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Discoverers of Thyroid Landmarks

Jean-François Coindet
Caleb H. Parry
Robert J. Graves
Adolphe Chatin
William W. Gull
George R. Murray
Edward C. Kendall
David Marine
Charles R. Harington
Saul Hertz
Edwin B. Astwood

Jean-François Coindet (1774-1834)

and the Treatment of Goiter with Iodine

Jean-François Coindet was the first to realize that iodine could be a successful treatment for goiter. Iodine had just been discovered a few years before the publication in 1820 of his lecture that startled his Genevan colleagues. For some centuries, seaweed and burnt sea-sponge had been well-used folk medicines to treat goiter. Coindet suspected that, because of the way that iodine had been discovered as a residue of extracted seaweed, iodine itself might be the active ingredient in burnt sponge that affected goiter. He tried it and it worked.

Coindet was a native Genevan who went to Edinburgh, then a mecca for medical training, for his MD and returned to Geneva in 1799 to begin his medical practice. He was quite successful and even at one point represented Geneva in the Swiss confederation. Goiter was particularly well-known in many areas of Switzerland although the cause was obscure. When Coindet thought that iodine might be good for goiter, he had a sample of sea sponge tested just to be sure it contained iodine: it did. So he abandoned the use of natural products and used iodine directly. His paper was picked up all around Europe, including an English translation in a London medical journal, and the treatment was tried equally widely. The treatment was reasonably successful when used as Coindet had directed.

As is so often the case, human nature leads many to try something different rather than to follow directions. In his own hands, Coindet's therapy worked well in most, though not all, patients. the goiters usually either disappeared or got a great deal smaller. But, as one did not need a prescription to buy iodine, some Genevans reasoned that, if a little was good, a lot would be even better. A few took to wearing small flasks of iodine hung around their necks and sipped a bit whenever the urge struck them. The result, to Coindet's chagrin, was that some of these Genevans lost weight, developed palpitations and tremor, and had a sustained increase in appetite. So iodine got a bad reputation and was seen as toxic. Coindet reported these unusual outcomes the next year, 1821, and its use as a goiter therapy dropped off markedly. We now realize that what Coindet had seen was iodine-induced hyperthyroidism which could reasonably be named "Coindet's disease."

Iodine was used for other diseases, such as syphilis, and Coindet, of course, knew nothing about iodine deficiency or hyperthyroidism; neither concept was established until many decades had passed. But he had found a medical therapy for goiter, shown a medical use for this new element, and set the stage for later discoveries about iodine and the thyroid. The citizens of Geneva may have found iodine too much of a good thing but that does not mean it is not actually a good thing; when all else fails, read the directions!

Saul Hertz (1905-1950)

and the Treatment of Hyperthyroidism with Radioiodine

Saul Hertz was a bright, ambitious student. Born and raised in Cleveland, he went to relatively nearby Ann Arbor for his undergraduate work at the University of Michigan and then chose to further afield for his medical degree at Harvard which he received in 1929. After his internship and residency back in Cleveland, he returned to the Boston area in 1931 to take up further training at the Massachusetts General Hospital (MGH) under the nationally known professor of medicine, J. Howard Means. Means' forte was in thyroid function and disease and he had set up a thyroid clinic at the hospital. Hertz was so eager to be in this milieu that he agreed (and was able to) work without a salary. He did enough so that Means arranged for a fellowship with a modest salary after only three months. As there were no full-time positions of any sort at that time in the depths of the Great Depression, Means was able to keep Hertz on with periodic reappointments of two- to three-year terms. In 1934, Means named Hertz as the Director of the Thyroid Clinic, which in reality meant that he was in charge of the room where the basal metabolism tests were done. Hertz worked away at a number of projects as well as seeing patients with thyroid disease. He also was able to do fairly crude (at least to us today) bioassays. For example, with a bioassay based on thyroid histology, he and his colleagues were able to show that the urine of hypothyroid patients had something in it that stimulated the thyroid gland (note that thyrotropin or TSH had barely been recognized i the mid-1930s and it was not yet clear that it was in fact a separate hormone).

