A Century of Heparin

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The year 2018 was the centennial of the naming of heparin by Emmett Holt and William Howell and the 102nd anniversary of Jay McLean's discovery of an anticoagulant heparphosphatide at Johns Hopkins Hospital in Baltimore. This article discusses recently discovered historical artifacts that shed new light on heparin's christening, including McLean's unpublished letter written in 1950 that represents one of the most complete accounts of heparin's discovery before his untimely death. In addition, the article describes the finding of a plaque dedicated to McLean and explores the circumstances of its removal from public display, as learned from interviews with present and former staff members.

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The term *heparin* was coined by William H. Howell (Figure 1A) and L. Emmett Holt, Jr (Figure 1B) at the Johns Hopkins Hospital in 1918[1] by adding the suffix *-in* (used to denote a type of biochemical compound or substance), to the Latin word for the liver, *hepar*. This name was given to a water-soluble anticoagulant "phosphatid, not previously described, … found in greatest abundance in the liver."[1] This linguistic morphologic derivation was intentional, to "indicate (the phosphatide's) origin from liver," and it follows the similar naming convention of a series of compounds that had been isolated and named, such as cephalin (a group of phospholipids from the brain) and cuorin (a group of phosphatides from the heart).[2]

Early Work

In explaining why heparin is novel and different from previously isolated substances, Holt and Howell first acknowledged Jay McLean's (Figure 1C) efforts in the laboratory 2 years earlier and credited him with drawing attention to the existence of this anticoagulant. They wrote that McLean used a method previously published by Erlandsen to isolate cuorin and managed to obtain the corresponding nitrogen to phosphorus (N/P) ratio for cuorin. However, when McLean tried to isolate heparphosphatide using a method published by Baskoff, he did not obtain the corresponding N/P ratio for heparphosphatide (1:1.5). After McLean left the laboratory for a research fellowship in Philadelphia,[3] Holt worked on heparphosphatides in Howell's laboratory in Baltimore, by separating cephalin within heparphosphatide using a modified protocol to yield a water-soluble anticoagulant without opalescence.

The presence of opalescence, Holt and Howell wrote, was an indication of contamination with cephalin and reduced heparin's anticoagulant properties. The difficulty in separating cephalin and heparin was the result of their roughly similar solubilities. Repeated purifications to remove cephalin or prolonged exposure of the compound to air led to decreased prothrombotic activity and increased anticoagulant properties of heparin in preparations that contained cephalin. This new water-soluble substance, named heparin, had a consistent N/P ratio of 2.5:1, caused potent anticoagulation, and was thus distinct from the heparphosphatide isolated by McLean in 1916. Holt and Howell believed this new substance was a phosphatide because it gave reactions for nitrogen and phosphorus.

In his unfinished account of this discovery,[3] McLean wrote that he was initially interested in the prothrombotic properties of cephalin and wanted to isolate phosphatides from other organs, not just the brain. In reading the German chemical literature, he found that Erlandsen and Baskoff had extracted substances from the heart (cuorin) and the liver (heparphosphatide), in a way similar to how cephalin was extracted from the brain. For brain extracts, the end result was "almost all cephalin, but in the heart and especially in the liver it was something else which was mixed with cephalin." McLean wrote that he made multiple batches of cuorin and heparphosphatide and tested their prothrombotic power. He noted that with the passage of time and with exposure to air, the earlier batches of cuorin and heparphosphatide not only lost their prothrombotic activity, presumably from the degradation of cephalin or the deactivation of cephalin's prothrombotic activity, but also started to exhibit anticoagulant activity, more so in the heparphosphatide preparations than the cuorin preparations.[3,4]

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The Appendix can be viewed in the online version of this article [https://doi.org/10.1016/10.1016/j.athoracsur.2019.03.104] on http://www.annalsthoracicsurgery.org.

