Haemophilia Care:
Past, present and future

Dr Paula Bolton-Maggs

Executive Committee WFH

Consultant Haematologist

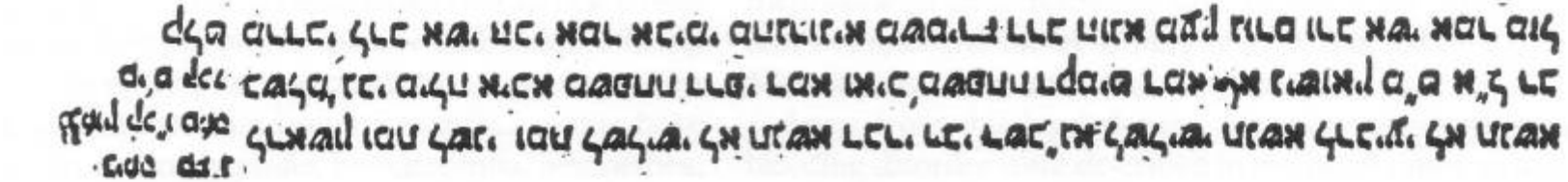
Manchester UK

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACION MUNDIAL DE HEMOFILIA

Haemophilia – described in ancient texts

- For it is taught: if she circumcised her first child and he died (as a result of bleeding from the operation), and a second one also died, she must not circumcise her third child.
  - 4th century Rabbinic writings



Babylonian Talmud, 4th century
Yevamoth 64b

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

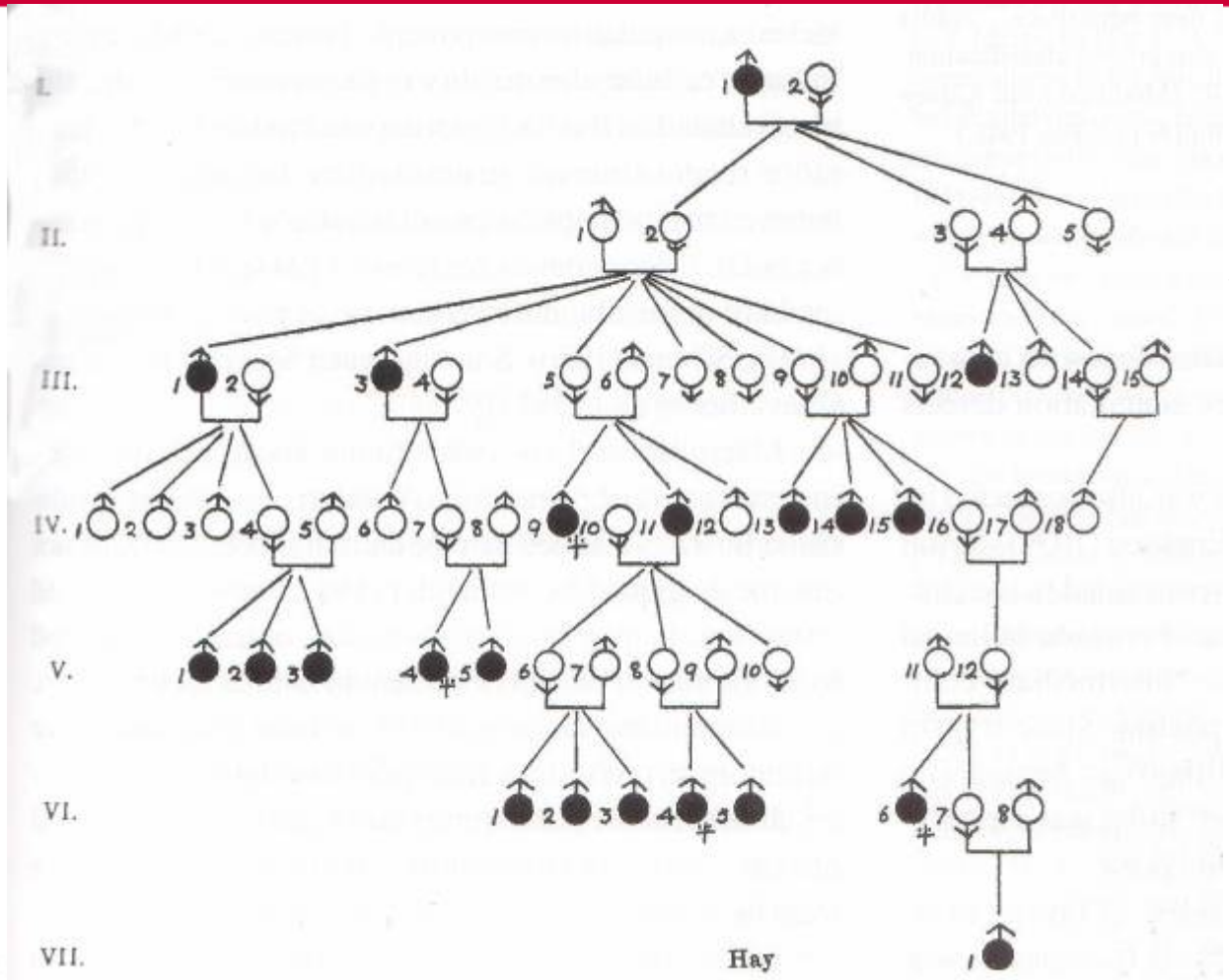
An early account of haemophilia in the USA