In 1939, Hertz attended a lecture with Means and two other colleagues from the Thyroid Clinic; the speaker was Karl Compton, the president of the Massachusetts Institute of Technology (MIT) and a practicing physicist. The talk mentioned a curious new idea: that one could artificially make radioactive isotopes of common elements. Hertz and Means wondered if there was such an isotope for iodine. the idea was clear: if there were such an isotope, one could do all sorts of studies on thyroid function that would be impossible otherwise. One might even be able to destroy by radiation enough of the thyroid gland in hyperthyroid patients to render them euthyroid. Compton was not sure of the answer but a few days later he wrote Hertz that it would indeed be possible to make radioiodine.

Hertz and his co-workers began with a home-made iodine radioisotope (128-I) with such a short half-life (25 minutes) that experiments had to be done on the spot. First they did several studies in rabbits and showed that the thyroid gland took up the radioiodine avidly, that the rabbit thyroid took up even more of the radioiodine if TSH were injected first. But how cold they use this isotope to treat hyperthyroid patients? The isotope lasted such a short time that there was no prospect of treating anyone.

The cyclotron had just been invented a few years before and was already being used to generate new isotopes. By 1940, Hertz and co-workers had two new radioiodine isotopes with much longer

half-lives: 130-I (12.5 hr half-life) and 131-I (8 day half-life). For a while they continued to do physiologic studies but now in man instead of rabbits, including some with Graves' disease. these last, as expected, had high thyroid uptake of the radioiodine. Finally, in early 1941, they began to treat hyperthyroid patients with radioiodine. It was then a major gamble, however obvious it may seem today. They had no way of knowing if the new therapy would work. They also had no idea how much to give but rather simply picked an arbitrary dose that more or less mimicked what they knew was taken up by the patients' thyroid glands. Although now it is hard to know exactly what they used as a dose, the average dose was probably about 4 mCi. they treated about one patient per month and had enough information to present their data to the annual meeting of the American Society for Clinical Investigation in May, 1942. Some patients had not recovered entirely but the majority had clearly improved. They had shown a new and nonsurgical treatment for hyperthyroidism.

Hertz continued with the work but in 1943 left to join the US Navy then, as was the rest of the United States, completely caught up in the Second World War. When he returned to Boston in 1945, still i the Navy, he was able to follow up his treated patients and write his classic paper on the radioiodine treatment of hyperthyroidism in 1946.

By this time, he was not alone: others at the MGH had treated hyperthyroidism with radioiodine while Hertz was away in the Navy and published simultaneously with him. Hertz unfortunately became embroiled in several personality conflicts and had to leave the MGH. He died at a tragically young age in 1945. His legacy is, however, clear: he was the principal author of a new and successful treatment for hyperthyroidism.

Edward C. Kendall (1886-1972)

and the Discovery of Thyroxin(e)

On Christmas Day, 1914, Edward C. Kendall saw crystals through his microscope. He was elated because at long last he had been able to purify and isolate the substance he had been seeking for over four years with no assurance that he would ever succeed: the active principle of the thyroid gland. He and his colleague named it “thyroxin.”

At the time, endocrinology was in its infancy, at least insofar as understanding what these mysterious substances called “hormones” really were. Kendall had not started out to find any hormone. He had gotten his PhD from Columbia University just a few years before in 1910 at the age of 24 years. His topic was pancreatic enzymes and he knew nothing about the thyroid gland, not even that it contained iodine. But his first job was not in academia; rather, he found work in industry and his assigned task was to work on the isolation of thyroid hormone. He rapidly became disenchanted with industry with its time-clock mentality and moved back to New York City to work in a hospital. Still, he had adopted the task of finding the thyroid’s hormone as worthy of pursuit. But the medically-oriented staff at the hospital saw no need for the isolation of this hormone. After all, what use would it be? There already was an effective therapy for hypothyroidism, so what was the point? That attitude did not endear itself to Kendall’s mind and he sought employment elsewhere. He tried the Rockefeller Institute but they did not accept him. Then, a chance encounter in Missouri where he was attending a meeting resulted in an offer to work at the Mayo Clinic in Rochester, Minnesota. He accepted and moved to Rochester where he remained for the rest of his active career. More importantly, the Clinic, then a world-renowned center for thyroid surgery, actively wanted him to pursue the very topic he wanted: the isolation of the thyroid hormone.

