Heparin Centennial: A Century of Clinical and Scientific Progress

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The year 2016 marks one hundred years since the discovery of the universally used anticoagulant drug heparin. Over this period of time heparin has remained one of the most challenging and rewarding drugs for scientists and clinicians. Despite the development of numerous synthetic and biotechnology based anticoagulant drugs, heparin and its derivatives have remained the standards of care for thrombotic and cardiovascular indications. The chemistry, biology and clinical behavior of this drug is intriguing and has fascinated both the scientific and clinical communities for many decades.

The scientific quest on heparin began in 1916 when a medical student, Jay McLean accidentally discovered anticoagulant activity in a dog liver extract. The discovery or finding was not in accordance with what his assignment called for. For this reason his then mentor, William Howell, was displeased with him for some time, only to later follow his work to rediscover the anticoagulant activity in dog liver. The history of heparin is very well documented highlighting the interesting interactions between McLean and Howell. Even today, there is controversy regarding the credit for the discovery of heparin. McLean was a medical student at Johns Hopkins when he made the discovery that dog liver homogenates contain lipid soluble substances which had anticoagulant properties. Soon after this finding, McLean left Johns Hopkins and another student by the name of Holt also found an anticoagulant substance in aqueous extracts of dog liver. After Holt's findings, Howell took an interest in this project and called the anticoagulant substance Heparin (from the Greek word for liver). Several years later, Howell and his group presented their findings at the American Physiological Society meeting. In 1926 Howell presented further refinement of the process to extract the anticoagulant substance from liver extracts. Until this time the credit for the discovery of heparin has been debated. While it is difficult to establish who really discovered heparin, McLean is generally credited as the discoverer of heparin. McLean's work in Howell's laboratory changed the focus of research towards anticoagulants. The clinical use of heparin began in the late 1920s. The initial batches of heparin, when used clinically, produce side effects such as nausea, vomiting and headache. This prompted further purification of this agent by various groups. The American pharmaceutical group Hynson, Westcott and Dunning produced commercial amounts of heparin. Several investigators in other countries started working to further refine heparin production. This work was pioneered by the Canadian group led by Charles Best, then Chair of the Physiology department at the University of Toronto and was carried out at the Toronto (Canada) based Connaught Laboratories. The group developed methods to extract heparin from bovine liver and later from bovine lungs. This work led to the development of commercial grade heparin for clinical use.

The introduction of heparin as an anticoagulant attracted many chemists and biologists to further study this agent. In 1929 a Swedish scientist, Erik Jorpes, visited the department of Physiology in

Toronto to work with Dr. Best. He became interested in the study of heparin and upon returning to Sweden initiated a major program. The composition of heparin was rather complex and difficult to investigate. It became a challenge to many people. Jorpes also prompted clinicians to use this drug. A Swedish surgeon Crafoord was the first to use it clinically in 1938. The use of heparin was expanded at the Banting Institute in Canada when Gordon Murray used heparin in the first surgical indication. Simultaneously, Canadian physiologist Louis Jacques identified heparin to be a carbohydrate like substance. Several international scientists worked with the Canadian and Swedish groups to understand the chemistry and biology of heparin. These included groups at the University of Chicago and in Brazil. Carl Dietrich from São Paolo, who was working with Jacques, separated heparin into its components and eventually characterized these components. The Chicago group also separated heparin on chromatographic columns to show its components. The stock yards in Chicago provided a rather large source of hog mucosa to be used as raw material for heparin production. Industry became very interested in producing heparin from various sources. The Swedish and the French later developed methods to fractionate heparin based on molecular weight. This led to the development of Low Molecular Weight Heparins, a class of drugs which has revolutionized the management of venous thrombosis.

The fractionation and characterization of these various components of heparin resulted in the identification of small molecular weight chains called oligosaccharides. This led to the development of synthetic pentasaccharides, one of which is now used clinically. The development of heparin as an anticoagulant was a landmark project which not only provided an anticoagulant for clinical use, but also was a major platform to understand pathogenesis and treatment of thrombotic disorders. The foundations for the understanding of current concepts of hemostasis and thrombosis are developed on the basis of our understanding of the physiologic modulation by heparin and related drugs. Currently the heparins are also isolated from other mammalian sources including sheep (ovine) and cow (bovine) tissues. Furthermore, the concept of blended heparins has also emerged. Beside synthetic approaches, biosynthetic and hybrid approaches to produce heparin and heparin-related drugs are currently pursued. The development in the understanding and clinical utility of heparin and heparin related drugs will continue for some time. Although considered to be an old drug, the advances in cellular and molecular sciences will continue to provide us newer information on this universal anticoagulant to improve its production, to refine the drug products and to identify additional indications. Thus heparin, low molecular weight heparins, and synthetic or biosynthetic oligosaccharides will continue to impact the management of thrombotic and vascular disorders for years to come.