DIED]—In Frederick county (Virginia) Mr. ISAAC ZOLL, aged 19. His death was occaſioned by a ſlight cut in one of his feet, with an ax. From the time of his receiving the wound, till he expired, no method could be deviſed to ſtop the bleeding: if the wound was bound up, the blood guſhed out at his mouth or noſtrils.—Five brothers to the above perſon have bled to death, at different periods, from the following accidents: One received a prick with a thorn—another, a ſcratch with a comb—a third, a prick with a needle—a fourth bruiſed his cheek againſt a ſtove—and the fifth received a cut in one of his thumbs. The father of the above perſons has had two wives, and by each, ſeveral children; thoſe who died in this ſingular manner were all of the firſt wife.———At Charleſton,

Salem, Massachusetts Gazette, 1796

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Documentation of the sex-linked inheritance



6 generations, 172 years, 20 haemophilic males
Later traced over 400yrs and 13 generations; originating from UK in 1630

First pedigree of haemophilia published by Hay in 1813 in USA

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Haemophilia - Past

- 1893 Wright: blood clotting time is prolonged
- 1911 Addis: addition of normal blood could correct the abnormal clotting
- 1840 Lane had described benefit of blood transfusion
- 1923 Feissly demonstrated superiority of plasma
- 1947 Pavlovsky observed that blood from one haemophiliac could correct the defect in another
- 1952 Biggs confirmed two types of haemophilia – report of Mr. Christmas
- 1950s Unravelling the coagulation pathways - several

Causes of death recorded for haemophilia by Carrol Birch, 1937 (98 cases)

Cause of death	No of cases	Notes	
Operation	25	Circumcision	15
		Tooth extraction	6
		Vaccination	1
		lanced haematoma	2
		Tonsillectomy	1
Trivial injuries	23	Cut lip, bitten tongue, injuries to finger, scalp etc.	
Epistaxis	6		
Internal bleeding	21		
CNS bleeding	7		
Haematuria	4		
Lung haemorrhage	5		
Birth trauma and umbilical bleeding	7		

Only 6 patients survived to age 40 yrs

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Haemophilia diagnosis

- ‘the number of cases in a given country depends upon the previous education of the medical men and the interest which they take in the disease’
  - Legg 1872

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Milestones in Haemophilia

Time	Events
1950s	Mainstay of treatment is FFP which often required stay in hospital National haemophilia register established in UK under MRC Haemophilia Society started
1964	Judith Pool discovers how to make cryoprecipitate for the treatment of haemophilia A
1968	Rosemary Biggs holds a tea party and the UKHCDO is started

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

History of haemophilia

- FFP was the mainstay of treatment until cryo was introduced in 1965
- The volumes required caused heart failure
  - Up to 1 litre twice a day for adults for 4-8 d
- Allergic reactions could be life-threatening

Historical recollections

- ‘My first patient with severe haemophilia had been to hospital 27 times and had seen 17 different doctors before he was 5 yrs old’ Peter Jones
- ‘A teenage haemophiliac had a tooth extracted and I held a swab to the socket intermittently for 18 days’ Stuart Douglas

