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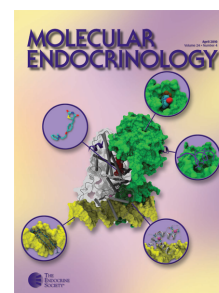
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Where You Go Depends on Where You Are Early Investigations on the Use of Deoxycorticosterone in Addison's Disease: A Historical Vignette

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Editorial: Where You Go Depends on Where You Are Early Investigations on the Use of Deoxycorticosterone in Addison's Disease: A Historical Vignette

Although "fortune favors the prepared mind," serendipity often tilts the scale. This is a story of serendipity favoring one over another prepared mind. It illustrates that how far one goes in one's professional career may depend not only on intellectual ability and preparation, but on being in the right place at the right time.

In 1935, a third-year medical student, Bernard E. Simon (class of 1936 at the College of Physicians & Surgeons of Columbia University) and a young member of the biochemical teaching staff, Lewis L. Engel (Ph.D., 1936, Columbia University), were peremptorily dismissed from the school by the Dean, Dr. Willard C. Rappleye, for participating in an antiwar organization. Simon applied to and was accepted at the Johns Hopkins School of Medicine for the Class of 1937. Engel went abroad for further post-doctoral training and enrolled with Leopold Ruzicka (personal communication from George L. Engel) at the Swiss Federal Institute of Technology in Zurich, Switzerland for the period of 1935–36. Ruzicka, as well as Tadeusz Reichstein, who was appointed his assistant in 1932, were students of Staudinger. All three were to receive the Nobel Prize independently. Engel subsequently spent the year 1936–37 with Cooke and Kennaway at the Research Institute of the Royal Cancer Hospital in London. Lewis Engel was the older brother of the twins, Frank L. and George L. Engel, medical students in the Class of 1938 at Hopkins.

In the late 1920s and early 1930s, interest in the adrenal cortex, its physiology, and diseases was intense. Adrenal cortical extracts of varying potency were prepared by Stewart and Rogoff (1), by Hartman, *et al.* (2), and by Swingle and Pfiffner (3), among others. They were all of relatively weak potency, although by means of their use, survival of the adrenalectomized animal was demonstrated and, indeed, Frank A. Hartman and his collaborators (4), Rowntree and his associates (5), and George A. Harrop *et al.* (6) were able to document beneficial effects of these extracts in patients with Addison's disease.

Meanwhile, attention was focused on the underlying physiologic function of the adrenal cortex, particularly in regard to sodium and water metabolism. Soddu (7) in 1898 had noted that the injections of sodium chloride increased the survival of adrenalectomized dogs by hours. Later, Lucas (8) and then Rogoff and Stewart (9) noted a decrease in the blood chloride following adrenalectomy. Baumann and Kurland (10) extended these observations to include sodium as well

as chloride. Marine and Baumann (11) and Rogoff and Stewart (12) confirmed the increased survival of the experimental adrenalectomized animal by the injection of Ringer's solution or sodium chloride. It was also noted that the serum sodium fell in the adrenalectomized animal.

