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.