Milestones in Haemophilia

Time	Events
1970s	Development and availability of concentrates allowed home treatment programmes. Establishment of haemophilia comprehensive care centres in many countries
1982 1984	Sequencing of FIX gene Sequencing of FVIII gene
1980s	HIV and hepatitis viruses emerge as a major problem Heat treatment introduced Screening methods for these viruses in blood donors
1990s	Introduction of genetically engineered products

Robert Massie – the patient perspective

- ‘When I was 12, two things happened which had an extraordinary impact.
- One was that in 1968, I was taught to self-infuse.
- Secondly, the factor VIII concentrates began to appear. These made an enormous difference because not only were they much more powerful, but the key piece was that they could be kept cool rather than frozen. That opened up an absolutely enormous vista for me to do things on my own because I could take my bottles of factor with me. Eventually they could be kept at room temperature..I could literally pack a back pack and go. I was able to give myself shots on camping trips or in the bathroom of a 747. Just at the moment of adolescence, when your life is expanding anyway, my ability to manage haemophilia improved in a way that allowed me this freedom.’

From ‘The Gift of experience’, a collection of oral histories

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

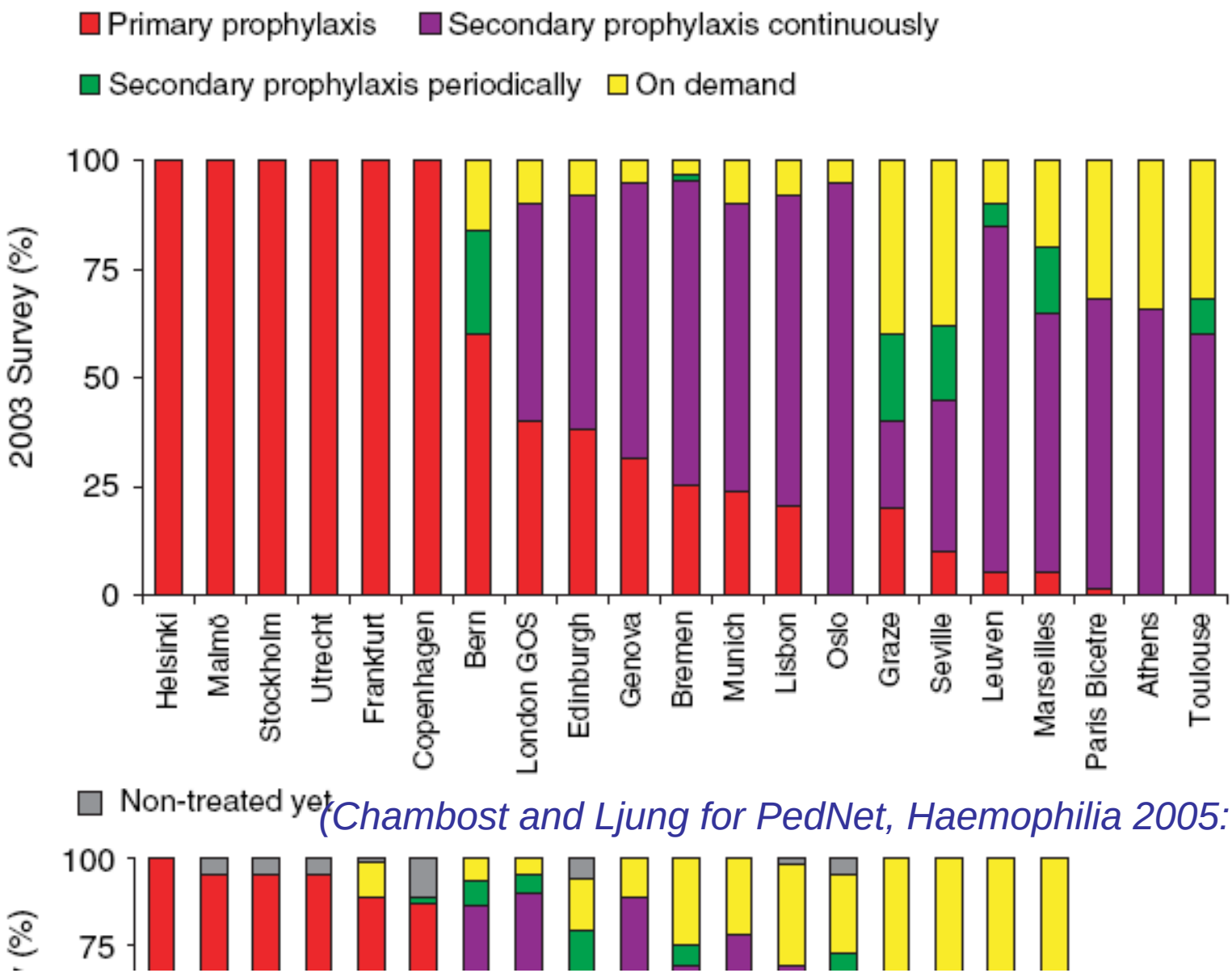
Haemophilia – the present

- In wealthy countries, good quality of treatment, nearly normal life
  - Recombinant products
  - Prophylaxis
  - No bar to surgery
  - Normal employment prospects and lifestyle
- In many countries, no or inadequate treatment

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Prophylaxis for children

- Recommended as best therapy by
  - WHO 1994
  - UKHCDO 1994
  - USA National Hemophilia Foundation 1994
  - Canadian Hemophilia Society 1993
- Where it is not feasible, intensive ‘on demand’ therapy should be given.



(Chambost and Ljung for PedNet, Haemophilia 2005: 11; 92-99)

Fig. 1.
boys tr
Europe

Prophylaxis – when to stop?

- Study from van Creveld klinik
- 11/49 patients who stopped in early adult life
  - Started prophylaxis later
  - At a lower dose
  - Low bleed frequency
  - Joint scores no worse than those who continued
- Probably a milder phenotype

Surgery in Haemophilia

