than trying to separate it from lead, he turned its inseparability to advantage, using it as a marker or tracer for lead itself in chemical work (7). In 1923 he turned to biology and showed that plant roots were able to take up and release this naturally radioactive lead (8) (in 1943 he won a Nobel prize for his work). The radioactive lead was different from other lead atoms in that it was radioactive, but the two were treated by the plant identically. At the same time, the ability to detect it by measuring its radioactivity meant that one needed only a small amount and so one could avoid the potential interference of a large amount with the plant's natural processes.

Hevesy realized that the ideal tracer for any biologic process would be an element or a compound that was similar enough to a known biologic substance that it would be treated by the organism as if it actually were the known substance and yet different enough that it could be detected separately from the known substance. The marker, or tracer, also needed to be present in only small amounts, so there had to be a highly sensitive method to detect the tracer. The tracer would be like a reporter: it would not affect a biologic process, because there was so little of it, but, because the tracer would be metabolized in the same way as the substance it was tracing, it would tell us how the process functioned.

However, once Hevesy established the principle, he faced the problem of applying it to biology in general or to medicine in particular. The problem at the time was essentially insoluble; there were then only a few known radioactive substances that could be used, and none were common biologic elements. The naturally radioactive lead was one; radon, which actually was used in humans to test the circulation time of the blood, and bismuth were others. There was no radioactive iodine.

The discovery of artificial radioactivity

Only 2 years before the Boston investigators had their idea about radioiodine in 1936, the Parisian husband and wife physicist team Frédéric Joliot (1900–1958) and Irene Curie (1897–1956) (Marie Curie's daughter) discovered artificial radioactivity. This was a truly remarkable discovery, and it happened partly by accident. In late 1933, the Joliot-Curies were irradiating aluminum foil with polonium, a source of alpha particles, in an attempt to confirm their hypothesis that neutrons and positrons would be emitted simultaneously. They showed that their idea was wrong because positrons, but not neutrons, continued to

come from the aluminum target after the polonium was removed, but they now had an entirely new and unexpected phenomenon to explain: why was radiation coming from the aluminum when there was none going in? Had they in fact made a radioactive substance, or was it just a faulty instrument? Instruments then were all homemade and needed to be checked carefully. They were still working on the problem on New Year's Eve 1933 when they had to leave for an important dinner party. They shut down their experiment, asked Wolfgang Gentner, their student assistant, to check the Geiger counter, and departed. He left them a note that the counter "was in accurate working order." The positrons were real and the aluminum foil was in fact itself radioactive. Over the next 2 weeks they not only confirmed their remarkable finding but also devised a rapid chemical technique to show, within its half-life of only 3.25 minutes, that they had created a new radioactive element, radiophosphorus (9). They published quickly in *Nature* in early 1934 (10); their 1 page paper established an entirely new class of phenomena and won them the Nobel prize in 1935.

The Italian physicist Enrico Fermi (1901–1954), another Nobelist (1938), saw the Joliet-Curies' note and tried the experiment himself but used neutrons instead of alpha particles as a radiation source. His note, also in *Nature* a few months after theirs, described 22 new radioactive elements. Two of the elements Fermi radiated were iodine, with a stable atomic weight of 127, and telurium, the element just before iodine on the periodic table. Irradiated iodine showed an "intense effect" with a half-life of 30 minutes; it was probably ^{128}I (11). There were now almost two dozen artificially radioactive elements, whereas a year before there had been none.

Ernest Lawrence (1901–1958) at the University of California at Berkeley, who was to become yet another Nobelist (1939), had improved his cyclotron in 1932, just 2 years before the Joliot-Curies' discovery. Their report (10), or possibly their slightly earlier one in French (12), made him and his team look to his cyclotron, which was a source of high-energy nuclear particles. He quickly found that he, too, had been making radioactive elements but simply had never looked for them; the radiation detectors always were shut down at the same time as the cyclotron and thus he never knew of the spontaneous radiation from new, cyclotron-generated elements. Now his cyclotron became a ready source of new elements, many of which could be used as tracers. Cyclotrons, however, were not easy to make or get in the mid-1930s; the few that existed were made and used by physicists, not biologists or physicians.

The treatment of hyperthyroidism in the 1930s

The main treatment for hyperthyroidism in the 1930s was surgery. Formerly fraught with danger and avoided if at all possible, thyroidectomy became widely acceptable in the 1920s when its mortality rate was decreased notably by the pre-operative use of stable iodine. Still, although surgery was the standard therapy in the 1930s, it was not innocuous; there was still a surgical mortality rate of 1–2% at best and perhaps 8–10% in the hands of less-skilled surgeons.

For those who wanted to avoid the standard surgical treatment, what alternative was there? Radiation was one. Its use to treat hyperthyroidism was not a new idea in 1936. Radium was used in the early twentieth century but was not particularly effective. It did lead, however, to the use of x-irradiation, which was a fairly popular alternative to surgery until the 1920s. External radiation with x-rays, though a form of "blunderbuss," helped about a third of patients with moderate to severe hyperthyroidism (13). For milder cases, a large amount of stable iodine might help, although no one knew why; many, however, would relapse when the iodine was stopped (14). Surgery remained the standard therapy even though no one really knew how it worked; some of the overactive thyroid tissue always was left behind and yet most patients did not have a recurrence. In the early 1930s, physicians had no way of using their limited physiologic knowledge of iodine economy to treat hyperthyroidism.

So, by 1936, the threads needed to weave together the fabric of a new way to study the thyroid gland and treat its diseases were there. A radioactive iodine, if one were able to make one, could be a tracer of thyroid function. If one had enough, perhaps enough could get into the gland, internally radiate the thyroid cells, and destroy enough thyroid tissue to help a hyperthyroid patient. But until 1936 no one had thought to weave the threads together to make the fabric.

RADIOIODINE AS A TRACER OF THYROID FUNCTION

Boston

On November 12, 1936, Harvard Medical School held one of its regular Thursday luncheons at the Longwood Avenue campus; the speakers' charge at these gatherings was to broaden the views of the medical audience. In attendance that day were several physicians from the Thyroid Clinic of the Massachusetts General Hospital, including Saul Hertz, who was in charge of the Clinic; Howard Means, his chief, and two attending physicians at MGH who were on the voluntary, unpaid staff but who had a major interest in thyroid disease, Earle Chapman and Jacob Lerman. They had come to hear Karl Compton (1887–1954), the president of the Massachusetts Institute of Technology (MIT) and a renowned physicist, speak on the subject "What Physics Can Do For Biology and Medicine." Before he spoke, Compton had asked one of his young assistant professors of physics, Robley Evans, for some ideas. Evans thought that "artificially radioactive isotopes" and their potential for studying metabolism would be a good topic. At this point Evans probably had only a vague recollection of the exact details of Fermi's note; the thyroid physicians had never heard of it.

Compton told how radioisotopes of many different elements could be made on demand and then used to trace metabolic events in living organisms. At the end of his talk, Saul Hertz asked him whether there might be a radioactive isotope of iodine. He and the thyroid group had pulled the threads together in almost an instant; they saw the way to study and treat the thyroid. Compton said he did not know but would find out. He seems to have asked Evans, who then recalled Fermi's 1934 note. More than a month

later, on December 15, 1936, Compton wrote to Hertz, apologized for the delay, and said that "iodine can be made artificially radioactive. It has a half period of decay of twenty-five minutes and emits gamma rays and beta rays." A week later Hertz wrote back that he hoped to do "animal experiments" and devise "a useful . . . therapy in cases of overactivity of the thyroid gland."