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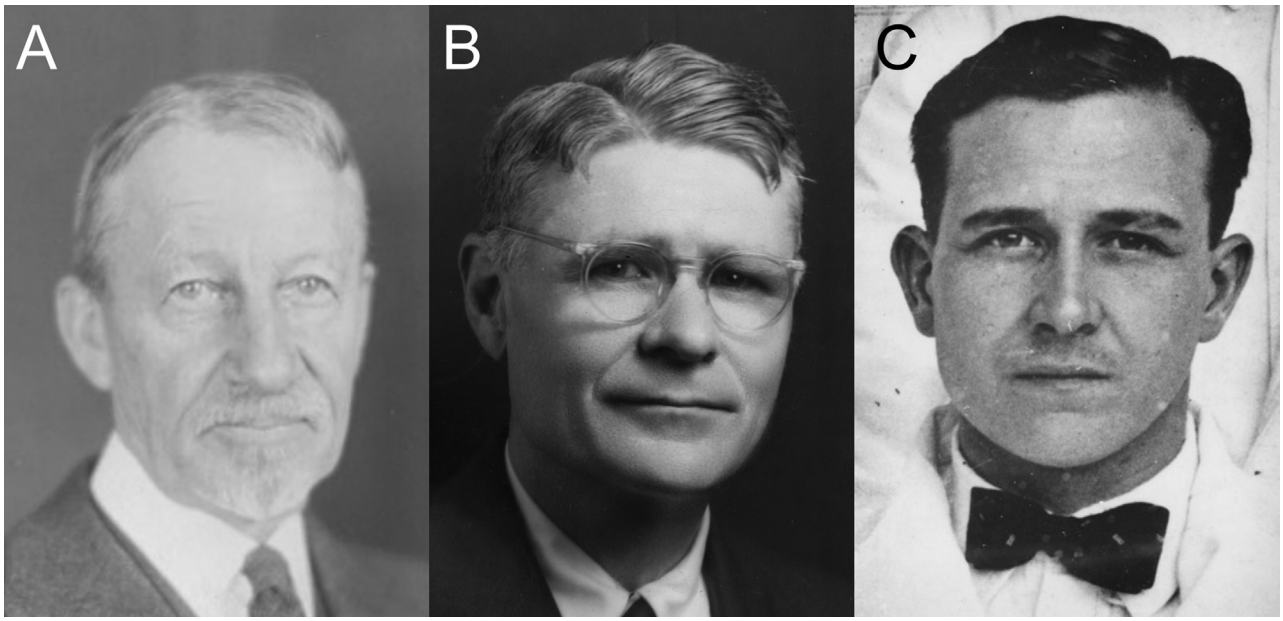

Figure 1. (A) William Henry Howell (1860-1945). (B) Luther Emmett Holt, Jr (1895-1974). (C) Jay McLean (1890-1957). (A, C: Image courtesy of the Alan Mason Chesney Medical Archives, Johns Hopkins Medical Institutions, Baltimore, MD; B: Image courtesy of The Lillian and Clarence de la Chapelle Medical Archives at New York University, New York, NY.)

With these data in hand and having performed repeated experiments, McLean wrote that he then approached Howell and discussed the presence of a natural anticoagulant in the liver phosphatide preparation, albeit masked by cephalin, that gradually became unmasked with time. In an attempt to overcome Howell's initial skepticism, McLean demonstrated the anticoagulant activity by adding the liver phosphatide to fresh feline blood—the blood did not clot. After multiple in vitro studies, McLean and Howell proceeded to administer this substance in vivo in dogs. In a newly uncovered letter in the Johns Hopkins Medical Archives (Appendix), McLean gave a detailed description of the in vivo canine experiments in which an intravenous injection of heparin led to uncontrolled bleeding over the femoral incision site. In a letter to Charles Best of the University of Toronto (Toronto, Canada), one of the co-discovers of insulin, McLean wrote that he never received the appropriate academic credit for his role in heparin's discovery and the discovery of an anticoagulant in heparphosphatide.[5]

After McLean and Holt had left Howell's research laboratory, Howell continued to pursue isolation of heparin from liver and worked to refine isolation protocols for the anticoagulant. He soon realized that "heparin" does not contain phosphorus, and therefore is not a phosphatide, but rather a complex carbohydrate.