- Any surgical procedure can be performed in haemophilia
- There has been no attempt to evaluate the optimal dose to achieve haemostasis
- There is a complete lack of uniformity in practice

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

(Srivastava 2004)

Variable recommendations for treatment Major surgery in Haemophilia A

Desired level	Dose IU/kg	Duration (days)	Source
80-100	40-50	Not stated	Rizza 1981
80-100	40-50	10-14	Lusher 1999
80-100	40-50	12	Rickard 1995
50-150	50-60	Up to 17	Nilsson 1994
50-100	30-50	Until healing	Escobar 2003

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Lower doses for major surgery?

Time	Desired level of FVIIIC (%)	Desired level of FIXC (%)
Pre-operative	80-100	60-80
Days 1-3	20-40	15-30
Days 4+	15-30	10-20

18 patients with severe haemophilia, 20 surgical procedures; 1 bled d11 due to surgical cause. Duration 8-16d. Trough levels about 35%, lowest 11% with no bleeding.

(Srivastava et al. Haemophilia 1998, 4, 799)

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

- **Guidelines (Rickard 1995) would lead to use of 50,000-80,000 units FVIII per patient**
- **This study used 12,000 to 20,000 units per patient**

Inhibitor management

Great strides have been made in inhibitor therapy in the past two decades:-

- At least 80% of inhibitors can be eliminated by immune tolerance
- Bleeding can be treated far more effectively than before (FEIBA and rVIIa)
- Death rate has normalised.
- Morbidity and quality of life is almost as good as non-inhibitor pts and comparable to other chronic disease groups.
- This has been achieved at great financial cost. A small number of inhibitor patients are enormously expensive.

BUT Problems with haemophilia care in developing countries

- Inadequate knowledge
  - Education is essential
- Lack of laboratory diagnostic facilities
- Inadequate supply of affordable safe factor

What is the WFH?

- **International non-profit organization founded 1963**
- **World Health Organization (WHO) recognition in 1969**
- **113 National Member Hemophilia Organizations**
- **Extensive network of lay & medical volunteers**
- **Headquarters in Montreal, Canada (26 staff)**
- **Elected Executive Committee (15 members)**

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Today's Reality

- 70% not diagnosed
- 75% not treated
- Many will die young or grow-up severely disabled