Almost immediately, in early 1937, Compton and Means developed a joint MIT-Harvard project to produce and use radioactive iodine (all of the staff at MGH had appointments at Harvard Medical School). As a professor at Harvard, Means had access to certain unrestricted funds that he used to start the project.

Compton delegated the MIT part of the project to Evans. Although there was no cyclotron at MIT, Evans had decided, probably based on Fermi's brief report, that radioactive iodine could be made. Evans' background was certainly suitable. He had received his doctorate in 1932 at the California Institute of Technology under Robert Millikan (another Nobelist), had spent 2 years at the University of California at Berkeley working with Ernest Lawrence on a National Research Council (NRC) fellowship, knew well the ongoing work at the Berkeley cyclotron, and was quite familiar with the medical use and toxicity of radium and radon. In 1936, although based at MIT, he was working on the toxic effects of radium (^{226}Ra) in patients who unwittingly swallowed radium while they were painting it onto watch dials to make the dials glow in the dark. Evans' physician colleague in the radium project was Joseph Aub (1890–1973), a well-known Harvard physician who worked at the Huntington Memorial Hospital next to Harvard Medical School and whose main work was the study of patients with cancer. For the radioiodine project, Evans collected still active radium and radon sources previously used to treat patients with cancer; it is not clear whether he made a small amount of radioiodine with these naturally radioactive neutron sources or had simply read about the technique.

At the MGH, Means put Hertz in charge of the radioiodine project's biologic and medical work. Hertz, raised in Cleveland, Ohio, and a graduate of Harvard's medical school (1929), had returned to Cleveland for his house-staff training. He came back to MGH in 1931 to study metabolic disease for 6 months on a purely voluntary basis without salary. He must have shown early promise because Means not only kept him on but, after only 3 months, arranged a Dalton Scholarship for him later in 1931. In 1934, Means named Hertz to direct the Thyroid Clinic at MGH; technically, the position was director of the Metabolism Laboratory, i.e., the room in which BMR was measured in patients with suspected or proven thyroid disease. The appointment was, however, not permanent because there were no funds for a long-term commitment; Means had to reappoint Hertz periodically for Hertz to stay on.

To get the project under way in mid-1937, Evans recruited Arthur Roberts, a young physicist with a newly minted Ph.D. who, in the depths of the Great Depression, was still unemployed. Hertz's vigorous support of Roberts over other applicants probably was responsible for Roberts' being chosen although they had never met. Roberts had never done any biologic work, had never been to Boston, and knew nothing about the thyroid gland; he simply had put his name into a physics job bank. Jobs were few, so when he got a completely unexpected telegram from Evans with a job offer at a salary of $2000 per year from the Harvard funds, he eagerly accepted. His job was to set up and run all of the necessary physics. Roberts recalls that one of the conditions of the job was that Evans would be a coauthor on all publications resulting from the project. Hertz and Roberts were now a team, combining medicine and physics, with Means and Evans as their respective overall supervisors.

When he got to MIT, Roberts found no counting equipment and no evidence that radioiodine had been made (Roberts, personal communication). He had to figure out how to make, extract, and concentrate radioiodine and then set up a counting apparatus, based on a Geiger-Müller counter, to measure how much radioiodine he had. To make the radioactive iodine, he used the radium-beryllium neutron source that Fermi had used and an ingenious technique worked out by Leo Szilard to produce ^{128}I. He put the neutron source near a container of ethyl iodide, which is liquid at room temperature. When a neutron struck a stable ^{127}I atom in the ethyl iodide, the neutron converted the ^{127}I to ^{128}I. The quantitative amount of ^{128}I was vanishingly small and its separation from the vast amount of iodine in the ethyl iodide could have been formidable. The truly ingenious part of the process was the recognition that the recoil energy of the newly radioactive ^{128}I would break the ethyl-iodide bond and release the ^{128}I as free iodide. Because the ^{128}I was now free iodide, the answer to the separation problem turned out to be simple. Ethyl iodide is not miscible with water, whereas free iodide is easily soluble in water. Roberts just mixed the irradiated ethyl iodide with a small amount of water after 1 or 2 hours of exposure to neutrons. The water phase contained all the ^{128}I.

Hertz and Roberts did their first experiment with ^{128}I on the first of a series of rabbits in late 1937; they probably had no more than 0.05 μCi. Hertz had to come over to MIT to do the animal work for a simple, but limiting, reason: the half-life of ^{128}I is only 25 minutes. The work, both the biologic studies and the analyses, had to be done immediately after they made the radioiodine; there was simply no time to go back and forth across the Charles River between MIT and MGH. The short half-life was also a serious limit on the kind of experiment they could do; none could last more than 15–20 minutes because they needed a few half-lives to count the radioactivity. But ^{128}I was what they had, so that was what they used.

The two collaborators (neither Evans nor Means took part in the experimental work) injected the tiny amount of ^{128}I into the rabbit's ear vein and traced its distribution with a Geiger-Müller counter, also built by Roberts. After 15–30 minutes, 35–45% of the radioactivity was in the thyroid gland, as they had hoped, and most of the rest (40–50%) was in the urine. That winter they studied 48 rabbits; some were normal and some had artificial thyroid hyperplasia induced by injections of thyrotropin (TSH) (Hertz had been studying the effect of TSH on thyroid histology for several years on the then-common assumption that TSH-induced hyperplasia was an animal model of Graves' hyperthyroidism [15]). They found that their as-

sumptions consistently were true: the normal thyroid gland concentrated the ^{128}I and the hyperplastic gland took up even more. Their report, the first to show radioiodine uptake by the thyroid gland, appeared in May 1938 (16); they noted that their findings "may be of . . . therapeutic significance." The original draft of their short paper had Hertz and Roberts as the coauthors because they had done the work and written the paper; Roberts recalls that these were then the criteria for authorship. They were reminded of the earlier agreement with Evans, whose name was added to the manuscript while it was in press after Hertz wrote to the editor (Evans dictated the letter for Hertz to sign).

They knew that there was no prospect of treating disease with an isotope that had a 25-minute half-life and with the quantity available. By early 1938 they also knew that a cyclotron could make longer-lived isotopes of radioiodine in quantity, but they did not have the money to build one. Once again the physicists took action. Compton and Evans went to New York City on May 19, 1938, to the offices of the John and Mary Markle Foundation to ask for $30,000 to build a cyclotron (17). They were in luck. Harvard's professor of physiology (and, not incidentally, a colleague of Means) was Walter B. Cannon, America's senior physiologist; he, too, was in New York that day as a consultant to the Foundation. By the end of the day the two physicists had in hand a check for $30,000. They hoped the cyclotron would be built quickly, but in fact it took 2 years; they had to recruit M. Stanley Livingston from Berkeley, who had direct experience with Lawrence's machines and was familiar with their construction. When it was finished in 1940, it was the first cyclotron built exclusively for biologic and medical use.

In the meantime, other cyclotrons, including Lawrence's at Berkeley, helped the MGH-MIT team by sending them some of the newly discovered, longer-lasting radioisotopes of iodine. The amounts were small and useful for physiologic studies but not for attempts at treatment. As an example, the Massachusetts group would send tellurium targets to Berkeley, probably making use of Evans' connections. There the targets would be bombarded in Lawrence's cyclotron with the creation of three different radioiodine isotopes: ^{126}I (13-day half-life), ^{130}I (12.5-hour half-life), and ^{131}I (8-day half-life). The Berkeley group then would send the radiated tellurium targets back to Cambridge by first-class mail where the iodine was extracted and prepared for use.

