MARK W. SKINNER

WFH President
In compliance with the EACCME* policy, WFH requires the following disclosures be made at each presentation:

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Support</td>
<td>None</td>
</tr>
<tr>
<td>Director, Officer, Employee</td>
<td>None</td>
</tr>
<tr>
<td>Shareholder</td>
<td>None</td>
</tr>
<tr>
<td>Honoraria</td>
<td>None</td>
</tr>
<tr>
<td>Advisory Committee</td>
<td>None</td>
</tr>
<tr>
<td>Consultant</td>
<td>None</td>
</tr>
</tbody>
</table>

* European Accreditation Council for Continuing Medical Education
The Journey Begins

50 YEARS OF ADVANCING TREATMENT FOR ALL
The threat to the life of just one haemophiliac would be sufficient reason for us to travel to this meeting. We are here however to help the hundreds of thousands of haemophiliacs by adding another organization which can be instrumental, in liaison with national societies.

– Frank Schnabel
June 1963
Copenhagen, Denmark
EARLY VISIONARIES – INTERIM (1963) AND FIRST OFFICERS (1964)

Mr. Frank Schnabel (Canada)
Sir Weldon Dalrymple-Champneys (UK)
Prof. Kenneth Brinkhous (US)
Mr. Henri Chaigneau (France)
Dr. Cecil Harris (Canada)
Dr. E. Neumark (UK)
Dr. Knut-Eric Sjolin (Denmark)
Prof. J.P. Soulier (France)
Mr. John Walsh (US)
Prof. S. Van Creveld (The Netherlands)
WFH NATIONAL MEMBER ORGANIZATIONS 1963

Blue – 12 nations represented in the inaugural meeting 1963
**WFH NATIONAL MEMBER ORGANIZATIONS 2012**

- **Blue** – 12 nations represented in the inaugural meeting 1963
- **Red** – Additional countries joining through July 2012 (122 in total)
“The hemophiliac cannot live unless his blood is induced to clot by the addition of normal blood (or blood plasma).

...and now there is fresh frozen blood plasma which can be stored to provide a constant life-saving supply.

...sponsor needed research which will some day bring a cure or a control, by solving the mystery of blood coagulation.”

Source: NHF 1958
A Peanut Factor for Hämostasis in Hämophilia

H. BRUCE BOUDREAUX & VERNON L. FRAMPTON

Department of Zoology, Louisiana State University, Baton Rouge, Louisiana.


It is known that there are unpredictable apparent remissions of clinical symptoms enjoyed by hemophiliacs; but these remissions have not been correlated with any influences such as time of year, food eaten, weather conditions, other diseases, or physical condition of the patient. The lack of "antihemophilic factor" associated with classic hemophilia has been attributed\(^1\) to a hypothetical block during the metabolic synthesis of the factor resulting from the action of the mutant gene of hemophilia, such as occurs in the nutritional mutants of Neurospora and in eye pigment development in certain mutants of Drosophila\(^2\). In the cases of Neurospora, and Drosophila, and other organisms studied, the addition of the substances the synthesis of which is blocked genetically results in normal metabolism. If this is the case in hemophilia, it may be possible to supply, by mouth or injection, the unavailable material necessary for normal production of the hemostatic substance lacking in hemophiliacs. However, the few instances of success of various supplements, such as vitamin E and B\(_\text{12}\), X-rays, and estrogens, have not been confirmed\(^3\).

Source: Nature 1960; Personal Archives; Japan Committee for People with Hemophilia
“Over the past several years there has been increasing recognition that concentrates of anti-hemophilic globulin have a distinct role in the treatment of hemophilia…

…development …has been hampered by the expense involved in production…

It is difficult to predict …the exact role that the concentrate developed by Dr. Pool … will finally play in the treatment of hemophilia.”
1960’s & 1970’s

1960’s

1st Cryoprecipitate Produced

1970’s

1st FVIII Concentrate Commercially Available

1st Prothrombin Complex Concentrates Developed
MEDIAN AGE OF DEATH – IMPACT OF HIV

Sources: Chorba et. al; NIH NIHAID
1960’s
1st Cryoprecipitate Produced

1970’s
1st FVIII Concentrate Commercially Available
1st Prothrombin Complex Concentrates Developed

1980’s
1st Recombinant FVIII Developed

1990’s
1st Recombinant FVIIa Developed
1st Recombinant FIX Available
Introduction of Multidisciplinary Care
MULTIDISCIPLINARY COMPREHENSIVE CARE

One of the most successful public health programs.

Essential to achieving optimal health outcomes.

Essential to reducing healthcare utilization.
Health is a state of complete physical, mental and social well-being and not merely the absence of disease infirmity.