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Our Mission

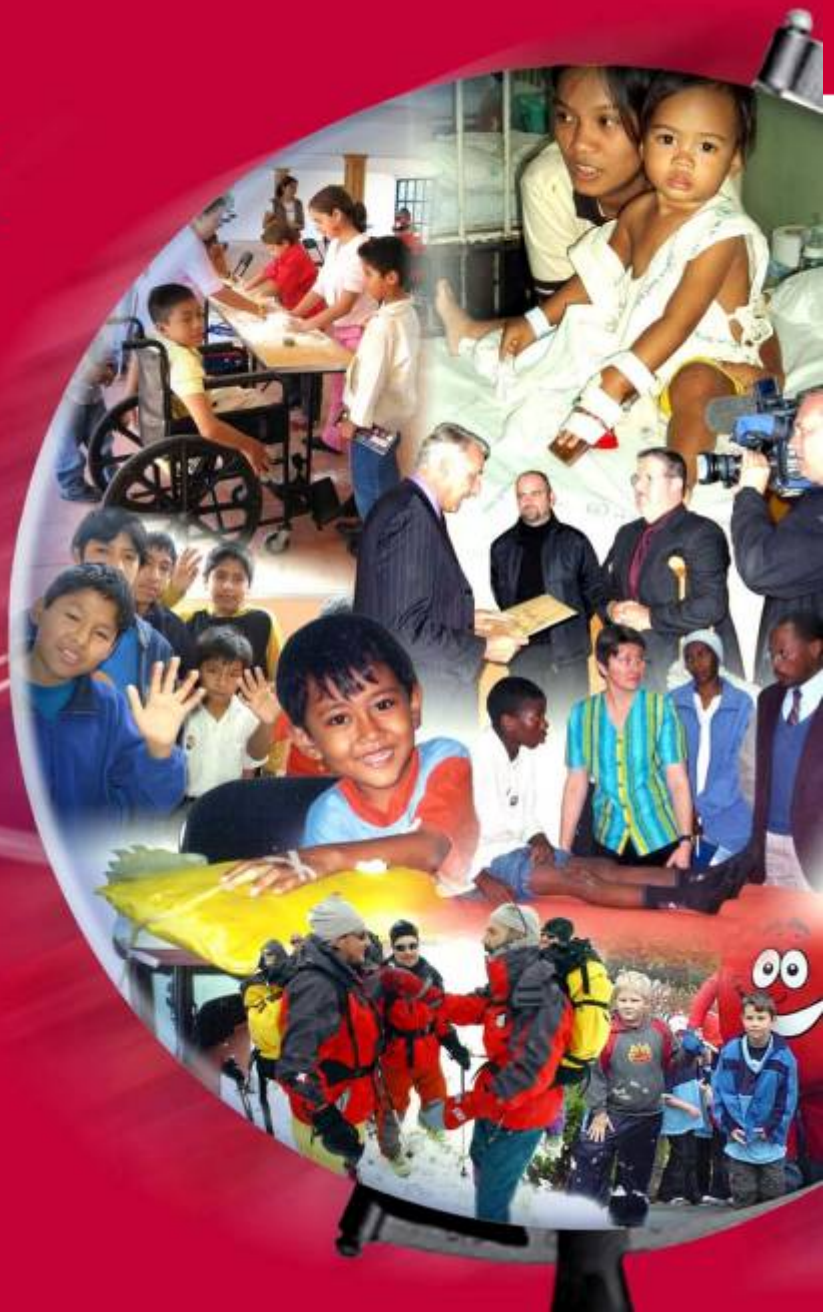
The World Federation of Hemophilia improves and sustains care for people with inherited bleeding disorders around the world.

WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

45 Years - 2008

Treatment for all

A Vision for Improvement



The Vision

Treatment for All

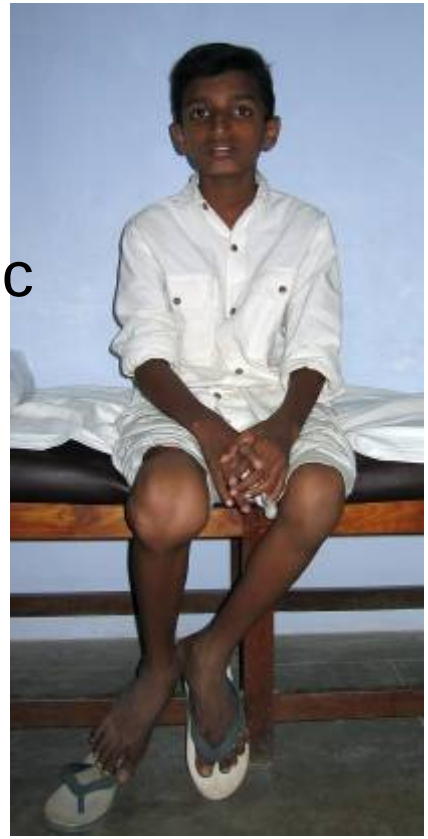
- It means…
  - safe, effective treatment products are available for all people with inherited bleeding disorders.
  - proper diagnosis, management, & care by a multidisciplinary team of trained specialists.
  - expanding services beyond haemophilia, to those with von Willebrand disease, rare factor deficiencies & inherited platelet disorders.

