HEPARIN:
Structure, Cellular Functions, and Clinical Applications

Edited by

Norman M. McDuffie

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University of Saskatch
Saskatoon, Saskatche

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FOREWORD

It is an honor, indeed, for me to have this opportunity to say a few words at the opening of this important international symposium on heparin.

One cannot overestimate the importance of the substance or substances referred to generically as heparin, for few agents have had a more profound influence on the development of medicine and surgery. Not only has heparin been the leader in antithrombotic therapy ever since its introduction some 40 years ago initiated a new field of therapeutics, but it also has made possible dramatic advances in cardiac surgery, vascular surgery, acute and chronic hemodialysis, and a variety of other medical and surgical procedures. Furthermore, were it not for heparin, many experimental studies in animals and on blood, which have been and continue to be fundamental for important clinical developments, never could have been carried out. Thus, while few, if any, have ever suggested that heparin be included in any survival kit, it would be interesting to contemplate the nature of medicine or medical practice today without its presence. Such considerations, along with the fact that ever since its introduction heparin has continued to enjoy a sustained growth, both in volume of use and variety of applications, provide sufficient reason that new knowledge, both of a basic and applied nature, be reviewed at appropriate intervals. This is such a time, particularly since a number of important advances have occurred recently.

The site for this symposium is a most fitting one. It takes place in a country where heparin was first introduced for clinical use, and where pioneering work on this compound has continued uninterrupted for some two score years; and it takes place in an institution whose Department of Physiology has been a world leader in heparin research by virtue of its many significant advances to our knowledge. But, perhaps most importantly, it offers the many scientists who have come near and far to attend this meeting the opportunity to honor a senior and elder

statesman at the University of Saskatchewan who has devoted his entire research career to the investigation of these unique macromolecules, and whose studies on this subject are so well recognized internationally that a word association between heparin and L. B. Jaques has developed spontaneously.

As frequently happens with imortant medical breakthroughs, serendipity played a major role in Jay McLean's discovery of heparin. Howell had asked him to investigate tissue sources of thromboplastin other than brain, and had suggested he try to extract such a material from the heart and the liver. The heart material turned out to be less potent than the controversial brain extract but the liver preparation actually prevented clotting rather than accelerating it. The rest is history!

I have no intention to review the heparin story. Its early phase is well covered in previous publications by McLean and such other famous heparin pioneers as Erik Jorpes, Charles Best, and Gordon Murray, and a complete classified bibliography of all heparin publications through July 1958 is available. And as for the period since then, no purpose would be served by my doing this, particulaly since Professor Jaques will be addressing us later on "Forty Years of Heparin Research: Past and Future."

This symposium is not designed to cover all aspects of our knowledge of heparin; such an undertaking would be much too formidable for a three-day meeting. Rather the organizers, under the wise leadership of Dr. McDuffie, have chosen certain topics of current interest for major consideration. These include the structure of heparin and related compounds, its interactions in carrying out its functional activity, the cellular role of heparin, and selected aspects of clinical application.

Before concluding these introductory remarks, I would like to say a few words about the man being honored by this symposium and for whom the published proceedings undoubtedly will be dedicated. As many of you know, almost two decades went by, following the initial discovery of heparin in 1916, before purified preparations of this substance were made available for clinical investigation in man and this occurred almost simultaneously and independently in Canada and Sweden. It is indeed fortunate for us that, just at the time that Connaught Laboratories made such preparations available to Dr. Gordon Murray for patient studies, Louis Barker Jaques, who had been born in Toronto some 22 years earlier, decided to pursue a Masters Degree in Physiology at the University of Toronto and was assigned to assist Murray in his studies. This collaboration between a brilliant academic surgeon and a dedicated and determined student, so reminiscent of the Banting and Best association some ten years earlier, soon resulted in the first demonstration of the clinical usefulness of heparin, namely, in vascular surgery. From this early trail-blazing work, Jaques has main-

tained a commitment and devotion to heparin research which is unique; he is the only one of the early pioneers who has maintained a total interest in this agent. This interest now spans four decades and includes 128 publications of original research work on this substance.

Among Jaques' firsts are the demonstration of the use of heparin in preventing thrombosis, the use of pharmacodynamic studies for establishing dosage, identification of differences in heparins among various mammalian species, variability of activity among commercial preparations, methods for the determination of heparin such as protamine titration, metachromatic staining, and clotting times, demonstration of the platelet aggregating effect of commercial heparin preparations, heparin's reaction with toluidine blue, identification of iduronic acid as a major component of heparin, and the identification of circulating heparin in canine anaphylaxis. Thus Jaques' career has spanned not only the entire active period of investigation of this substance, but his own studies have covered the entire spectrum of heparin investigation: its chemistry, physiology, pharmacology, and therapeutics. And in the tradition of the "complete" scientist, he has adopted, adapted, and created techniques to solve problems rather than seeking problems to be solved by a specific technique.

The first 12 years of Jaques' research career were spent in the Department of Physiology at the University of Toronto, but in 1946 at the age of 35, he was summoned to the University of Saskatchewan as Professor and Head of their Department of Physiology, a position he held for the next 25 years. In 1971 he relinquished this responsibility, and since then has served as Director of the Department's Haemostasis-Thrombosis Research Unit. His importance to the University has been recognized in many ways; one evidence of this has been his appointment in 1972 as the first W. S. Lindsay Professor of this University's College of Medicine.

While his research accomplishments and the leadership he has given to the heparin field speak for themselves, all of us have admired this man for his personal qualities as well. He has taught us all that one need not be flashy to be impressive—all one has to do is to have the facts. And where heparin is concerned, Louis Barker Jaques has more than anyone else in this world today. All of us here salute you Professor Jaques and wish you many more years of wise counsel, leadership, and productive research.

SOL SHERRY

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PREFACE

The International Symposium on Heparin was held at Saskatoon, July 6–8, 1977. The purposes of the symposium were multiple. Foremost among them was the opportunity to honor a persistent and gifted scientist who had unflaggingly devoted over 40 years to heparin research. Although Louis Barker Jaques' contributions are legion, the timing of the symposium was perhaps equally dictated by the novel findings emanating from research centers in Boston, Uppsala, São Paulo, Toronto, Montreal, London, and Saskatoon. The mid-1970's produced a surge in application of new techniques to the age-old problems of heterogeneity and polydispersity of the mucopolysaccharides. Results of these studies suggested better understanding of the complex molecules termed heparin could be obtained. With this objective in mind, the symposium was organized to bring together experts from diverse disciplines that related to the heparin problem. Individuals were encouraged to discuss at length older and newer concepts pertaining to the heparin molecule, its pharmacology, physiology, and clinical application.

The response was most gratifying. The interaction between the participants was extraordinary, and I commend to the reader the edited discussion sections of the book.

The final word at the symposium was left to Professor Jaques whose commentary on the field and the conference closes the book. I am indebted to all participants and particularly those individuals who worked diligently toward the completion of the book.

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