Heparin Centennial
A Century of Scientific and Clinical Progress

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Anticoagulants

Parenteral
- Heparins
  - UFH
  - LMWHs
  - U-LMWHs
  - Oligosaccharides
- Anti-Thrombin
  - Argatroban
  - Desirudin
  - Bivalirudin

Oral
- VKA
  - Warfarin
  - Phenprocoumon
  - Acenocoumarol
- Non-VKA oral anticoagulants
  - Ximelagatran
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
Anticoagulation - Historic Perspective

1900’s    Leech extract for parenteral anticoagulation (hirudin)
1916       Discovery of heparin (McLean)
1938       Clinical use of heparin (Crafoord)
1939       Identification of dicumarol (Link)
1950       Clinical use of vitamin K antagonists
1980       LMW heparins
1990       Synthetic heparin (fondaparinux)
1990       Parenteral antithrombin agents (Markwardt/Okamoto)
2000       Oral thrombin inhibitors
2010       Oral FXa inhibitors
Present   Development of other protease inhibitors
          Diversification of heparins
Johann Friedrich Dieffenbach, a German surgeon. In 1822 he employed leeches in surgical procedures.
Professor John Haycraft

Isolated the anticoagulant from leech saliva & named it as hirudin in 1874.
MYSTERIOUS HEPARIN
THE KEY TO OPEN HEART SURGERY
Molecular heterogeneity of heparin

Composed of Oligosaccharides of varying lengths: 5-50 kDa
Discovery & Development of Heparin

1916  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’ lab showed N-sulfated glucosamine in heparin. Jorpes with Charles & Scott produced sufficient amount of heparin & Crafoord used it in humans (Stockholm & Toronto)
Pioneers in heparin discovery

McLean

Howell

Jacques
Much of the purification of initial heparin was done under the guidance of Dr Best, Dpt of Physiology.
The Swedish Connection

Jorpes                Crafoord                Bergstrom

Chemist             Surgeon                  Jorpes’    
        Graduate student
Fractionation & depolymerization of Heparin

UFH
15 kDa

LMWH
4-6 kDa

Ultra LMWH
2-4 kDa

Pentasaccharide
1.7 kDa

Heparin derived oligosaccharides
< 2.5 kDa

Anti-Xa/IIa = 1.0

Anti-Xa/IIa = 2.5 - 7.5

Anti-Xa/IIa = ≥ 50

Depolymerization inflicts structural changes
<table>
<thead>
<tr>
<th>Year Range</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>1960 – 1970</td>
<td>Fractionation of heparins based on MW &amp; charge density, Cifonelli, Chicago</td>
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<tr>
<td>1970 – 1980</td>
<td>Depolymerization of heparin to manufacture LMWHs &amp; ULMWHs, Dietrci, Sao Paulo</td>
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<tr>
<td>1980 – 1990</td>
<td>Synthesis of heparin oligosaccharides such as pentasaccharide, Choay and colleague, Paris</td>
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Landmarks in the development of LMWHs


2010 – 2015  Further characterization of LMWHs & development of guidelines for standardization & quality assurance

Beyond 2015  Additional approaches to prepare LMWHs & analogues such as the chemo-enzymantic methods & biosynthetic approaches. Preparation of heparins from other mammalian sources (ovine & bovine). Newer formulations.
Some of the commercially available LMWHs

- Lovenox®
  - 2000 UI anti-Xa/0.2 ml
  - Solution injectable - 2000 UI anti-Xa correspondant à 20 mg
  - 2 seringues pré-remples
- Zibor 3500 NE
  - anti Xa/0.2 ml
- Reviparin sodium injection 0.25 ml
  - Clivarine®
  - Solution for s.c. Injection:
    - (0.25 ml) contains:
      - 1432 anti-Xa IU (Pharm. Eur.)
      - Sodium chloride 1.5 mg
      - Water for injection (Pharm. Eur.) q.s. 0.25 ml
- Fraxiparine®
  - 0.3 ml
  - 2 850 UI Axa / 0.3 ml
  - 2 850 IU Axa / 0.3 ml
- Fragmin®
  - dalteparin sodium injection
  - For subcutaneous injection
  - 15,000 IU (anti-Xa) per 0.6 mL
Generic Enoxaparin Injections
Variations in composition & pharmacologic profiles
Clinical Developments of LMWH