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

International Haemophilia Training Centre (IHTC)

Vellore, India

Haemophilia Clinic

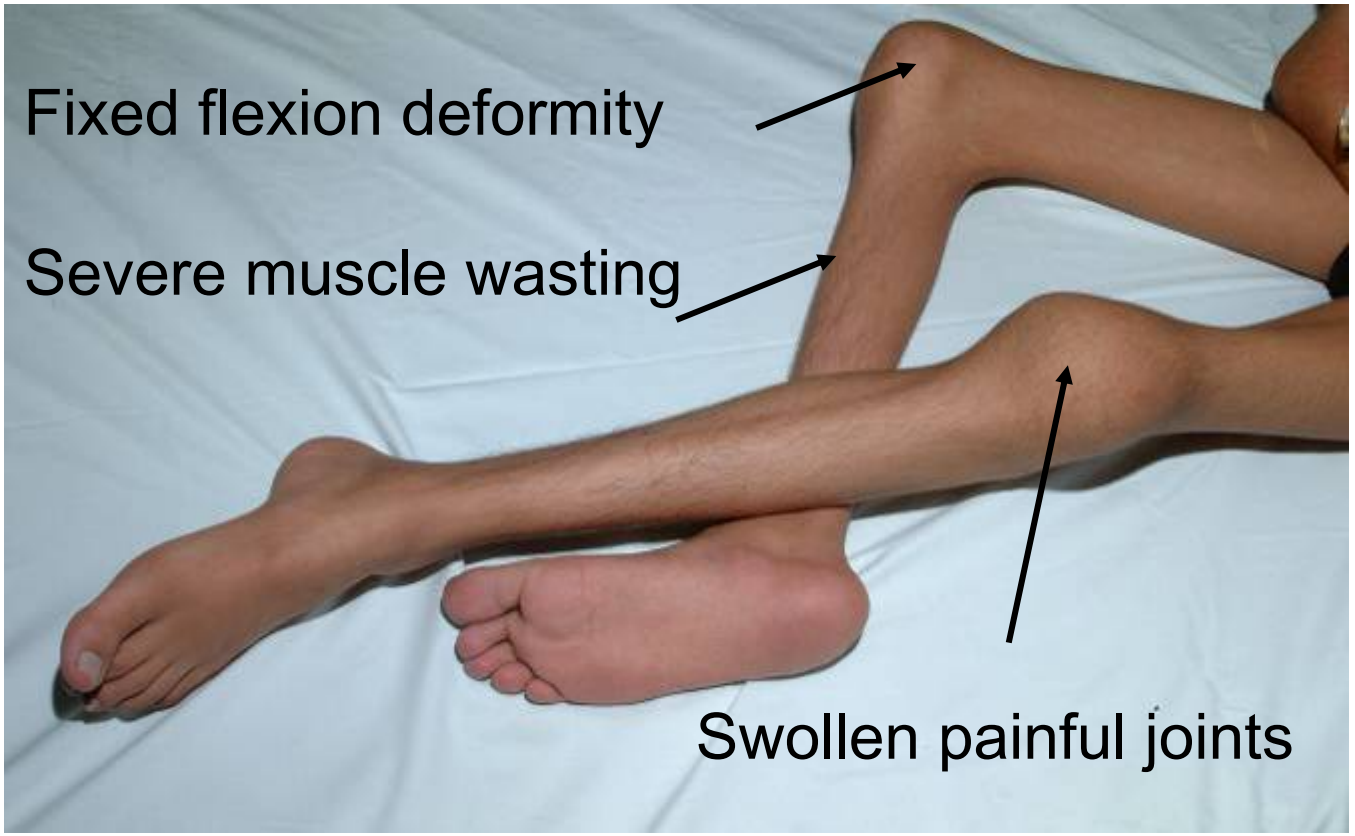


Fewer than 10% of children with severe haemophilia attend school regularly. Only about 20% of adults are gainfully employed, leading to breakdown of the family

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Alok Srivastava

Severe haemophilia A aged 15 years from Libya
Inadequate treatment over several years



Confined to a wheelchair, cannot walk
Cannot go to school
What future?