Now, he had to produce. He was a PhD, not a physician. He was 27 years old. While he had had some success with isolating certain active fractions of various thyroid extracts, clearly none were anything like a pure preparation. He decided that, rather than follow his fractionation by assaying biologic activities of the fractions, he would do occasional bioassays but mainly use the iodine content of a fraction as a parameter of thyroid hormone activity. While in retrospect this is obvious to us, for him at the time it was a major gamble. If he guessed wrong, all would be for naught. In fact, he made reasonable progress but not as much as he would have liked. By December of 1914, near the end of his first year at the Clinic, he was still frustrated. He was also worried because he had submitted an abstract to the fledgling American Society for Biological Chemistry (ASBC) which in those years met over the Christmas holiday so as not to interfere with teaching schedules (not much of a worry today!). So the real reason he was working on Christmas Day was not so much that he was intensely devoted to his work (which he was) but that he needed results to present in his paper at the meeting only a few days hence.

The week before Christmas, then, saw him in the laboratory trying to isolate thyroid fractions that had an increasingly higher iodine content. He had a preparation that contained 60 per cent iodine but it failed to crystallize and so was likely still impure. On December 23, he accidentally boiled off the

alcoholic solution he was working with and was left with an insoluble white crust. Clearly upset, he nevertheless assayed it for iodine and found, to his delight, that this crust had the highest iodine content of any preparation to date. Then on Christmas Day he was simply making his final crystallization and saw the sheaves of thyroxin crystals that so amazed the scientific and medical community over the next year. At age 28 years, his reputation was made and the Mayo Clinic was pleased that their investment in the young chemist had paid off so highly.

But was his reputation made? As it happened, he was unable to repeat his own isolation of crystals for the entire year, 1915. He solved the problem (it had to do with the metal lining of the large extraction vats used to hydrolyze the animal thyroid glands) but for that year he was anxious indeed. Then he attacked the problem of the substance's chemical structure. For various reasons, he became convinced that the hormone had an indole nucleus to which was attached three iodine atoms (in a curious way, his proposed structure was the first "T3"). In fact the name, "thyroxin," was derived from a contraction of "thyro-oxy-indol" and there was, of course, no terminal "e" at the end of the word. His fame spread, his proposed structure was widely adopted as correct, and the structural determination added further luster to his reputation. But try as he might, he could never get a synthetic molecule that had thyroid hormone activity. It had never really occurred to him that the structure might be wrong.

His reputation remained high into the 1920s. He was actually President of the ASBC in 1926, the same year that Charles Harington in London, England, did in fact not only find the correct structure but also managed to synthesize the hormone and demonstrate the biologic activity of the artificial material. Kendall was devastated: he later wrote, "the failure to synthesize thyroxin was a bitter disappointment." He also accepted Harington's addition of a terminal "e" to the name - thus, now "thyroxine" - so that the name was consistent with the names of other amino acid derivatives.

There is for us, however, no need to feel sorry for Kendall. He turned to another gland, the adrenal, in search of its hormone and, although he made errors and premature announcements here as well, he succeeded probably beyond his dreams (although one never really knows what others dream of) when in the late 1940s cortisone appeared to "cure" rheumatoid arthritis. He shared the Nobel Prize in 1950 with two others and had no need to worry about his reputation.

Edwin B. Astwood (1909-1976) and the

Treatment of Hyperthyroidism with Antithyroid Drugs

"Ted" Astwood did not come to endocrinology by a smooth and easy route but rather as a chance encounter for a mind seeking a challenge. When in 1943 he wrote about an entirely new treatment for hyperthyroidism, namely, medical therapy with drugs that blocked thyroid function, it had come about because his mind sought and found an explanation to a puzzle.

Ted grew up in Bermuda where his father supported the family well and supported Ted for some years into his career. His mother, enamored of the Seventh-Day Adventist (SDA) religion, directed Ted to an SDA college for his higher education. Thinking he would go into mathematics, Ted switched to medicine as his family saw mathematics as suitable for a life in banking and Ted thought otherwise. Still, his mother's sensibility again directed Ted to the only SDA medical school, the College of Medical Evangelists in Loma Linda, California. He lasted two years before his developing agnosticism led him away from California to Montreal where he finished his medical training at McGill University; he received his MD in 1934. He interned at Montreal's Royal Victoria Hospital; here is where he seems to have found endocrinology. He met there investigators such as Hans Selye and J. S. L. Browne and his life course was set.