– WHO Constitution
Adopted June 1946
WFH VISION

Working to achieve Treatment for All those living with bleeding disorders regardless of where they live.
**WFH Milestones in Development**
*Adapting and Responding to Needs Around the World*

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1963</td>
<td>WFH Founded</td>
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<tr>
<td>1969</td>
<td>WHO Recognition</td>
</tr>
<tr>
<td>1972</td>
<td>1st International Training Centers</td>
</tr>
<tr>
<td>1973</td>
<td>1st Hemophilia Care Workshops 1st HTC Directory</td>
</tr>
<tr>
<td>1983</td>
<td>World Hemophilia AIDS Center</td>
</tr>
<tr>
<td>1990</td>
<td>1st World Hemophilia Day</td>
</tr>
<tr>
<td>1991</td>
<td>1st Musculoskeletal Congress</td>
</tr>
<tr>
<td>1994</td>
<td>1st <em>Hemophilia World</em> published 1st HTC Twinnings</td>
</tr>
<tr>
<td>1995</td>
<td>1st NMO (HOT) Twinning; <em>Haemophilia</em> Journal launched</td>
</tr>
<tr>
<td>1996</td>
<td>WFH Programs Department established</td>
</tr>
<tr>
<td>1996</td>
<td>1st Operation Access 1st WFH Website Humanitarian Aid Program</td>
</tr>
<tr>
<td>1999</td>
<td>1st NMO Training 1st Global Survey Report</td>
</tr>
<tr>
<td>2000</td>
<td>1st Global Safety &amp; Supply Forum</td>
</tr>
<tr>
<td>2001</td>
<td>1st Lab Train the Trainers</td>
</tr>
<tr>
<td>2002</td>
<td>1st Regulatory Workshop</td>
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<tr>
<td>2003</td>
<td>GAP Program launched</td>
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<tr>
<td>2004</td>
<td>IEQAS launched</td>
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<tr>
<td>2005</td>
<td>1st Treatment Guidelines</td>
</tr>
<tr>
<td>2006</td>
<td><em>Treatment for All</em> vision adopted 1st Advocacy Initiative</td>
</tr>
<tr>
<td>2011</td>
<td>1st Global Research Forum</td>
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</tbody>
</table>
Global Alliance for Progress
2003-2012

50 YEARS OF ADVANCING TREATMENT FOR ALL
GAP 10-YEAR STRATEGIC GOALS 2003-2012

• Enroll 20 countries over 10 years
• 50,000 increase in people with hemophilia diagnosed / identified globally
• To close the GAP between the:
  1) estimated and actual number of people known with bleeding disorders
  2) amount of treatment products needed versus that available
  3) number of people born with hemophilia and the number who reach adulthood
GLOBAL ALLIANCE FOR PROGRESS (GAP) 2003-2012

20 countries enrolled in the WFH GAP program
Today’s Reality

50 YEARS OF ADVANCING TREATMENT FOR ALL
1 in 1,000 men and women has a bleeding disorder

6,900,000 People Worldwide

Source: M. Skinner; Haemophilia (2012), 18 (Suppl.4) 1-12
<table>
<thead>
<tr>
<th>Bleeding Disorder</th>
<th>WFH Published Estimates (* - Prevalence Estimate; ∞ - Incidence Estimate)</th>
<th>WFH Prevalence Estimates World Popn. 6,927,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>105 in 1 million∞ (1 in 10,000*)</td>
<td>363,668</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>28 in 1 million∞ (1 in 50,000*)</td>
<td>96,978</td>
</tr>
<tr>
<td>Women with hemophilia</td>
<td>1.56 per person with hemophilia; 50% at bleeding risk</td>
<td>359,303</td>
</tr>
<tr>
<td>Von Willebrand Disease</td>
<td>1,000 in 1 million∞ (1 per thousand symptomatic)</td>
<td>6,927,000</td>
</tr>
<tr>
<td>Factor I (Afibrinogenemia)</td>
<td>0.5 in 1 million*</td>
<td>3,464</td>
</tr>
<tr>
<td>Factor I (Dysfibrinogenemia)</td>
<td>1 in 1 million*</td>
<td>6,927</td>
</tr>
<tr>
<td>Factor II</td>
<td>0.5 in 1 million*</td>
<td>3,464</td>
</tr>
<tr>
<td>Factor V</td>
<td>1 in 1 million*</td>
<td>6,927</td>
</tr>
<tr>
<td>Factor V+VIII</td>
<td>1 in 1 million*</td>
<td>6,927</td>
</tr>
<tr>
<td>Factor VII</td>
<td>2 in 1 million*</td>
<td>13,854</td>
</tr>
<tr>
<td>Factor X</td>
<td>1 in 1 million*</td>
<td>6,927</td>
</tr>
<tr>
<td>Factor XI</td>
<td>10 in 1 million*</td>
<td>69,270</td>
</tr>
<tr>
<td>Factor XII</td>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Factor XIII</td>
<td>0.33 in 1 million*</td>
<td>2,309</td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>WFH identified number</td>
<td>1,584</td>
</tr>
<tr>
<td>Bernard-Soulier Syndrome</td>
<td>WFH identified number</td>
<td>323</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>Equals 1 person with a bleeding disorder per 880</td>
<td>7,868,924</td>
</tr>
</tbody>
</table>