The next year, in 1939, Hertz, Roberts, Evans, and Means confirmed the rabbit work with these longer-lasting radioiodine isotopes. They also were able to make an important finding: the rabbit's thyroid gland took up more radioiodine if they gave it with only a small amount of stable, nonradioactive iodide than if they gave it with a large amount of carrier (note that all four were now coauthors) (18). They clearly recognized that the "carrier" iodide lowered the thyroid uptake of the radioiodide. They did not forget the therapeutic potential, but at the time their calculation of what it would take to treat a patient was discouraging; they estimated that with the rapidly decaying ^{128}I it would take the impossibly large amount of 750 mCi to treat hyperthyroidism.

Throughout 1939 and most of 1940, they stuck to the study of rabbits; they did not give radioiodine to humans. Hertz was working full-time in Means' department but still on a periodically renewable appointment as was the custom (permanent jobs in academic medicine were few then). Means had renewed Hertz's appointment every year or two since 1935, each time telling him in writing that, at the end of the appointed time, Hertz would have to leave. However, each time the term was up, Means renewed it. In 1939 Means not only renewed Hertz's appointment but did so for 3 years; he also found the funds to provide the unmarried Hertz with the then-substantial salary of $4500 per year. Means emphasized once again that the appointment would not be renewed again after 1942 ("you must be prepared . . . to fall back on practice as a means of livelihood"). One gets the impression that Means' renewal of Hertz's appointment in 1939, after informing him 2 years before that he would not renew it, was at least in part because of Hertz's work with radioiodine. Means' pattern of renewal despite prior notice that Hertz should plan to leave after the end of a term later may have led Hertz to think that the appointment was more permanent than it was.

Berkeley

In the meantime, there was real interest in the human applications of radioisotopes made by the Berkeley cyclotron. The improved cyclotron was housed in an old wooden building scheduled for destruction by the University but rescued by Ernest Lawrence, its inventor. The cyclotron was the center of intense and exciting work in physics. Lawrence's team, which included his brother, John Lawrence, a physician, worked fast after 1934 and produced a range of new radioactive elements. One of John Lawrence's tasks was to find biologic and medical applications for these elements. This task arose in part from innate interest but also in part because a substantial fraction of the cyclotron's funding came from medically oriented foundations; in contrast to today, there were then few sources of grants for research in physics (most of the physicists and radiochemists working with the cyclotron had little use for this biologic and medical work because it got in the way of their own research [19]). Later, in 1939, the Berkeley team was the first to report the successful treatment of a disease, polycythemia, with a radioactive element, ^{32}P.

In 1937 Joseph Hamilton (1907–1957) was a young physician who had decided not to practice medicine. He had come to Berkeley as a research fellow to work with Ernest Lawrence with the idea of applying the new radioisotopes to human physiology and disease. For example, that year he showed that a normal human volunteer and co-worker, Alfred Marshak, rapidly would absorb radioactive sodium from the gut. The technique and the detection instrument were simple: the volunteer held a copper-clad Geiger counter in his hand inside a large lead-lined box and then drank the radioactive sodium. Hamilton also studied radioiodine (^{128}I), which was absorbed from the gut in "3 to 6 minutes" (20). As far as we know, in 1937 and early 1938, this all was done without knowledge of the MIT-MGH team's work.

Hamilton was probably thinking about using radioiodine to study the human thyroid gland in the spring of 1938, perhaps spontaneously or perhaps now stimulated

by the Boston-Cambridge team's work. Hamilton's problem was the same as that of the Massachusetts group: the available radioiodine, ^{128}I, had too short a half-life to be practically useful. Both the Berkeley and the Massachusetts groups apparently were unaware that Michigan physicists had found a radioiodine with a 13-day half life (^{126}I) earlier in 1938; in Michigan they also had found ^{131}I with its 8-day half-life but had misidentified it as tellurium 131 (21). Hamilton's problem was solved in the spring of 1938, after he talked to Glenn Seaborg (yet another future Nobelist), then a young radiochemist at Berkeley. Seaborg went to the cyclotron with his colleague, Jack Livingood, and bombarded tellurium instead of ethyl iodide. Within a week they had several more radioiodines, one of which had an 8-day half-life and which they identified as ^{131}I (22).

Mayo Soley, who had advised Hamilton in the studies on Alfred Marshak, now started to work with Hamilton. Soley was a physician who had trained at MGH under Means and was now in the thyroid clinic at the University of California at San Francisco Medical Center across the bay from Berkeley. Soley knew Hertz personally because they were both in Means' department at the same time in the mid-1930s, although Soley was 4 years behind Hertz at Harvard Medical School. Soley wrote Hertz on June 23, 1938, that he had seen Hertz's first radioiodine paper the month before and that he thought it was "the first notice in the literature." He also mentioned that he and the Berkeley group were "ready to go on clinical studies using radioactive isotope of iodine which has a half-life of 13 days." This would have been ^{126}I, one of the several found by Seaborg. However, when the Berkeley group began their human thyroid studies in late 1938, they used ^{131}I, with an 8-day half-life, and never did use ^{126}I.

Hamilton and Soley's concept, like Hertz and Roberts', was to use radioiodine as a tracer of what they thought was a small amount of administered stable iodine; they initially did not conceive of it as a tracer for endogenous circulating iodide. They gave radioiodide with 14 mg of stable iodide to six hospitalized patients without thyroid disease, to one with hypothyroidism, and to several goitrous patients, some with hyperthyroidism and one with thyroid cancer (23). Most of the radioiodine went into the urine of each of these patients and there was no clear difference between those with and without thyroid disease; they must have been disappointed (in retrospect, we now know that 14 mg is quite a large amount of stable iodine and that it "swamped" their radioiodine). They nevertheless were able to show that if the thyroid tissue removed at surgery 2 days after giving the radioiodine was hyperplastic, it had more radioiodine in it. The one cancerous thyroid tissue removed surgically after giving radioiodine contained little radioactivity. With the use of a Geiger counter, they showed that some of the radioiodine was taken up by the thyroid gland; although the result was not quantitative and they did this in only one patient, this seems to have been the first attempt at an "uptake test" in a human. They could draw no substantial conclusions in 1939, but they had done human studies for the first time with the radioiodine, ^{131}I, we still use for therapy.

Hamilton and Soley, using the relatively long-lasting ^{131}I, went on to show systematic radioiodine uptake by the human thyroid gland over several days (24). They found, however, that the normal gland took up an average of only 3.5% of the dose of radioiodine, because they still were giving the 14 mg of carrier iodide. Four adults with hypothyroidism had, as expected, a very low uptake.

The two investigators were puzzled by one result. Two goitrous patients without hyperthyroidism had a high radioiodine uptake, which they expected because of the hyperplasia. But five other patients with goiter who also were hyperthyroid had no more radioiodine in their thyroid glands at the end of 24 hours than did normal persons (although their thyroid glands had a blip in radioiodine uptake of 10–12% a few hours after the dose); we now might attribute this to fast turnover within the gland. Their results were unclear because of the carrier iodide but their data showed that radioiodine was in fact taken up by the human thyroid and could be shown to do so *in vivo*. A realistic test for thyroid function now was in sight. Of note is that the Markle Foundation now was supporting Hamilton and Soley's work as well the Massachusetts team, in part because Means himself had so advised the Foundation.

