NEWS IN ANGIOLOGY
The current world must face a general overload of information. With respect to medical knowledge, it is estimated to double approximately every two to nineteen years, depending on the specialization. One hundred years ago a physician could know everything about medicine. At present it is clear that no single person can keep up with such an exponential expansion of information.

Angiology belongs to those branches of medicine where new knowledge is developing very quickly. Looking back and comparing the past with the current situation, a significant progress in ethiology, diagnostics, prevention and therapeutic methods of vascular diseases is evident. It is also clear that most of the advances were not achieved suddenly by a breakthrough discovery. On the contrary, our increasing knowledge depends on the activity of many known and also unknown colleagues from all over the world who are bringing together small contributions. In this natural process, a future comprehensive view and solution of a problem is usually obtained.

*News in Angiology* represents an interesting project and a good result of scientific cooperation. The idea is outstanding in comparison with other publications it contains 60 contributions altogether creating a textbook of the second generation. This type of publication, bringing mostly systematic overviews of relevant topics, remains valuable even in the era of electronic data management. It may be helpful in finding a way through the sources of information in vascular diseases and in assessing their validity.

I wish to thank and congratulate with all the authors and persons contributing to this book.

Karel Roztocil
*IUA President*
I was very glad when Pier Luigi Antignani, on behalf of the authors of “News in Angiology”, asked me to write the preface to this book.

Usually it is not easy to present the work of colleagues if you have been working with them for a long time and you share solid ties and mutual professional esteem.

However, in this case it is different, so it is easier to present a book that completes in such an exemplary way a scientific and training path that began many years ago.

“News in Angiology” is, in this historical moment, the most comprehensive and updated text on training and information regarding arterial, venous and lymphatic diseases. The authors’ vast experience and the ability of such an international and outstanding “parterre” to captivate the reader are the premise of a worldwide success.

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   B.B. Lee, P.L. Antignani
For nearly half of a century, heparin has been one of the most adventurous and mysterious drugs. Despite the development of numerous synthetic and biotechnology drugs, heparin and its derivatives have remained to be the standard 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 community for many decades.1-4

The mystery of heparin began when a medical student named Jay McClean accidentally discovered its anticoagulant activity in dog liver extract in 1917. 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 McClean and Howell. Even today, there is controversy regarding the credit for the discovery of heparin. McClean was a medical student at John Hopkins when he made the discovery that dog liver homogenates contains lipid soluble substances which had anticoagulant properties. Soon after this finding, for some reason, McClean left John Hopkins and another student by the name of Holt also found the anticoagulant principle in aqueous extracts of dog liver. The group developed methods to extract heparin from bovine liver. After Holt’s findings, Howell took an interest in this project and called the anticoagulant substance heparin which is from the Greek word hepar, for liver. Several years later, Howell and his group presented their findings at the American physiological society meeting. In 1926 Howell presented further refinement on the process to extract the anticoagulant principal from liver. Until today, the mystery of the discovery of heparin has remained unresolved. While it is difficult to establish who really discovered heparin, McClean is generally credited as the discoverer of heparin. McClean’s work in Howell’s laboratory changed the focus of research towards anticoagulants. The commercialization of heparin began in the late 1920s. The initial batches of heparin, when used clinically, produced such side effects as nausea, vomiting and headache. This prompted further purification of this agent by various groups. An American pharmaceutical group Hynson, Westcott and Denning produced commercial amounts of heparin.5-7

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. This work was carried out at the Toronto (Canada based) Connaught laboratories. The group developed methods to extract heparin from bovine liver. Later heparin was extracted from bovine lungs. This work led to the development of commercial grade heparin for clinical use.4

The introduction of heparin as an anticoagulant attracted many chemists and biologists to further study this agent. In 1929 a Swedish scientist, Eric 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 Swe-
den initiated a major program there. The composition of heparin was rather complex and difficult to investigate. It became a challenge to many researchers. Jorpes also prompted clinicians to use this drug. A Swedish surgeon named Crafoord used it clinically. The surgical use of heparin was expanded at the Banting institute in Canada, where Gordon Murray employed it for surgical indications. Simultaneously, 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 the university of Chicago as well as Brazilian groups. Professor Carl Dietrich from Sao Paolo, working with Jacques, separated heparin into its components and eventually characterized his components. The Chicago group also separated heparin on chronographic columns to show its components. The stock yard from Chicago provided rather large sources of raw material such as hog mucosa for heparin production. Industry became very interested in producing heparin from various sources. The Swedish and the French later developed methods to fractionate heparin into low molecular weight heparins (LMWHs). This led to the development of low molecular weight heparins, a class of drugs which has revolutionized the management of venous thrombosis.\(^7\)\(^9\)