Source: M. Skinner; Haemophiliia (2012), 18 (Suppl.4) 1-12
REALITY – PERCENTAGE IDENTIFIED BY COUNTRY ECONOMY

Percentage of people with hemophilia identified by economic grouping

Source: WFH Global Survey 2010
CLOSING THE GAP IN DIAGNOSIS

Yearly global increase in people diagnosed with:

- Hemophilia
- VWD
- Other bleeding disorders (rarer factor deficiencies & inherited platelet disorders)

Source: WFH Global Survey 1999-2011 (2011 preliminary est.)
CLOSING THE GAP IN DIAGNOSIS

GAP Objective:
Increase the global number of people diagnosed / identified with hemophilia (PWH) by 50,000 in 10 years (2003-2012).

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of PWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>105,971</td>
</tr>
<tr>
<td>2011(est.)</td>
<td>163,824</td>
</tr>
<tr>
<td>Total increase</td>
<td>57,853</td>
</tr>
</tbody>
</table>

Over 50,000 in the first 9 years!

Source: WFH Global Survey 2003; Preliminary estimate 2011 Global Survey
Hemophilia A age distribution for country groups based on World Bank economic rankings.

Source: WFH Global Survey 2009
CLOSING THE GAP IN MORTALITY

Comparison in the ratio of people with hemophilia - children (age <13 years) to adults (ages >18 years) using USD per capita Gross Domestic Product (GDP)

In 6 years, a 5% increase in the number of children surviving into adulthood!

Source: WFH Global Survey 2002 & 2009 – 39 country comparison
Over 40% of the countries reporting data to the WFH indicate cryoprecipitate and FFP are being used to treat people with hemophilia.

Source: WFH Global Survey 2010; B. Evatt et. al. Haemophilia 1999
REALITY – GEOGRAPHIC DISPARITY IN FVIII CONSUMPTION

75% of treatment products are consumed by 15% of the world’s population.

Source: P. Robert, Market Research Bureau 2011
CLOSING THE GAP IN PRODUCT ACCESS

Per capita FVIII use by gross domestic product group for countries:

- <US$ 2,000
- US$ 2,000-10,000
- Worldwide

Globally, the mean FVIII IU per capita has increased by >225%!

Source: WFH Global Survey 2001-2010
People with current “clinically significant” inhibitors.

- Hemophilia A
- Hemophilia B

Defined as those who do not respond to normal treatment.

Source: WFH Global Survey 2007-2010
The Future

50 YEARS OF ADVANCING TREATMENT FOR ALL
2000’s – ADVANCING ON ALL FRONTS

SD Cryo Biosimilars

Current Therapy

Long-Lasting Products

Gene Transfer

Sources: Vox Sanquinis 2006; NEJM 2012
CELL PHONES & LANDLINES

• What will be the future evolution of treatment?
• Will developing countries benefit from the technology advances?
  – SD cryoprecipitate
  – Biosimilars
  – Long-lasting products
  – Gene transfer

Source: High & Skinner. Molecular Therapy 2011
Optimal Treatment

50 YEARS OF ADVANCING TREATMENT FOR ALL
OPTIMAL TREATMENT

• The aim of treatment is to reduce the frequency of joint bleeds and the crippling effect.
• Concept of prophylactic treatment to maintain FVIII/FIX levels >1% was pioneered in Sweden in the 1960s.
• Prophylaxis prevents subclinical bleeds (microhemorrhages)

Source: Manco-Johnson et. al. *NEJM* 2009
IS 1% THE CORRECT TARGET?

• Normal FVIII / FIX activity is 50% - 150%
• Patients and clinicians have been conditioned to accept converting from a severe to a moderate state as a desired end-point
  – e.g., maintaining a 1% baseline factor level

Is 1% sufficient to prevent sub-clinical bleeding or is it simply based on historical supply constraints, economics and treatment protocol burdens?
ASPIRE TO THE ABSENCE OF JOINT BLEEDS

- Demonstrated association between joint bleeds and baseline factor levels
- No expected joint bleeds in patients with baseline factor activity of ≥15%
- 18% reduction in joint bleed frequency with every 1% increase in residual clotting factor activity

Source: Den UijL et. al. Haemophilia 2011
Affordable Treatment
The 80:20 Challenge