Bright thought he was, Ted did not stay on at the Royal Vic for further training. He had had a run-in with the chief of the medical service, who was an author of one of the widely used textbooks of medicine at the time. On rounds, Ted was asked what he thought was the diagnosis in a patient; he made one. The chief carefully explained why that could not be right. Ted pursued it and found that he had in fact been correct. The next day's rounds brought a question from the chief and Ted quietly explained that his diagnosis had been correct. The chief went on to point out how it was not so important to get the right diagnosis but to come to a conclusion with a rational explanation even if it might be wrong. Ted thought otherwise (one of his characteristics) and left for Baltimore the next year. He really did not have a plan and was fortunate to land a position in surgical pathology. This was essentially a research position and he now got into endocrine research on his own, examining the hormonal control of the rat mammary gland and of changes in fish color. After two years, he had been recognized as an up-and-coming physician-investigator and won a Rockefeller Fellowship for three years of further training.

Now Ted moved to Cambridge, Massachusetts to work in Harvard's Biology Laboratories under Frederick Hisaw, the discoverer of relaxin and a powerhouse in the emerging field of pituitary hormone physiology. A PhD degree was forthcoming for Ted after only two years; Ted had invented assays for estrogen and for progesterone and had defined a new hormone that he called "luteotropin" that we now know is prolactin (prolactin had been recognized a few years before but Ted established its relevance to the hormonal support of the rat's corpus luteum). By now it was the depths of the great depression and he had to find a "real" job. He did so back in Baltimore in Johns Hopkins'

department of obstetrics, mainly as a researcher. He stayed only a bit over a year as the 29-year-old scientist-physician was then called to Boston to join the staff at the Peter Bent Brigham Hospital, one of Harvard's major teaching hospitals, with a joint appointment in the pharmacology department (the latter appointment was fortunate as there was literally no research space in the hospital). His major interest was in adrenal physiology.

But things were to turn in another direction. Sometime in 1941, he noticed a paper written from Johns Hopkins' nutrition department by old acquaintances, Cosmo and Julia Mackenzie. They had noticed that rats fed certain sulfa drugs developed goiter. Because of his knowledge of endocrine feedback loops, Ted quickly recognized that what was happening was that the rats' thyroid glands got larger because the sulfa drugs interfered with thyroid function and so stimulated the secretion of thyrotropin (TSH) which in turn made the thyroid gland grow. Ted proved this by giving the drugs to rats after their pituitaries were removed with the result that the thyroid glands now failed to grow: the goiter was pituitary-dependent. Further, as a physician, Ted saw the drugs' utility: if such a drug could be given to persons with hyperthyroidism, it might lower the excess thyroid function and cure the disease.

In 1942, then, Ted focused on thiourea and thiouracil as possible antithyroid agents. It was reassuring that, given to normal persons, these drugs did not seem to do much. But, initially at least, they seemed not to do much in patients with hyperthyroidism either. Then after a bit more experimentation, the approximately correct dose was defined and three patients with hyperthyroidism had a clear improvement in their disease; this result became his 1943 paper. There were difficulties. He and his colleagues had happened unwittingly to have picked drugs that had a fair number of side effects. But the answer was, for them, to push on. Ted had moved again in the mid-1940s to the Tufts-New England Medical Center and now his group tested literally hundreds of similar agents for antithyroid activity over the next several years; most of the drugs were supplied by one or another pharmaceutical firm. The result was the recognition of propylthiouracil and methimazole as effective treatments by the late 1940s. They remain to this day the only two antithyroid drugs available in the United States.

Ted went on to other work with his main focus being on the thyroid gland for most of the next 30 years. Honors came his way: the Lasker Award in 1954 and election to the National Academy of Sciences. But he held to the old school of physicians' behavior: he would never patent any of his discoveries. He retired early at age 62 years and died of cancer in 1976. He trained many in his unit; all remember their time with Ted as one of the high points of their lives.