The two Berkeley collaborators published both of their papers in the *American Journal of Physiology*, which implies that they felt the work was of more physiologic than clinical interest. Curiously, it was their physiologist colleague Israel L. "I.L." Chaikoff (1902–1966) and his colleagues in Berkeley's nearby physiology department who clearly outlined the difference between radioiodide as a tracer for an *administered* dose of iodide and radioiodide as a marker for the metabolism of *endogenous* iodide. Chaikoff studied rats rather than humans and used mostly ^{131}I prepared, essentially carrier-free, by Hamilton himself. By early 1941 Chaikoff's group showed that as little as 30 μg of stable iodide could depress markedly radioiodine uptake by the rat's thyroid from 65 to 7%. They realized that "the distribution of the tracer dose reflects the movement of circulating endogenous iodine." (25)

Paris

One should not get the impression that this was entirely an American effort. It should not come as a great surprise that Parisian investigators were curious about radioactive iodine as well inasmuch as they had "invented" artificial radioactivity. In fact, as early as 1937 Charles Leblond used ^{128}I to study its uptake by the thyroid glands of rats and guinea pigs (26). Leblond, who later made his reputation in Montreal where he has lived for more than 50 years, is a French-born physician, biologist, and histochemist. In 1937 he had just returned to Paris, after 2 years at Yale, to become a biologist in Joliot's physics laboratory. His ^{128}I was, of course, supplied directly by Frédéric Joliot. Leblond reported, as had Hertz and Roberts, that the animals' thyroid glands took up and concentrated radioiodine (27). His work was roughly contemporary with that of the Massachusetts group, whose work Leblond referred to when his report finally appeared in 1940. But by then Europe was embroiled in the Second World War and Leblond had moved to Montreal to teach anatomy; his research continued to focus on animals and he did not study human disease.

RADIOIODINE AS A TREATMENT FOR HYPERTHYROIDISM

The initial use

Back on the East Coast in 1939 and 1940, the MGH-MIT team continued working with rabbits although their goal still was the treatment of hyperthyroidism. Without their own cyclotron they still were dependent on others' cyclotrons for the longer-lived radioiodine isotopes such as ^{131}I; their focus remained on ^{128}I. Even so, Hertz and Roberts were able to show one reason why stable iodine, then used to treat mild human hyperthyroidism at MGH, might help such patients; they showed that stable iodine blocked some of the increased radioiodine uptake, i.e., slowed down thyroid function, known to occur in the TSH-stimulated rabbit thyroid (28).

The new MIT cyclotron finally started operating in September 1940. The first radioiodide made on September 26 was simply more of the ^{128}I; they gave the entire amount—1 μCi, or 20 times more than they had for their first experiment 3 years earlier—to a single rabbit for a physiologic study. Then on November 4 they gave a longer-lived radioiodine (probably mostly ^{131}I) to a woman with hyperthyroidism. Their intent was not to treat the disease (she was scheduled for surgery) but rather to study human iodine physiology. They counted the radioactivity over her thyroid gland and in her urine for a week before surgery and, with some assumptions, estimated that her thyroid gland took up about 80% of the administered dose of radioiodine. This was the first quantitative thyroid radioiodine uptake at MGH.

From late 1940 to early 1941, Hertz and Roberts used their cyclotron's radioiodine to study, but not treat, more patients with Graves' hyperthyroidism. Most of the radioiodine they used was ^{130}I, which has a half-life of 12 hours; when it was used within a few hours of production, about 10% of the cyclotron product was ^{131}I, with its 8-day half-life. At first, like Hamilton and Soley, they used the radioiodine as a tracer for a known amount of administered stable iodine, even though they knew from their rabbit work that the radioiodine taken up by the gland thereby would be lowered, but they learned rapidly. Soon they were able to calculate that in hyperthyroid Graves' disease the thyroid gland took up 80–90% of the radioiodine if the administered radioiodine solution contained less than 2 mg of stable iodine (they calculated the thyroid radioiodine uptake as the difference between the radioactivity given and that appearing in the urine over the next 2–3 days). All but 3 of this group of 22 patients received the then-standard treatment for hyperthyroidism, surgery (29). They also found that the thyroid glands of patients with Graves' eye disease, but with little or no clinical hyperthyroidism ("eye cases"), took up less radioiodine than did those of the usual patients with Graves' disease (30). They finished these two "diagnostic" or "tracer" studies in the first half of 1941; the data in the second study were presented at the annual meeting of the American Society for Clinical Investigation (ASCI) in May 1941. Roberts had to present the paper because Hertz had a flare-up of his ulcerative colitis. Neither paper appeared in print until early 1942, by which time the Second World War had started.

In these studies, Hertz and Roberts had studied only two normal persons, so there were no real controls. Still, the "thyroid uptake," that is, the difference in radioactivity between the collected urine and the dose given, became a standard test although for some years BMR remained the final judge of a patient's clinical status.

Hertz and Roberts first gave radioiodine with the intention to treat hyperthyroidism to a patient at MGH on March 31, 1941; they carried the radioactive iodine from MIT in Cambridge across the Charles River to MGH. The MIT cyclotron product contained mainly ^{130}I with about 10% ^{131}I; they calculated the amount of both ^{131}I and ^{130}I given to each patient but thought that ^{130}I was the better therapy because its radiation was delivered rapidly to the thyroid cells over a day or two. They never used ^{131}I as primary treatment as we do now because they considered its delivery of radiation over a week or two too slow. Their observation that more than two mg or so of stable iodine would lower the thyroid uptake of radioiodine—which in turn would have blunted the treatment effect—now paid off; as Roberts wrote in his notebook, the thyroid uptake of radioiodine in the first treated patient "show[ed] the importance of limiting tracer doses of iodine," that is, of avoiding large amounts of stable iodine (the "tracer dose" or the amount to be "traced") when giving the radioiodine.

They did not mention that they had begun to treat hyperthyroid patients with radioiodine in either of their two 1942 "tracer" papers or at Roberts' presentation in May 1941, probably because of prudent caution. They had no way to know how much radioiodine to give for effective therapy, nor did they know whether it would work at all; no one had done it before. What if the treatment did not work? Or if the doses were wrong?

The two co-workers continued to treat about one new patient per month for the rest of 1941 and so had treated eight hyperthyroid patients by the end of the year (a ninth was given radioiodine but "planned" surgery followed shortly afterward). They were careful to give only a little stable iodine with the radioiodine; none of the patients got more than 2 mg and six of the eight got less than 1 mg. The radioiodine was for them relatively "carrier-free." Five of the eight patients got divided doses of radioiodine over a week or two; the total estimated radioiodine given to each of the eight patients ranged from 1.5 to 6.2 mCi with an average of 3.9 mCi. In retrospect, it is hard to know exactly how much radioiodine the patients actually got. At the time, the accuracy of the measurement instruments was poor; the actual doses given may have been as much as twice the doses they calculated. Further, the unit of measurement itself, the curie, had not been standardized; their estimates are not directly comparable to our current curie (estimates of the curie then varied as much as fivefold among laboratories). Nevertheless, even by modern standards, most of their patients got a reasonably effective dose of radioiodine—the patients did in fact get better—and the records show that most of the radioiodine they gave was taken up by the patients' thyroid glands.