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

What is the future for this young man?

- Too late
- His joints cannot be rescued
- He will remain very disabled
- Unable to complete his education and poor prospects of long term employment
- Poor quality of life; dependent upon family

This outcome could have been prevented by adequate treatment

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Leading a normal life with haemophilia

Social integration

Full education
Normal job prospects
Fully contributing member of the workforce

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Reasons for Inadequate care

- Haemophilia not a government priority
- Inadequate infrastructure and diagnosis
- Inadequate education and training
- Poorly developed blood transfusion service
- High cost of replacement therapy

(Brian O'Mahony, Past President, WFH)

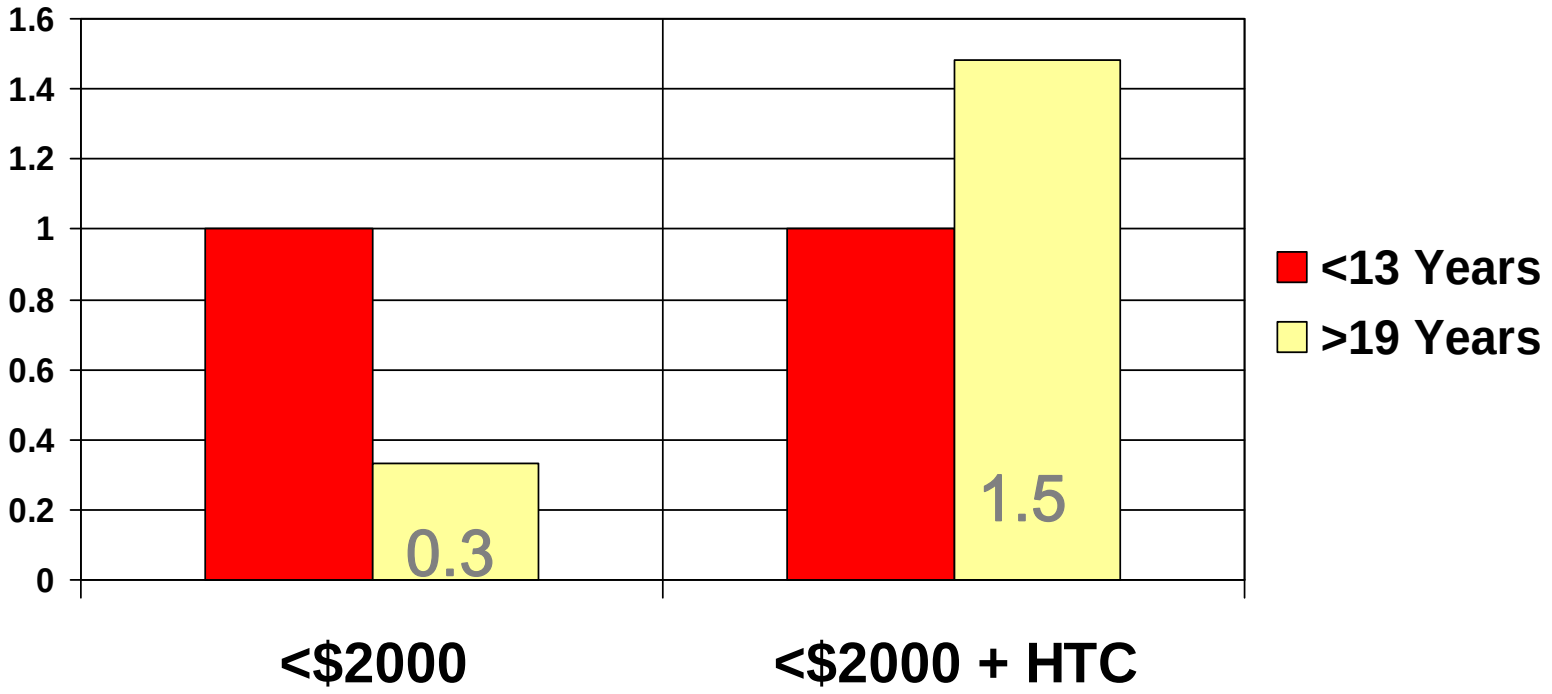
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Haemophilia - global

