

Short Note

The Discovery of Heparin

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SHORT NOTE

The story of heparin began in 1880, with a report by a German researcher describing the possibility that mammals harbor indigenous anticoagulants [1]. In 1905, Morawitz reviewed peptone shock research and concluded that analytic methods available at the time precluded precise identification of the anticoagulant [2]. This remained the case until the following decade, when William Henry Howell began to study the problem. Howell was born in Baltimore, in 1860, and became interested in chemistry and medicine at an early age. In 1879 he entered Johns Hopkins University and five years later he obtained a PhD in biology. His dissertation was entitled, "Experiments upon the Blood and Lymph of the Terrapin, and the Origin of the Fibrin Formed in the Coagulation of the Blood." In 1889 Howell became Chairman of the Department of Physiology at the University of Michigan, only to return to Hopkins four years later, where he assumed the same title [3].

One of Howell's goals was to determine which tissues contained clot-promoting factors. For this he enlisted the aid of a second year medical student, Jay McLean. McLean was born in San Francisco in 1890, and despite the ruination of his family by the 1906 earthquake, he received a BS degree from the University of California in 1914. McLean was tasked with examining the purity of cephalin preparations as Howell believed that a balance existed between antithrombin and thromboplastin molecules in the blood, and that cephalin release by platelets and leukocytes neutralized antithrombin. In separate studies, McLean extracted phosphatides with anticoagulant properties from canine livers that caused excessive bleeding in experimental animals. McLean chose to concentrate his efforts on cephalin, however, because he thought a procoagulant would be more useful than an anticoagulant in the World War that was raging [4]. Howell continued McLean's work on anticoagulants, as McLean had to devote his attention to medical school, and eventually coined "heparin" from the Greek "hepar" or liver.

Charles Best (of insulin fame) first assembled a team at the University of Toronto, in 1928, to purify heparin for clinical use [5]. Best was born in West Pembroke, Maine, in 1899, the son of a family physician. In 1916 he moved to Toronto to prepare for entry at the university the following year. Best received a BA, in 1921, with honors in physiology and biochemistry. After graduation, he continued to study biochemistry and physiology, and in 1925 he received an MD from the University of Toronto. Following graduation, Best embarked upon a traveling fellowship through several European laboratories. When he returned to Toronto, he continued research on insulin and glucose

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metabolism, but also began studies of histamine in lung tissue and choline metabolism. The histamine studies required continuous blood pressure measurement by arterial cannulas, which often clotted. Best studied and expanded upon the work of David Scott and Arthur Charles, who had devised a way to purify heparin to a high level of potency at the Connaught Laboratories, in Toronto [6]. Their cumbersome method required more than 50 steps to complete, but it eventually led to a commercially practical source of heparin from ox lung. By 1937, heparin was available for use on a small scale.

Gordon Murray was a Toronto surgeon who had collaborated with Best in very early studies of heparin's use in venous thrombosis. In May 1935, he began clinical trials with heparin to prevent venous thrombosis. Several years later Murray experimented with regional heparinization to prevent arterial thrombosis [7]. Similar successful trials were performed by Clarence Crafoord in Stockholm [8].

Until the 1940s, Howell received sole credit for the discovery of heparin. McLean began a campaign to correct the record by embarking on a number of national lectures and writing letters to Best. McLean was more successful than many other unrecognized researchers in that his obituary credited him with the discovery of heparin; no mention was made of Howell. Six years later, in 1963, a memorial plaque was presented to the Johns Hopkins University School of Medicine by the New York Academy of Sciences at a conference entitled, "Bleeding in the Surgical Patient." The inscription read, "In recognition of his major contribution to the discovery of heparin in 1916 as a second year medical student in collaboration with Professor William H. Howell, this plaque is presented to the Johns Hopkins Medical School at the Conference on Bleeding in the Surgical Patient held by the New York Academy of Sciences, May 3, 1963" [9].

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