Another confounder was that Hertz gave each patient a fairly large amount of stable iodine beginning 1–3 days after the radioiodine. He did this at Means' insistence in order, as Means later put it, to "protect the patients against

the mischief from thyrotoxicosis [when a] treatment of unknown efficacy was being tried out. I insisted on it." (31) Hertz knew that the effective radiation from the ^{130}I was delivered to the thyroid cells in the first day or two and they did not start the stable iodine until 1–3 days after the radioiodine. He also thought that the stable iodine was a good idea because it might keep the radioiodine in the gland longer and enhance the local destructive ability of the beta radiation; still, he had no evidence for such an effect. Although they had demonstrated (by calculating the thyroid uptake) that most of the radioiodine got into their patients' thyroid glands, whether or not the stable iodine interfered with the destructive effect of the radioiodine was an important issue.

When the time came in February 1942 to write an abstract for the annual meeting of ASCI in May, all of the eight patients had been followed for at least 3 months (two more were treated before the meeting but had not been followed long enough to be sure of their outcome). There are no extant data that show the clinical status of these eight patients when Hertz wrote the abstract nor is there a copy of the text he presented at the meeting itself. He wrote in the abstract that there were both "failures and successes" but did not say then what he meant by success. Later evidence indicates that a success was a patient who [1] received radioiodine followed by stable iodine, [2] got better clinically and by BMR, and [3] still had a normal BMR at least 3 or 4 months after the stable iodine was stopped. Later, at the end of 1942, Hertz judged five of these first patients as "cured" and two as "improved" but still taking stable iodine. One had gone to surgery within 2 weeks of the radioiodine so its effect was unclear. Of interest to the modern reader is that two of these eight patients were 9-year-old girls. Hertz sent off the abstract with Roberts as the sole coauthor (32).

Meanwhile, in California, the Berkeley group, who readily acknowledged Hertz's priority on the radioiodine treatment of hyperthyroidism (33), was not idle. Hamilton, now working with John Lawrence, finally began to treat a few patients with hyperthyroidism beginning on October 12, 1941. Some of their delay probably occurred because they first wanted to show that animals' thyroid glands could in fact be destroyed with radioiodine (34). By late winter, two of their three hyperthyroid patients were in "complete clinical remission"; the third got better after a second dose of radioiodine. Hamilton, too, sent in an abstract for presentation at the same May 1942 ASCI meeting (35).

Both Hertz's and Hamilton's abstracts were presented at the May meeting. These were 2 of only 44 papers presented and it does not appear that they had much impact. Nevertheless, these were the first public reports of the successful treatment of hyperthyroidism with radioiodine. The principal difference between the two reports was not whether the therapy worked; both reported that it did. Rather, the difference was that Hertz was an enthusiast, immediately convinced of the therapy's utility despite possible unknown hazards, such as a possible carcinogenic effect, that were of concern to Means (now, 50 years later, we know that such an effect is highly unlikely). Hamilton was much more cautious and did not think that radioiodine should be used to treat hyperthyroidism until the long-term effects of this "potentially lethal agent" were well understood (34). Neither paper was presented to the logical audience, the American Association for the Study of Goiter (now the American Thyroid Association), for the simple reason that its annual meetings were canceled for the duration of the war. The Association did not meet again until 1946.

The war years

The war slowed down all clinical investigation not clearly related to the war itself. When the United States entered the Second World War in late 1941, Hamilton stayed at Berkeley but worked full-time for the Manhattan District on plutonium and fission products. Soley left for Iowa where he later became dean of the university's medical school. Roberts stayed in Cambridge, Massachusetts, but in May 1942 shifted his work from radioiodine to radar and moved to the Radiation Laboratory ("Rad Lab") for the duration of the war at twice the salary; his work with Hertz was over and he never returned to the thyroid gland. Hertz had volunteered for the U.S. Navy in 1940, before the United States had come into the war and before he had treated any hyperthyroid patients, but had been turned down for physical reasons.

During the rest of 1942 Hertz continued to treat hyperthyroid patients with radioiodine (^{130}I) from the MIT cyclotron, generally with larger doses than he had used before. Most of the patients were treated at MGH. As agreed with Means in 1939, Hertz's term as the full-time director of the Metabolism Laboratory was over in mid-1942 and he was to leave. Nevertheless, Means, rather than letting Hertz go entirely and keeping him only on the voluntary staff, as he had Chapman in 1934 (see below), kept Hertz on and provided him with a partial salary, mostly from funds provided by the Markle Foundation, which still supported the research on the radioiodine treatment of hyperthyroidism. Hertz now spent half his time at MGH on the radioiodine project and the other half in his newly opened Boston office in private practice. Means put Rulon Rawson, who had joined his group in 1941, in charge of the Thyroid Clinic.

By early January 1943, Hertz had expanded his series of 7 hyperthyroid patients treated with radioiodine without surgery to 19 patients; all had follow-up treatment with stable iodine that was later stopped (2 more treated patients were called eye cases—possibly Hertz wanted to try to treat the exophthalmos with radioiodine). In the project's regular report to the Markle Foundation in January 1943 (officially submitted by Evans but written largely by Hertz), they said that 10 of these 19 patients were "cured" and 9 either were "improved" or were treated too recently to tell; these nine were still taking stable iodine at the time of the report. At least two patients, who had received 3 mCi and 4 mCi of ^{130}I, respectively, were euthyroid without relapse of hyperthyroidism more than a year after the stable iodine had been stopped, which must have augured well that other patients would do the same. The therapy seemed on the way to a clear success.

Then, although his private practice had been open for less than a year, in early 1943 Hertz, now 38 years old and married with one daughter, abruptly decided to volunteer for the U.S. Navy as a medical officer. This time, more than a year into actual war, the navy accepted him.

He went on active duty in April; his four brothers were already on active duty (one, Roy, later became a well-known scientist at the National Institutes of Health). Hertz's volunteering for the military was probably due to a mixture of patriotism, problems with colleagues in the Thyroid Unit (he and Rawson did not get along at all), and a desire to be able to continue as a clinical investigator (the Markle Foundation grant was to end in June and he hoped for a "billet in research" in the military). Unrelated to Hertz's decision to leave, there was also some unpleasantness just before he left for the navy. Its nature is now unclear, but Hertz, writing to Means in June from Pensacola, Florida, alluded to the "incident . . . at MIT" in mid-April when he "turned his cheek" after "it was badly slapped," admitted that he was "a bit of prima donna," and thought that he "had fallen from grace." Other sketchy evidence suggests that Means may have turned down Hertz's request for an academic promotion.

In a rush to add more patients to his series before he left for the navy, Hertz treated eight more new hyperthyroid patients in 5 weeks during March and April 1943 after having treated none in the previous 3 months. He now had a total of 27 patients treated with radioiodine without surgery. He discussed the project's status with Means before he left (but did not tell Means when he was leaving); Means' notes show that Hertz thought that the dose of radioiodine for hyperthyroid patients should be larger (12–15 mCi), that a second dose should be tried before offering surgery to a patient not cured by the first dose, and that stable iodine should be stopped for a month before the second dose. Means agreed to "allocate" any new cases and "keep a close eye on them." Hertz asked Earle Chapman, who 7 years before had been present at the lecture by Compton, to take over the care and follow-up of Hertz's radioiodine-treated patients as well as the rest of his modest private practice. Chapman agreed.