In December 1922, at the 35th Annual Meeting of the American Physiological Society,[6] Howell reported on an aqueous isolation protocol for water-soluble heparin, which was subsequently published in the February 1923 issue of the society's journal. With a Baltimore pharmaceutical company, he also commercialized this particular compound for experimental work. In 1924, he published the full protocol for the aqueous extraction of the anticoagulant.[7] Howell discovered that the inhibitor was a complex carbohydrate rather than a phosphatide and contained glucuronic acid. He further discussed the chemical composition of heparin in a 1924 Pasteur lecture.[8] Notably, as Howell told the audience, the anticoagulant was still water soluble, free of protein, and contained no phosphorus. However, Howell continued to use the name heparin for the inhibitor because other researchers, such as Henry Best and colleagues in Toronto,[5] had begun to adopt it.

Controversy Over the Discovery of Heparin

Whether this water-soluble carbohydrate form of heparin reported in 1922 was a completely new compound different from the water-soluble phosphorus-containing heparin he had already named with Holt in 1918 is not clear. Howell himself wrote in February 1924, in a letter to Frank Hartman of the Henry Ford Hospital,[9] that it was the same compound, but in his publication in November 1924 detailing the aqueous method to extract heparin,[7] he highlighted that the active material in fact does not contain phosphorus, contrary to what he and Holt had previously reported in 1918.[1] Some later authors opined that this "new heparin was strangely similar to Doyon's 1911 water-soluble anticoagulant from peptone shock."[10]

Recent chronologic narration and historical reconstructions[11-13] attribute the controversy over credit for heparin's discovery to McLean's campaign in the middle 1940s and later. Although McLean always considered himself the discoverer of heparin,[11] he began his campaign for credit of the discovery in the mid-1940s. It is likely that he was discreet initially to prevent controversy with Howell and his colleagues in Baltimore. After

Howell's death in 1945, however, McLean set out to claim credit for heparin's discovery. Just 3 months after Howell's death, McLean participated in an interview with radio celebrity Milton Cross, in which he was introduced as the "discoverer of heparin." From 1945 to his death in 1957, McLean wrote letters to numerous scientists and physicians, compiled a monograph on heparin, conducted further heparin-related research, gave lectures to professional audiences, and assembled a biography. The campaign was largely successful because McLean convinced many of his contemporaries that he was the discoverer of heparin, or at least a co-discoverer, despite the issues regarding the naming, organic solubility, and chemical structure of heparin.

At the time McLean commenced his campaign, heparin was widely recognized as a water-soluble and complex carbohydrate and thus chemically different from the heparphosphatides he had isolated in 1916 by organic extraction and from the water-soluble heparin isolated by Howell and Holt using organic extraction in 1918. McLean asserted that the preparations isolated in 1916 and 1918 exhibited anticoagulant properties because of the presence of a water-soluble carbohydrate form of heparin isolated by aqueous extraction by Howell in 1922 (Appendix, last page: "so the 1916 heparin was heparin and strong too!"). McLean even created a custom stamp espousing his views (Figure 2) to imprint on reprints (Charles Best papers, Thomas Fisher Rare Book Library, University of Toronto, Toronto, Canada) of his 1916 article.[4] McLean's claim was disputed 2 years after his death by Silver and colleagues,[14] who demonstrated that McLean's heparphosphatide in 1916 was likely a combination of phospholipids, inositol phosphatides, sphingomyelin, and phosphatidylserine, all of which had anticoagulant activity.[10,14] Another notable dissenter to McLean's campaign was Louis Jaques,[15] who believed that McLean simply did not isolate water-soluble, carbohydrate-form heparin because McLean was studying fat-soluble phosphatides derived from the liver. Thus, Jaques concluded that McLean could not have discovered the carbohydrate-form heparin we know today. The only way McLean could have "discovered" heparin would be to redefine the term "scientific discovery," shifting the focus from the biochemical isolation of the compound to crediting "work (that) led directly to development and application, as is true of history in general, e.g. the discovery of America by Christopher Columbus in 1492."[15]