It was on this background that Robert Loeb and his associates at Columbia (13, 14) reported that, in three subjects with Addison's disease, there was a decreased serum sodium content (13) and that in the dog, adrenalectomy was followed by a diuresis of sodium and a consequent fall in serum sodium (14). Subsequent to these observations, in March 1933, Loeb reported on a patient with Addison's disease (15) in whom the serum sodium was low and in whom a beneficial effect was demonstrated following the administration of sodium chloride. Somewhat later that year, in *The Journal of the American Medical Association (JAMA)*, Harrop, Weinstein, Soffer, and Trescher (16) reported on the diagnosis and treatment of Addison's disease, in which the efficacy of a high salt diet was promulgated, and the use of a low salt diet as a diagnostic test was suggested. Loeb's work was briefly cited, but his findings were not described in detail, nor was the significance of the Loeb report emphasized. "The tendency of patients with Addison's disease during the acute relapse to show hemoconcentration, reduction in plasma total base and chlorides, and rise in nonprotein nitrogen has been repeatedly observed by ourselves and has recently been reported by Loeb" (16). Thirty-nine days later, in the *JAMA*, a letter appeared, written by Harrop (17), in which he stated, "Credit for the conception of sodium deficit in suprarenal insufficiency and in Addison's disease belongs solely to Dr. Loeb. I greatly regret that the paper failed to give proper distinction to this work, which I regard as one of the most important contributions to the solution of the problem of suprarenal cortical function that has yet been made. . . . No analyses for sodium were made by us either for diagnosis or for therapeutic reasons until after Dr. Loeb's studies were completed" (17). Harrop continued his studies on electrolyte metabolism in adrenal cortical insufficiency at Hopkins, but little was added to the then current knowledge. On May 1, 1937 (18), Harrop left Hopkins, where he was Associate Professor of Medicine in charge of the Chemical Laboratory (Metabolism & Endocrinology), to join Squibb.

During this period, in 1929, George W. Thorn received his M.D. from Buffalo, where he had been working on studies on the adrenal cortex with his mentor, F.A. Hartman. Thorn spent a year as a house officer at Millard Fillmore Hospital and then went into private practice for three years. However, he continued to work with Hartman on the effect of cortin (the Hartman adrenal cortical preparation). In 1932, Hartman received the Gold Medal of The American Medical Associ-

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ation (presented with Greene, Maisel, and Thorn) for "original investigative work in the development and use of a hormone (cortin) from the adrenal cortex, and excellence of presentation" (19). In 1933, Thorn was offered a three-year fellowship sponsored by the Rockefeller Foundation, the first year of which he spent at the Massachusetts General Hospital (1934–35) and the second year (1935–36) as Assistant Professor of Physiology with Hartman at Ohio State, the institution to which Hartman had moved. During the tenure of his fellowship with Hartman at Ohio State, Thorn studied the effects of cortin on the renal excretion and balance of electrolytes. The third year, 1936–1937, Thorn spent at Johns Hopkins with Harrop. In 1937, Thorn (in an article introduced by G.A. Harrop) (20), independently reported on the effect of administered adrenal cortical hormone on the renal excretion of electrolytes in normal subjects and, together with Harrop (21), reported the effect of suprarenal cortical hormone upon the electrolyte excretion in the intact normal dog. As noted, Harrop left Hopkins on May 1, 1937.

In 1936, at about the time of Thorn's arrival at Hopkins, the Engel twins, Frank and George, learned that Warfield T. Longcope, the Chairman of Medicine at Hopkins, was looking for a steroid chemist. They informed their brother, Lewis, who contacted Longcope and informed him of his experience with Ruzicka and Reichstein and of his training at the Royal Cancer Hospital (personal communication from George L. Lewis). Longcope engaged Lewis Engel and, in 1937, he appeared at Hopkins.

B.E. Simon's recollection was that "George Harrop was in charge of endocrinology at Hopkins. He resigned to become Chief of the Squibb. A young man named George Thorn was placed temporarily, I think, in charge of endocrinology. Warfield T. Longcope, the Professor and Chairman of Medicine, advertised for a steroid biochemist to work with Dr. Thorn. The Engel twins heard of this and told Longcope that their brother was not only a steroid chemist, but had worked with two of the most outstanding groups in the world at the time. Lewis was asked to come to Hopkins as a biochemist for the endocrine group. As soon as he got to Baltimore, he looked me up and asked me to help him unpack in his new quarters. A large crate was delivered to his apartment. He got a claw hammer and pry bar and opened it. It was full of vials of compounds that had been synthesized in Reichstein's laboratory in Zurich. Among the compounds he showed me was one named deoxycorticosterone acetate. I was, therefore, the first one, beside Lewis, to have set eyes on this substance in the United States".