Chapman had graduated from Johns Hopkins' medical school the same year that Hertz had graduated from Harvard's, had been a house officer on Means' medical service at MGH during Hertz's early years with Means (1931–1934), had held earlier the same Dalton Scholarship as Hertz, and had gone into private practice in 1934 because, although he wanted an academic position, there were none to be had at MGH or anywhere else in Boston and he did not want to leave the city (he turned down an academic offer from Beirut, Lebanon, because he would have had to pay his own way there). Chapman was interested in thyroid diseases, had occasionally helped Hertz in the thyroid clinic, and was a regular attendee at the MGH thyroid unit's weekly conference where he "never passed an opportunity to engage in argument." (36) Active and vigorous, he devoted much time to teaching and patient care at MGH while maintaining his practice, much of which was to the "carriage trade" in the Boston area. During his long career he was able to publish more than 80 papers based largely on clinical experience although he had almost no grant support. Hertz probably asked Chapman to take over the radioiodine project in part because they were colleagues and in part because Chapman was exempt from the military due to a peptic ulcer.

The timing of Hertz's departure for the navy was a surprise to Means ("you quite took the wind out of my sails") although Means knew that Hertz would be leaving sooner or later. Means had wanted at least to say how much he appreciated Hertz and his work. On April 30, 1943, Means wrote Hertz, then in Pensacola, Florida, and asked for the manuscript—or, if not finished, the data—on the radioiodine treatment of Graves' disease; Evans also was eager both to get the data published and to be a co-auther. Means wanted the paper "in print at an early date" and, when Hertz had not answered by May 10, sent a telegram asking for an answer. A week later, Means wrote again to say that he would write up the data himself, based on the January 1943 report to the Markle Foundation, if Hertz did not reply. Finally, Means wrote again on June 1 and was quite angry. He considered Hertz's failure to answer, other than an uninformative postcard, "a piece of quite uncalled for rudeness" and that Hertz was "not only discourteous, but ungrateful." Hertz's long reply of June 4, 1943, smoothed things over, but one suspects that a bad tone was set. There is no question that in 1943 Means considered that radioiodine was an effective therapy for hyperthyroidism (although it was perhaps too early to tell just how effective), that he wanted the data published soon, and that he thought the four original investigators should be coauthors (he did not care whether he himself was a coauthor, because he felt he was "only . . . a well wisher"). From Hertz's reply it is clear that it was due to his reluctance that no paper then appeared ("I think it ill advised to rush into print without being quite sure of our ground."). Hertz's caution probably was justified—no one then knew whether the "cures" would be permanent or lead to eventual relapse—but in retrospect it was a missed opportunity; no paper appeared until 3 years later, in 1946, and then only after a complete break in the collaboration.

Even though Means knew that Hertz had asked Chapman to take over the radioiodine-treated patients, Chapman thought it best to check with Rawson. Rawson was not interested in radioiodine; years later, Chapman recalled that Rawson thought the project was a "waste of time." Chapman, ever forthright, disagreed (he said later that he told Rawson that "you can't tell me ionizing radiation doesn't do things to tissue") and took over the project, apparently without salary. Chapman understood that he was to follow Hertz's treated patients in a specific way; he wrote Hertz on May 25, 1943, "[Y]ou seem to have gotten into the Navy before I obtained the outline of the exact program you wanted followed. . . . However, I have tried to follow your verbal plan . . ." In Hertz's June 4 letter to Means, he said that he hoped that Chapman "will send me an up to date report on the RaI patients, so that I can include the latest information," probably thinking that he soon might write up the data. Means, writing to Hertz again on June 10, now agreed with Hertz that he would wait "until its value is established beyond doubt." He had been concerned about "the California and perhaps other competition" but felt that it was best "to wait now until Chapman has had all the cases back and we have evaluated their present status and sent you the results for study."

Within a month after Hertz's departure, Chapman decided on his own that it was impossible to tell whether any improvement in the radioiodine-treated patients was due to the radioiodine or to the stable iodine given afterward,

even though he knew that some of Hertz's patients remained well a full year after the stable iodine was stopped. Chapman wanted to start giving the radioiodine alone without the stable iodine. As one might expect, Means was strongly opposed to this omission. But Chapman vigorously overcame Means' resistance (Chapman later said that "the Professor was so mad at me" when "I said, look, Dr. Means, you'll never find out what the hell radioiodine will do if you keep on giving them potassium iodide"). He treated his first patient with radioiodine alone, using radioiodine obtained from Evans at MIT, on May 18, 1943. Chapman wrote Hertz that he had treated another patient with radioiodine, that is, one more in addition to Hertz's own series ("the clinic wanted it"), but did not say that he was omitting the follow-up stable iodine. Somewhat ingenuously, he wrote instead, "I think we will have to try the effect of RAI alone without using ordinary iodine if we are going to evaluate properly the role of radiation." The letter was friendly and supportive. In retrospect, it can be read as subtly telling Hertz that he, Chapman, was starting another series of his own radioiodine-treated patients. But at the time it justifiably would have led Hertz to believe that Chapman was continuing his, Hertz's, project.

Chapman wrote Hertz again 6 months later on December 8, 1943, to tell him how Hertz's patients were doing; Chapman said that he personally had seen all but five and discussed all of them with Means. He did not provide Hertz with any data but wrote that one of those listed as "cured" in the Markle report 11 months earlier had become thyrotoxic and had a thyroidectomy; three others listed in the report as still taking stable iodine also came to thyroidectomy because of hyperthyroidism. There are no data on how long it took the apparent relapses to occur after the stable iodine was stopped in these four patients. Whether these four actually were hyperthyroid is now uncertain at best; Chapman wrote further that they all had been evaluated by the other members of the Thyroid Unit and found to be hyperthyroid, but the later published data show that these patients all had a normal BMR before surgery (Hertz did not know this until much later). In his letter, Chapman also questioned Hertz's original diagnosis of hyperthyroidism in four others. He also brought Hertz up to date on his (Chapman's) use of radioiodine without stable iodine: "It seemed to us that . . . we could go one step further and observe the effect of radioactive iodine alone and in even higher doses. This I have done in six cases. . . . I hope we can continue your good work." Two weeks later, Hertz wrote Means that he had "received a good letter from Earle Chapman." Far from being offended by Chapman's omission of stable iodine and questioning his diagnoses, Hertz wrote: "I am glad that he is able to carry on and that he has done what appeared to us to be the logical thing of trying bigger doses and solo treatment with radioactive iodine. . . . I am glad we did not publish the cases to date and do foresee a really solid publication." Means replied to Hertz a week later that he was "glad you liked Chapman's report. . . . I am sure his desire is to carry on the way you would wish." Means again wrote Hertz 2 months later on February 25, 1944, "Chapman is really going to town with your radio iodine program" [by then Chapman had treated nine patients].

It is clear that, at the end of 1943 and in early 1944, despite Chapman's critique of Hertz's diagnoses and his sending of some of Hertz's patients to surgery rather than giving them another dose of radioiodine, Hertz did not disagree with Chapman's approach of omitting the stable iodine or using larger doses of radioiodine. It is equally clear that, based on Means' letters, Hertz had good reason to think of himself as still a member of the team and to consider Chapman's work as an extension of his own.