Treatment Product Cost : Cost for All the Rest

Source: Guh et. al. (CDC) Haemophilia 2011
A PARADIGM OF SCARCITY

• Treatment protocols dictated by scarcity of treatment products
• Constraints on utilization distort true demand
• Understanding unconstrained demand is vital
  – Production planning
  – Health policy planning
• Today, supply constraint should not be a factor
TIME FOR A 21ST CENTURY PARADIGM
A NEW BUSINESS MODEL

- Accelerating innovation of treatment products presents the opportunity to accelerate global access
- A 21st century business model is required
  - A new paradigm based on high-volume, lower margins
- Payers expect the optimization, innovation and efficiencies achieved in manufacturing will be passed on in final product pricing
The technology, knowledge and capacity exist to dramatically improve global access to clotting factor concentrates. It is now a moral imperative for governments, regulators and industry to rise to the challenge by:

- Improving market accessibility
- Adopting new market-based pricing strategies

The production, pricing and marketing strategy of companies bringing new products to market present an opportunity to significantly and favorably impact affordability and accessibility.
The Next Decade of Global Development
2013-2022

50 YEARS OF ADVANCING TREATMENT FOR ALL
Global Alliance for Progress
2013-2022

50 YEARS OF ADVANCING TREATMENT FOR ALL
50,000 increase globally in people with all bleeding disorders diagnosed / identified

50% of the newly diagnosed / identified from impoverished and underserved countries

Enroll 20 countries over 10 years

To continue closing the gap in:
– Diagnosis
– Treatment product access
– Mortality

Health Outcomes Surveillance
APPROPRIATE ORDER FOR ADVANCING THE DEVELOPMENT OF CARE

• What comes next? Is there one right answer?
• When should a country should introduce:
  – home-based care
  – prophylaxis (for whom and how long)
  – treatment for inhibitors & immune tolerance induction
  – high-purity or recombinant products
  – outreach to identify women with bleeding disorders
  – care for people with VWD, platelet or other rare bleeding disorders
• How will this impact tendering / purchasing decision?
• Will it be possible to ensure sustainability / treatment continuity?
The Cornerstone Initiative
2013-2022

50 YEARS OF ADVANCING TREATMENT FOR ALL
WFH – THE CORNERSTONE OF GLOBAL DEVELOPMENT

“The cornerstone was laid by the WFH for the next decade of hemophilia care development in China.”

WFH Hemophilia Conference
May 2007 – Wuling, China
Dr. Renchi Yang
9% of patients identified with a bleeding disorder worldwide are from countries with a GNI per capita of <$1,500 USD.

This group of countries represents one-third of the world’s population.

Source: WFH Global Survey 2010
• Through training the WFH will lay the foundation cornerstone upon which future building and development may occur
• Targeted to underserved and impoverished regions of the world
• Designed to develop basic care
  – Develop or improve diagnosis capacity
  – Provide basic training in the management of bleeding disorders
  – Strengthen patient organizations
• Evidence-based evaluations of rare diseases should not be confined to traditional analysis
• Utilize new concepts including:
  – Societal willingness to pay
  – Cost savings for bleeds prevented
  – Reductions in inhibitor incidence
  – Cost to manage co-morbidities other than joint disease
  – Quality of Life improvement

• In response WFH will enhance:
  – Global surveillance
  – Health outcome data collection
  – Analysis
• Promote their integration into the comprehensive care model
• Systematic data analysis will accelerate adoption of treatment advances and optimize clinical care
GUIDELINES

Guidelines for the management of hemophilia

A. SRIVASTAVA,* A. K. BREWER,† E. P. MAUSER-BUNSCHOTEN,‡ N. S. KEY,§ S. KITCHEN,¶
A. LLINAS,** C. A. LUDLAM,†† J. N. MAHLANGU,‡‡ K. MULDER, §§ M. C. POON,¶¶ and
A. STREET*;*: TREATMENT GUIDELINES WORKING GROUP ON BEHALF OF THE WORLD
FEDERATION OF HEMOPHILIA

• Graded and Annotated
• Where recommendations lack adequate evidence, the WFH aims to stimulate appropriate studies.
Research Mentorship
Expanding Global Capacity

50 YEARS OF ADVANCING TREATMENT FOR ALL
The World Federation of Hemophilia will continue to pursue two concurrent and complementary objectives to accelerate the utilization of the research potential and to expand contemporary comprehensive care of hemophiliacs.

– Frank Schnabel
WFH President 1963-1987
Bonn Blueprint 1980
A DEBT OF GRATITUDE – TODAY’S VISIONARIES AND LEADERS

Alison Street
Vice President
Medical
2008-2012

Rob Christie
Vice President
Finance
2004-2012
BE PART OF THE VISION. GIVE TO CLOSE THE GAP.

WORLD FEDERATION OF HEMOPHILIA

50 YEARS OF ADVANCING TREATMENT FOR ALL