The understanding of these various components of heparin and their fractionation and characterization resulted in the identification of small molecular weight chains called oligosaccharides. This led to the development of synthetic pentasaccharides which are now clinically used widely. 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 the pathogenesis and treatment of thrombotic disorders.\(^10\)\(^-\)\(^12\)

The history of the development of heparin dates back to 1912 when M. Doyon (1912; Lyon, France) described the release of an anticoagulant substance from dog liver which was never characterized. Was it antithrombin or heparin - nobody has provided an answer to this question. The step-wise development in this area is summarized below:

- 1917 - Accidentally discovered by a medical student J. McLean (Baltimore);
- 1928 - Howell recognized that heparin was a carbohydrate containing uronic acid (Baltimore);
- 1935-36 - Bergstrom in Jorpes’s lab showed N-sulfated glucosamine in heparin. Jorpes with Charles and Scott produced sufficient amount of heparin and Crafoord used it in humans (Stockholm and Toronto);
- 1946 - Wolfram identified D-glucuronic acid (sugar alley in Ohio);
- 1962 - Cifonelli and Dorfman identified L-iduronic acid in heparin (Chicago);
- 1968 - Perlan confirmed the L-iduronic acid using nuclear magnetic resonance (NMR) (Montreal);
- 1970s - Casu, Bianchini, Dietrich, McDuffie, Lindahl, Linhardt, Rosenberg, and many other scientists contributed to the study of heparin (Milan, Saskatoon, Stockholm, Iowa City, Boston);
- 1980 - Clinical development of LMWHs and ultra LMWHs;
- 1990 - Synthetic heparin analogues and heparinoids;
- 2000 - Biotechnology derived heparins;
- 2010 - Adulteration of heparin.

For nearly 100 years, until 2014, hundreds of scientists and biologists have continued to work on the chemistry and biology of heparin only to face newer questions regarding the structural complexity and multiple pharmacological and clinical effects of this drug.\(^4\)

The clinical use of heparin began in the early 1930s. Since then, besides the anticoagulant activity, many other pharmacological actions of this drug have been discovered. It is now widely known that almost 70% of the component of heparin exhibits other pharmacological actions which are non-anticoagulant. With the advent of molecular biology and cellular sciences, even a greater complexity on the pharmacologic actions of this drug is revealed. The step-wise clinical development of this drug is summarized below:

- 1929 - Heparin purification, university of Toronto;
- 1935 - Clinical supplies became available from various sources;
- 1940’s - War time use of heparin by Canadian army in France;
- 1939 - Surgical application of heparin;
- 1948 - Development of protamine sulfate as a neutralizing agent for heparin;
- 1950’s - Clinical development of heparin for vascular indications;
- 1955 - Heparin in cardiovascular indications, hemodialysis and cardio pulmonary bypass surgery;
- 1960’s - Heparin fractionation and LMWH’s;
– 1970’s - Heparins for post-surgical prophylaxis of DVT;
– 1980’s - Additional indications for heparins and chemically synthesized heparins in vascular and other indications including cancer

Since 1980 the heparins have become the standard of care for the management of venous thromboembolism.11-12 The development of LMWH was serendipitous. The observation that upon subcutaneous administration of unfractionated heparin, only the LMWH components were absorbed led to the fractionation and the depolymerization of heparin. Later additional processes were also introduced to manufacture LMWHs.13 Heparin and LMWHs are now used for cardiovascular, cerebrovascular and auto immune disorders. Heparin’s role in cancer is equally important and continues to be probed. It is likely that heparin and its derivatives will be used for many other indications. The mystery of its biologic action regulating cellular functions, interactions with proteins and molecular modulation will continue to challenge scientists and clinicians for years to come. The impact of synthetic methods and biotechnology in developing newer anticoagulants is rather profound.14 Despite this, equally profound are the advances in the understanding of heparin structure and biology which have continued to provide us newer derivatives with specific clinical targets.

Heparin has also faced certain challenges and numerous problematic issues have emerged over a period of time. Some of these are summarized below along with possible resolutions:

<table>
<thead>
<tr>
<th>Issues</th>
<th>Problems/resolutions</th>
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<tr>
<td>Look alike ampules</td>
<td>Dosage errors due to mixing of vials corrected by better labeling</td>
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<tr>
<td>Contaminated syringes (Serratia</td>
<td>Adverse reaction due to bacterial infections which were resolved by proper sterile</td>
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<td>Marcescens)</td>
<td>techniques</td>
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<tr>
<td>Generic heparins</td>
<td>Safety/efficacy issues due to product variance. Newer guidelines from regulatory</td>
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<td></td>
<td>agencies assuring quality</td>
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<tr>
<td>Contaminated heparins</td>
<td>Multiple adverse reactions and deaths. Contaminants identified and additional</td>
</tr>
<tr>
<td></td>
<td>analytical methods suggested for quality</td>
</tr>
<tr>
<td>HIT syndrome</td>
<td>Pathophysiology and management. Molecular pathogenesis is understood. Alternates are</td>
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The better labeling to identify potency, application of sterile techniques with proper packaging and good quality assurance has minimized contamination and potency mix ups. The quality of generic heparins has improved due to tighter controls. Attempts to contaminate heparin have been made by adding non-heparin substances to this drug. Additional analytical data requirements and specific structural data for regulatory purposes provide a control on the quality of generic products.