But all was not well. Before Hertz left, several members of the thyroid group, including Means, Rawson, and Hertz, had drafted another manuscript on the thyroid effect of thiocyanate that Means wanted in print. Means already had sent it to the *Annals of Internal Medicine* and sent it to Hertz in the late spring of 1943 for comment. Hertz criticized it harshly, saying that it was "repetitious and wordy," that it tried to fit facts to a preconceived theory, and that the diagnosis in one of the patients was clearly wrong. Once again, Means was offended: he wrote Hertz that he, Means, had written most of it, that the theory came after the facts rather than before, and that there was no question about the correctness of the diagnosis. Means also noted that the editor of the *Annals* also had liked it and suggested no revisions. This, too, was smoothed over in later correspondence, but Means' irritation was clear (he wrote to Evans that "this time he [Hertz] makes some positive suggestions instead of negative ones").

In the navy, Hertz was quite busy taking care of patients; he did not get a billet in research. The navy moved him several times: he went from Florida to Louisiana and then to the Naval Convalescent Hospital in Springfield, Massachusetts, where he was chief of medicine; he also had a recurrence of his colitis but remained on active duty. He visited the MGH Thyroid Clinic at least once in mid-1944. He wrote Means in November 1944 that he had been neglecting his MGH colleagues because of his workload and correspondence. He had not heard from Chapman "of late" and asked, [H]as Earl [sic] done any more cases or is thiouracil so good that Ra-I is by the board?" Edwin B. ["Ted"] Astwood [1909–1976] had published his landmark paper on the treatment of hyperthyroidism with antithyroid drugs on May 8, 1943 [37]). Hertz wondered where Means thought "Ra-I fit into the scheme of therapy in ex[ophthalmic] g[oiter] now?" Means replied that Chapman was "somewhat enthusiastic about the radio-iodine treatment and . . . I am sure he will tell you all about it when you meet him, or would if you dropped him a line." Thus, at the end of 1944, Hertz had not kept in close touch with Means or Chapman, knew neither what Chapman was doing nor the status of his own patients treated with radioiodine more than a year before, and was somewhat unsure of the place of radioiodine in the therapy of hyperthyroidism.

Sometime in the first part of 1945, with the war winding down, Hertz was transferred to the Chelsea Naval Hospital near Boston; he was able to live at his home in Brookline, Massachusetts, and occasionally attend the thyroid conferences at MGH. What his working relationships were then with his former MGH colleagues is unclear, nor is it known just what he now knew about either his own or Chapman's radioiodine-treated patients. The likelihood is that he assumed, as before, that the radioiodine project was still his or, at least, that he had a principal role. When

the war ended in mid-1945, Hertz stayed in the Navy and continued to live at home; he was not discharged from active duty until June 1946.

The JAMA *papers*

When the war finally ended in August 1945, there was a surge of interest in the peaceful uses of atomic energy as the country moved from war to peace, in part to counteract the awful images of the destruction brought about by the atomic bombs. The Manhattan District that developed the bomb, and its successor the Atomic Energy Commission began to promote the scientific and medical uses of radioisotopes and, for a time, there was a public perception that there soon would be a wealth of new treatments for a wide range of diseases. The use of radioiodine, the "atomic cocktail," for the diagnosis and treatment of thyroid diseases would fit right in because the radioiodine used after 1946, ^{131}I, was a by-product of the Manhattan District's work. Of course, the development of radioiodine as a test and a treatment had nothing to do with the atomic bomb, because all of that work preceded the bomb.

In the fall of 1945, probably in November, Hertz found to his dismay that Chapman and Evans had written up their own patients, treated with radioiodine but without stable iodine, as a separate series from Hertz's and had submitted the paper to *JAMA* without his knowledge. While Chapman's patients were in fact a separate group treated with a slightly different therapy, Chapman knew, of course, that Hertz was the first to use the therapy, that it was effective in at least some of Hertz's patients, and that Hertz had not yet written up his own patients while he was in the military. As far as we know, Hertz had had no further reports from Chapman since December 1943, almost 2 years before, nor is there evidence of further discussion between Hertz and Means about a publication. Equally, for that matter, there is no evidence that Hertz himself had followed up his own patients, up to the end of 1945 after he returned to the Boston area or that he had inquired after them in his occasional visits to MGH. We do not know what else, if anything, was going on behind the scene, but Hertz's discovery of Chapman's manuscript led to a major blowup and a complete breakdown of the relationship between Hertz and his colleagues that was never healed. This one was not smoothed over; perhaps the smoldering interpersonal irritations had come home to roost.

In November 1945, Hertz demanded a copy of Chapman's draft, which had been rejected by *JAMA* as too lengthy. Chapman sent Hertz the 61-page manuscript by mail—with 24 cents postage due. Hertz only now realized that his four patients, who had been sent to surgery by Chapman because they still had active hyperthyroidism, were not particularly hyperthyroid at the time of surgery because they all had normal BMR values. It is entirely possible that by the time of surgery the radioiodine treatment had cured the hyperthyroidism. Hertz also found that there were few notes on his patients by Chapman since Chapman's last detailed letter 2 years before; Hertz clearly felt that Chapman had done a poor job of following them and that he, Hertz, had to recall most of them to determine their thyroid status and complete his study (which he then did). Much acrimony then ensued between Hertz and Chapman. Chapman felt that what or when he wrote was no business of Hertz's. Hertz felt betrayed and thought that Chapman had made a "sneak attack" and engaged in "downright thievery." Hertz sharply criticized—to both Means and Chapman—not only Chapman's handling of his, Hertz's, patients but also Chapman's treatment of his own patients. Hertz now strongly objected to the use of radioiodine without stable iodine and to the larger doses of radioiodine that Chapman used; he seems to have forgotten that he thought both were good ideas 2 years before. Means tried to act as a mediator between Hertz and Chapman; he wanted the two to get together and work things out, apparently with the thought that the two might combine their work into a single paper. Hertz and Chapman met once or twice but the two never agreed. Their letters to each other now opened with "Dear Dr. Chapman" and "Dear Dr. Hertz" instead of the formerly friendly "Dear Earle" and "Dear Saul."

There were also some unpleasant meetings between Hertz and Means. Hertz seemingly never realized the cumulative effect of his periodic blowups on Means; even Hertz himself mentioned that a meeting with Means in late 1945 was characterized by "the violence of my personal and emotional reaction," however justified he felt. Means, who was responsible for running a department and getting his program back on a peacetime footing, could not tolerate the disruption. By January 1946, whatever the details, Means felt that Hertz "had so successfully antagonized my present colleagues, that it will be quite impossible for me to receive him back as a member of my thyroid clinic" and decided not to renew Hertz's appointment when he was discharged from the navy. He did, however, support Hertz's appointment at Boston's Beth Israel Hospital where Hertz for a time continued to use radioiodine. Means also, somewhat belatedly (February 1946), felt Hertz was justified in wanting to "get . . . in the print at a date line ahead of Chapman."

We still do not know why Chapman did not give Hertz's patients with apparent recurrent hyperthyroidism more radioiodine as Means and Hertz had discussed in early 1943. We do not know why Means agreed to Chapman's separate paper in 1945, if he did. Chapman clearly showed that stable iodine was not necessary for successful radioiodine treatment, but, on the other hand, it was equally clear by then that Hertz's original method also led to success. Nor do we really know why the former colleagues did not simply agree to continue the original collaboration and work together on the publication of what was, after all, a new therapy developed jointly by the MGH Thyroid Unit and MIT. All we know is that they did not, whatever we might surmise about ambition, abrasive personalities, or the stress of wartime; by January 1946, the collaboration had collapsed.