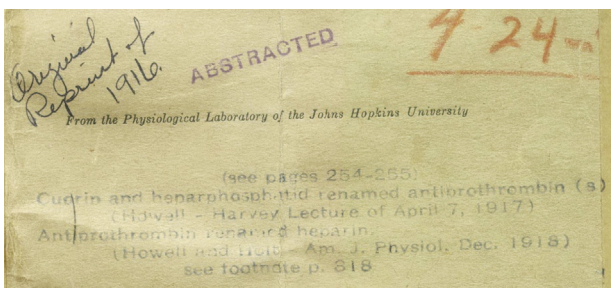

Figure 2. Jay McLean's custom stamp on reprints of his 1916 article, stating "Cuorin and heparphosphatid renamed antiprothrombin (s) (Howell – Harvey Lecture of April 7, 1917), Antiprothrombin renamed heparin. (Howell and Holt – Am. J. Physiol. Dec. 1918) see footnote p. 818." (Image courtesy of the Thomas Fisher Rare Book Library, University of Toronto, Toronto, Canada.)

Howell remained steadfast that he first isolated the water-soluble form of heparin. In a February 1924 letter to Dr Frank Hartman at the Henry Ford Hospital in Detroit, Michigan,[9] Howell wrote that heparin is "not a liver phosphatid prepared according to the findings of McLean" and it is a "substance [Howell] discovered and isolated by a method worked out by (himself) and published an account of it in the paper by Holt and [himself]."[1] In his papers from the 1920s characterizing heparin,[6,8,16] Howell did not credit McLean's work with the anticoagulant phosphatides. Finally, in an autobiographical sketch, he listed one of his chief accomplishments the discovery of the polysaccharide blood anticoagulant, which he named heparin.[11] Howell's claim as heparin's discoverer is understandable; by 1910 Howell had switched his research to focus almost exclusively on the study of blood coagulation,[17] and he dedicated the latter part of his life to this subject. In a 1951 biography of Howell,[18] Erlanger noted that 34 of 38 papers written by Howell from 1909 to 1945, in the final stage of Howell's career, dealt with blood coagulation.

More Recent Views on the Discovery of Heparin

More recent accounts of heparin's discovery[11-13,19,20] generally acknowledge the controversy over academic credit. Several articles have focused on McLean's prolonged absence from the heparin story.[9,21] A number of articles have been disparaging of McLean.[9,20,21] A plaque dedicated to McLean (Figure 3) was displayed for many years outside the Department of Pharmacology[12] at the Johns Hopkins Hospital, before it was taken down in the mid-2000s with "a moderate amount of intentionality" (personal communication, Philip Arthur Cole, MD, PhD, Director of the Johns Hopkins Department of Pharmacology and Molecular Sciences [1999 to 2017]), a decision influenced by the controversy surrounding credit.[11] The discovery of anticoagulants dates back to Schmidt-Mulheim and the observation of peptone shock, which was first reported in the German medical literature in 1880.[22] The mechanism of peptone shock was found to be the result of release of heparin from liver mast cells in the blood circulation.[23] Subsequent efforts to purify heparin by Howell, Best and colleagues in Toronto,[24] and Clarence Crafoord and Erik Jorpes of Stockholm,[23] eventually led to reduction of the toxicity of early heparin preparations, further characterization of heparin, and the recognition of its clinical utility. Heparin has been on the World Health Organization Model Lists of Essential Medicines since 1977,[25] when the first list was published, and has remained on the list since then, thus attesting to its value in modern medicine.