- Initially developed for post surgical prophylaxis of VTE
- Expanded indications for the medical patients & extended management of VTE
- Management of acute coronary syndrome
- Management of thromboembolic stroke
- Out-patient management of pregnancy associated VTE
- Clinical management of cancer associated thrombosis
- Management of auto-immune disease associated thrombosis (anti-phospholipid syndrome, Crohn’s disease)
- Pediatric indications
Stan Wessler  Pioneering work on mechanisms of heparin actions (Anti-FXa effects)
Sole anti-Xa oligosaccharides exert antithrombotic activity.

This concept lead to the synthesis of pentasaccharide (Arixtra)
Vijay Kakkar

- First published on the SC dosing of heparin for the prophylaxis of post-surgical DVT (1976)
- Carried out the first clinical trial on the low molecular weight heparin Fraxiparin (1980)
Heparin Induced Thrombocytopenia
Generation of Multiple Antibodies with Heparin

Heparin + PF-4 → Heparin-PF-4 Complex
Impact of HIT on the Rationale Development of LMWHs & Heparin Oligosaccharides

1. LMWHs have relatively lower affinity to bind to PF4 whereas heparin oligosaccharides exhibit even lower affinity.

2. LMWHs & heparin oligosaccharides do not mobilize PF4 from platelets.

3. Antibody subtypes due to LMWH PF4 are mostly non-IgG, which are nonpathogenic in nature.

4. Heparin oligosaccharide are rarely associated with the generation of HIT Abs & therefore have been used in heparin compromised patients.
The Development of Fondaparinux (Arixtra®)

The First FXa Inhibitor Drug

Pentasaccharide is a totally synthetic heparin derivative.

It is free of biologic contaminants & does not generate HIT associated antibodies.
The pentasaccharide team

Jean Choay

M Petitou

J.C. Lormeau
Professor Jeanine Walenga

Validated the use of sole anti-Xa agents as antithrombotics
Heparin Recall 2008
The Contaminant Crisis

1. USA
2. Germany & Switzerland
3. Japan
4. Canada
5. Denmark, Italy, France

- The recall expanded to other countries where heparin material was imported from China

- Heparin originated from N America & European source material was not found to have the contaminant
U.S. Identifies Tainted Heparin in 11 Countries

The New York Times
FDA Asks for $275 Million To Aid in Drug Inspections

The Wall Street Journal
The FDA and safety—beyond the heparin crisis

nature
Researchers pursue artificial heparin

The Philadelphia Inquirer
China: N.J. plant may be at fault in heparin crisis

In The News
What the Heparin Crisis Should Tell Us

BioPharm
Report Confirms Source of Contaminated Heparin

The Washington Post
Concerns flare again over use of heparin

The Seattle Times
Tainted Drug Imports Set Off Warnings, Not FDA Action

Bloomberg.com
Contaminated Heparin from China in 11 countries

Australia, Canada, China, Denmark, France, Germany, Italy, Japan, the Netherlands, New Zealand, USA
Three different batches of Chinese crude heparin differing in quality
Heparins 
Supply and Demand 

- Almost 80% of the US heparin supply is from China and India which is comprised of porcine heparin.
- The USFDA has expressed concern over the limitations and initiated alternate sourcing of heparin including bovine heparin from other countries.
- Loyola is primarily involved in the development of bovine and sheep heparins.
Diversification of Heparins

• Sources
  - porcine, bovine, ovine
• Cultural
• Economic
• Geopolitical
• Blended heparins
• Non-anticoagulant heparins
• Therapeutic glycosaminoglycans
Conclusions—Sulodexide given after discontinuation of anticoagulant treatment reduced the risk of recurrence in patients with unprovoked venous thromboembolism, with no apparent increase of bleeding risk.

Validates the concept of oral absorption of heparin related GAGs
The Future of Heparins.

• Newer formulations & delivery options for heparins.
• Synthesis of designer heparins & heparinomimetics.
• Use of alternate sources to obtain heparin & related products.
• Development of target specific heparins for such indications as cancer, autoimmune diseases & other vascular disorders.
• Expanded Indications
Will Heparins survive in the era of the NOACS?

Not only survive but may outserve the NOACS.