The unresolved mystery of heparin will continue to haunt the scientific and medical community for years to come. Although heparin still remains to be the most widely used anticoagulant drug, a lot of questions regarding this drug remain unanswered.

– The McLean vs. Howell’s claim has been discussed by historians for many years. McLean was a complex man full of mystery and intrigue. Howell had great discipline and was a well recognized scientist who liked power and control. He also had his likes and dislikes. McLean was not among his favorite ones. The two personalities were quite different and did not match. Regardless of this, they are both eventually credited to be the first ones to recognize and promote heparin.

– It is a complex pleiotropic mixture whose structure and pharmacology remain to be not completely known. The complex nature of heparin is equally as mysterious. The drug is poly-component and modulates its behavior according to the environment. The overall clinical effects represent a combined net effect of several diverse biologic actions. Some of which are still unclear to us.

– The endogenous role of heparin is not fully explored in the animal kingdom. Heparin and its derivatives are widely distributed in the animal kingdom. From the mollusk to the human, heparin and related substances are found, distributed in different organs. The exact role of endogenous heparin is also unknown. These are all of the mysteries about heparin.

– Heparin is challenged over time by the introduction of several additional anticoagulants however this agent has survived. Since its early clinical use many other anticoagulants have been developed to replace it. To date none of these agents have been able to provide a similar clinical profile as heparin. Notably heparin
is the only anticoagulant for surgical and interventionalist usage.

– Despite its role in medicine and surgery, heparin related clinical and scientific work was never recognized by the Nobel foundation. For unknown reasons scientific recognition of heparin has not been considered by various foundations. The scientists who worked on heparin are widely recognized in their own circles and have contributed significantly. Thus the science behind heparin should have been duly recognized.

– The scientists and clinicians who developed heparins were equally mysterious. Their personalities were contrasting and each believed strongly in their own convictions. They were all very passionate in their work and their beliefs. Besides interest in heparin many of them have other very diverse interests. Their pursuit to probe heparin and its mysteries were targeted and they eventually were successful in achieving their goals despite limitations.

– Despite the development of new anticoagulants, heparins will remain the anticoagulants of choice for vascular indications. Mysteriously, heparin withstood the test of time. It is the only drug which is endogenously present in different forms with multiple and adjustable functions. Without heparin, surgical procedures such as open heart surgery would not have been possible. The additional therapeutic effects of heparin still continue to be discovered.

– The mystery of heparin will continue in years to come. The scientific world will remain intrigued by heparins. Its heterogeneous structure and functionalities, multiple interactions with cells and proteins, effects on blood vessels along with polyelectrolyte nature provide a complex area of pharmacologic actions which cannot be matched by one single drug.

The author’s personal encounter with heparin was equally mysterious. Up until 1970 he had no idea about this wonder drug. Fortuitously he met Dr. Harry Messmore who was the chief of hematology at Loyola university medical center with interest in bleeding and coagulant disorders. He noted the author’s interest in pharmacology and persuaded him to work with him. In 1973 they encountered a female patient who was additionally diagnosed by Dr. Quick to have hyperheparinemia. Dr. Quick felt that this was the cause of her bleeding problem. The hemorrhage was stopped with a drip thrombin, however after a year of work up, the anticoagulant was found to be a molecular variant of antitrypsin. In the quest of looking for heparin in this patient’s blood they nearly used all techniques to study heparin. This hard work and intense investigation was a great lesson for both of them and prompted their interest in further studies of heparin’s chemistry, biology and pharmacology. Although their pursuit was for heparin, they learned so much about coagulation enzymes and step wise methodologies to extract anticoagulants and characterize these during in the course of their investigation. It also fostered a great bond between the author and his mentor, the late Harry Messmore who was a unique man with great vision. He prompted the author’s interest in LMWHs and synthetic heparins. The author who has been studying heparins for over 40 years, yet up to date, is still not comfortable to describe the true biologic attributes of this drug. Like many others, heparin has continued to fascinate him on a daily basis. He feels that there may be additional unexplored attributes to this agent which will impact on our approaches to treat thrombotic and cardiovascular diseases. Despite the advancement in physical, biological and medical sciences, the knowledge regarding heparin structure, pharmacology and clinical effects is still far from complete. Hopefully we will continue to probe the science of heparin and learn more about its role in nature and its possibilities.

**REFERENCES**