It was in 1937 that DeFremery, Laqueur, Reichstein, Spanhoff, and Ulydal (22) reported on the isolation of corticosterone from the adrenal and, shortly thereafter, Kendall, Mason, Hoehn, and McKenzie (23) reported on the isolation of the same compound. In that same year, Steiger and Reichstein (24) reported on the synthesis of deoxycorticosterone.

With Harrop no longer at Hopkins, Thorn, Engel, and Eisenberg (25) investigated and published in 1938 the effects of corticosterone and related compounds (*i.e.* deoxycorticosterone) on the renal excretion of electrolyte and then in 1939 (26) on the treatment of adrenal cortical insufficiency in the dog by means of subcutaneous pellets of deoxycorticosterone. The pellet technique had been adopted after the

method of Deanesly and Parkes (27, 28). In 1938, two years after his arrival at Hopkins as a Rockefeller Fellow, Thorn was appointed Associate Professor of Medicine to fill the vacancy caused by Harrop's departure. In 1941, Thorn, Engel, and Lewis (29) reported on the effects of 17-hydroxycorticosterone (cortisol) and related adrenal corticosteroids on sodium and chloride excretion (the deoxycorticosterone was now being obtained from Ciba and the 17-hydroxycorticosterone was obtained from Kendall, whose friendship Thorn had made years previously, when he was called to treat Dr. and Mrs. Kendall while acting as a camp physician) (30). Concomitantly, Thorn and his clinical colleagues, Howard, Emerson, and Firor (31), reported in 1939 on the use of deoxycorticosterone, both in oil and with pellets in the treatment of Addison's disease. For their work they received the Gold Medal of The American Medical Association, Thorn's second Gold Medal, but this time as the senior investigator for an "exhibit illustrating studies on deoxycorticosterone (a synthetic adrenal cortical substance)" (19).

During the same period, S.L. Simpson, who had earlier (1932) reported (32) on the beneficial effects of adrenocortical extract in the treatment of Addison's disease, reported in *The Lancet* (1938) (33) on the treatment with deoxycorticosterone of two patients with Addison's disease. He mentioned that the drug was obtained from Organon, but it is possible that DeFremery, with whom he had collaborated in some previous work (34), may have been instrumental in helping him to obtain material for study. One of the two patients showed only modest improvement; the second demonstrated improvement to a far greater extent. Later that year, in December 1938, at the Royal Society of Medicine, in addition to Simpson, Wilkinson (35), as well as Avery Jones, reported their successful experiences with deoxycorticosterone. Simpson had also demonstrated the therapeutic efficacy of pellets of deoxycorticosterone (1938), also based on the experience of Deanesly and Parkes (35). Presumably, the impending war effort markedly dampened any further active investigation.

Thorn and his coworkers (31) continued to publish extensively on the effectiveness of deoxycorticosterone in adrenal insufficiency, and the work was regarded as one of the more important advances in medicine during that period. Interestingly, Frank and George Engel had become house officers at The Mount Sinai Hospital in 1938, and in 1940, Frank, with Soffer and Oppenheimer (36), confirmed the effectiveness of deoxycorticosterone in oil and pellet in the treatment of Addison's disease. The pellets had been furnished by George Thorn (31).

Meanwhile, in 1939, Dr. Soma Weiss, a brilliant young physician, had been appointed the Hersey Professor of Medicine at the Peter Bent Brigham Hospital and Harvard Medical School. In 1942, he died of a subarachnoid hemorrhage. Thorn was appointed to the Hersey Chair that same year and remained at Brigham until his retirement. He subsequently became Chairman of the Medical Advisory Board of the Howard Hughes Medical Institute, Chief Editor of Harrison's Textbook of Medicine (8th edition), and the recipient of a host of honorary degrees and honors (30). Lewis Engel later became Chairman of the Department of Biological Chemistry at Harvard. Frank Engel became Professor of Medicine at Duke University but, unfortunately, died at a relatively

young age of a coronary occlusion. George Engel became Professor of Medicine and Psychiatry at Rochester. Reichstein and Kendall were awarded the Nobel Prize for their work on the adrenal steroids.

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