In the midst of this unpleasantness, Hertz quickly completed the follow-up of his patients in January and February of 1946 and wrote his manuscript; he hoped to get Means to agree to be a coauthor but that did not happen. Though Roberts was a coauthor, Roberts recalls that he had little to do with the paper and did not see it until after it was completed. It went through several drafts, which are still extant, sometimes with Means' name added and

sometimes not. Chapman shortened and resubmitted his own manuscript to *JAMA*, as suggested by Morris Fishbein, the editor. Hertz probably sent his manuscript to the journal *Endocrinology*, but, when he realized that Chapman's was going back to *JAMA*, Hertz withdrew his paper from *Endocrinology* (because it would take longer to appear in print) and sent it to *JAMA* as well on March 12. Neither Chapman nor Means knew this until later; at the time, Means still was trying to get Hertz and Chapman to resolve their differences. Means still was quite irritated (he wrote Hertz on March 18 that the "implications that Chapman is stealing your stuff strikes me as nonsense"); Means' pique was not improved when he learned that Hertz had submitted his paper "from the Thyroid clinic," that is, Means' department, without letting Means study it.

Thus, in March of 1946, completely independently of each other, two different manuscripts went to *JAMA* on the use of radioiodine to treat hyperthyroidism, one by Hertz and Roberts and one by Chapman and Evans. One can imagine Fishbein's confusion when he had in hand the two manuscripts; they described the same new treatment for the same disease and came from the same institution but had completely different authors. Fishbein was not only the editor of *JAMA* but a powerful figure in American medical politics. He discreetly wrote to Means on March 20, 1946, at Means' home address on Boston's Beacon Hill, to inquire politely about "the actual status of this situation."

Means wrote back, reassured Fishbein that the two manuscripts described entirely different patients, and said that in his opinion the therapy was "very promising" but that "any final evaluation ... is quite impossible." Fishbein replied that he would print both papers in the same issue of *JAMA* and offered to pay Means the "usual space rates" if Means would write an editorial. The papers (1,2) appeared in the issue of May 11, 1946, along with Means' unsigned editorial (38), in which he was cautiously optimistic ("Whether or not it will prove superior ... cannot be foretold now.... The late development of cancer ... although perhaps unlikely, is certainly within the realm of possibility."). It was hardly a coincidence that Fishbein included a short article by Karl Compton on the contributions of science to medicine as a prelude to the two papers on radioiodine treatment (39). So it happened that most of the actors present at the luncheon 10 years before in 1936—Hertz, Means, Chapman, and Compton—were now in print in the same issue of *JAMA*; the two papers can be seen as symbols of the peacetime use of radioactivity and probably were taken as such at the time.

Both papers found the treatment successful. Hertz, the first to treat anyone with radioiodine, had given radioiodine to 31 patients. His paper included 29 of these (he omitted two of the "eye cases"); he carefully did not call a success the remaining eye case or any case of a patient who had had a thyroidectomy ($n = 7$). Twenty of the remaining 21 patients were successes; all had stopped taking stable iodine for months or years and still had a normal BMR. The length of his patients' follow-up was excellent and was important evidence of success; none had relapsed. In the long run the added stable iodine had had little, if any, effect, probably because most of the radiation of the thyroid cells from the ^{130}I occurred in the first day or two. A few patients might have improved spontaneously while taking the stable iodine, begun 1–3 days after the radioiodine, but it is highly unlikely that this happened in all of Hertz's successes. Chapman had essentially the same results in 22 patients except that he used larger doses of radioiodine, produced radiation thyroiditis in many and hypothyroidism in four, and had a shorter follow-up. Hertz also mentioned that radioiodine "is produced in enormous quantities in nuclear-reacting piles. When ... readily available, this form of treatment may well prove ... effective, safe and noninjurious but also cheap."

The evidence was clear. There was now an effective radioactive treatment for hyperthyroidism despite the untoward results of a combination of ambition on the one hand and absence due to war on the other. The success occurred at the expense of the claim of academic theft, the poisoning of personal relationships, and bitter clashes among former friends and colleagues. Means' concern in 1943 that others might get into print first turned out not to be an issue; we doubt he ever imagined the problems that did arise.

AFTERMATH

After the war the Manhattan Project connected with medicine in a substantial way. Only a month after Hertz's and Chapman's papers appeared, the journal *Science* announced on June 14, 1946, the availability and distribution on request of a wide range of radioisotopes for scientific purposes (40). One was ^{131}I. After Oak Ridge started distributing ^{131}I in August 1946, no one used ^{130}I anymore because ^{131}I was so cheap ($1.70 per mCi); over the 3 years from 1946 to 1949 there were several thousand shipments of ^{131}I.

A week after the Manhattan Project announcement, the American Association for the Study of Goiter resumed its annual meeting that had been suspended for the 4 years of the war. Although 214 physicians attended, only 22 papers were presented. Three of these were on treatments of hyperthyroidism developed during the war years. Two were papers by Hertz (41) and Chapman (42) that were almost the same as those that had appeared in *JAMA* just the month before. At the meeting, radioiodine treatment was not seen as an overwhelming success and there was not much recorded discussion after the two talks; Hertz did say that he thought Chapman's doses of radioiodine were too high, and both he and Chapman still thought ^{130}I was the best isotope to use. Perhaps the lack of expressed enthusiasm was because Astwood gave the third talk on a nonsurgical treatment of hyperthyroidism. He brought the Association up to date on the use of antithyroid drugs as an effective therapy for hyperthyroidism (43); between 1943 and 1946 these agents had been used successfully in hundreds of patients, though not without some problems. Means himself said during the discussion that "treatment with radioiodine looks very promising ... but we cannot evaluate that form of therapy with any degree of accuracy yet. The data on antithyroid drugs are much greater and very impressive." (44) Mean did change his mind a few years later ("I am convinced that it [radioiodine] can now be said to be the best agent for treating exophthalmic goiter") (45) but by then Hertz was dead.

Of the four coauthors of the two *JAMA* articles, all lived long except Hertz, who died of carbon monoxide poisoning in 1950. Chapman died on Cape Cod in 1990 at age 87 and Evans lived even longer, dying at age 88 in 1995. Roberts is still alive in 1996 at 84 years of age and splits his time between Illinois and Hawaii, depending on the season.

In the long view, the development of radioiodine therapy for hyperthyroidism is an example of an idea that hesitantly but successfully built on other ideas, linked different sciences, and came to fruition. The collaboration between physics and medicine, uncommon at the time, was a success, even a triumph. The therapy now is well established worldwide. It is the preferred therapy in the United States although the antithyroid drugs are used more often elsewhere; few patients have surgery for hyperthyroidism. But science and medicine are not simply abstractions; they are human activities. In the early stages, the usefulness of the then-new radioiodine in elucidating thyroid physiology would not have emerged without the cooperation of disparate scientists around the country. The war, that nadir of human relations, certainly got in the way, but we doubt that the development of radioiodine as a therapy had to happen the way it did. Were the personal friction, pain, and aggravation necessary? The story suggests that the opposite is likely, that the therapy might have been defined better and sooner had the early spirit of collaboration persisted. Could not we learn from this episode to seek our goals more peaceably? As Llewellys Barker, then probably North America's most prominent internist, said in 1923 of the discovery of insulin, there is "glory enough for all." (46)

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