In conclusion, the story of heparin is intriguing and has a large cast of characters and no shortage of different perspectives, by the characters themselves as well as by contemporary scientists, physicians and surgeons, and

Figure 3. Plaque dedicated to Jay McLean and presented to the Johns Hopkins Medical School at the Conference on Bleeding in the Surgical Patient by the New York Academy of Sciences in May 1963. This plaque was displayed for many years outside the Department of Pharmacology and Molecular Sciences at the Johns Hopkins medical campus in East Baltimore (Level 3, Wood Basic Science Building, between the elevators outside the John J. Abel Library), until it was removed in mid-2000s. It was then kept in the Abel Library for several years, before it was accessioned by the Medical Archives in 2007. (Image courtesy of the Alan Mason Chesney Medical Archives, Johns Hopkins Medical Institutions, Baltimore, MD.)

biographers, and medical historians. The intention of this narrative is to be historical and neutral, and its purpose is to celebrate surgical heritage in light of the centennial of the naming of heparin,[1] as well as to illustrate the role of serendipity, persistence, and an open investigative mind. Indeed, the discovery of heparin is an example of complex progressive scientific discovery and its assimilation into the corpus of scientific and clinical knowledge.

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References

1. Howell WH, Holt E. Two new factors in blood coagulation - heparin and pro-antithrombin. *Am J Physiol*. 1918;47:328-341.
2. Levene PA, Komatsu S. Lipoids of the heart muscle. *J Biol Chem*. 1919;39:83-89.
3. McLean J. The discovery of heparin. *Circulation*. 1959;19:75-78.
4. McLean J. The thromboplastic action of cephalin. *Am J Physiol*. 1916;41:250-257.
5. Best CH. Preparation of heparin and its use in the first clinical cases. *Circulation*. 1959;19:79-86.
6. Howell WH. Heparin, an anticoagulant. *Am J Physiol*. 1923;63:434-435.
7. Howell WH. The purification of heparin and its presence in blood. *Am J Physiol*. 1925;71:553-562.
8. Howell WH. The problem of coagulation. Pasteur Lecture 1925. *Proc Inst Med Chic*. 1925;5:139-163.
9. Lam CR. The strange story of Jay McLean, the discoverer of heparin. *Henry Ford Hosp Med J*. 1985;33:18-23.
10. Mueller RL, Scheidt S. History of drugs for thrombotic disease. Discovery, development, and directions for the future. *Circulation*. 1994;89:432-449.
11. Marcum JA. The origin of the dispute over the discovery of heparin. *J Hist Med Allied Sci*. 2000;55:37-66.
12. Baird RJ. Presidential address: "Give us the tools…": the story of heparin—as told by sketches from the lives of William Howell, Jay McLean, Charles Best, and Gordon Murray. *J Vasc Surg*. 1990;11:4-18.
13. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. *Br J Haematol*. 2008;141:757-763.
14. Silver J, Turner D, Tocantins L. Lipid anticoagulants. *Prog Hematol*. 1959;2:264-281.
15. Jaques LB. Addendum: the discovery of heparin. *Semin Thromb Hemost*. 1978;4:350-353.
16. Howell W. The purification of heparin and its chemical and physiological reactions. *Bull John Hopkins Hosp*. 1928;42:199-206.
17. Fye WB. Heparin: the contributions of William Henry Howell. *Circulation*. 1984;69:1198-1203.
18. Erlanger J. William Henry Howell 1860-1945. *Biogr Mem Natl Acad Sci*. 1951;26:151-180.
19. Marcum JA. William Henry Howell and Jay McLean: the experimental context for the discovery of heparin. *Perspect Biol Med*. 1990;33:214-230.
20. Ricci S, Agus G. Ninety years from discovery of heparin. Story of a loser. *Acta Phlebologica*. 2006;7:91-97.
21. Couch NP. About heparin, or … whatever happened to Jay McLean? *J Vasc. Surg*. 1989;10:1-8.
22. Marcum JA. *Tampering With Nature: Empirical Methodology and Experimental Onto-epistemology*. New York, NY: Nova Scientific Publishers; 2013.
23. Marcum JA. The discovery of heparin revisited: the peptone connection. *Perspect Biol Med*. 1996;39:610-625.
24. Marcum JA. The development of heparin in Toronto. *J Hist Med Allied Sci*. 1997;52:310-337.
25. The selection and use of essential medicines. *World Health Organ Tech Rep Ser*. 2015:vii-xv, 1-546.