- Survival is enhanced by network of treatment centres
- Survival is enhanced by use of replacement therapy
- Optimum survival is associated with replacement therapy = or greater than 1 unit per capita

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

WFH Global Survey 1999 – Relationship of Economic capacity and No of Adult Patients:

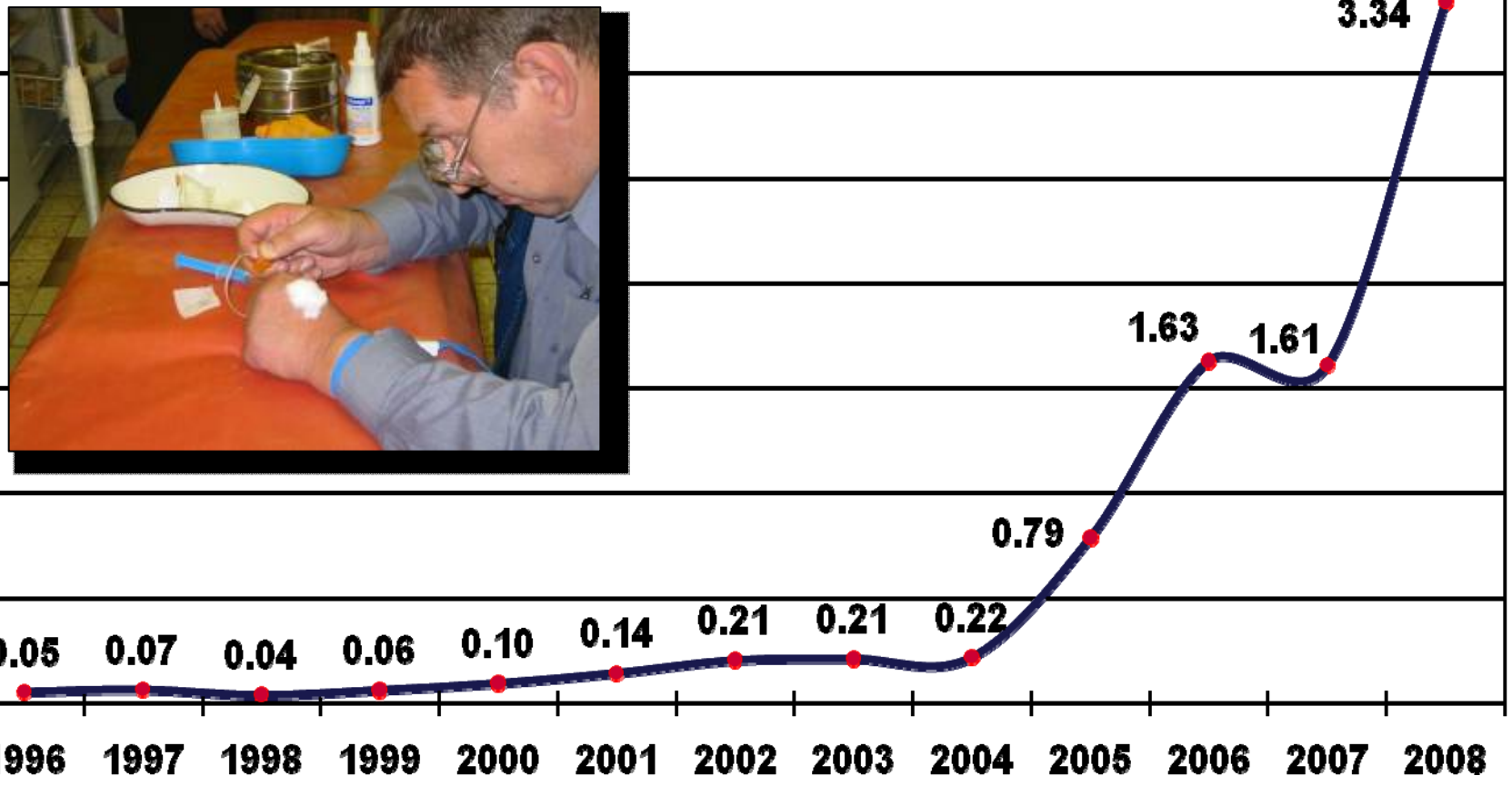


Per capita Gross National Product

Small expenditure for haemophilia with input of expertise and training can make a significant difference, even with limited funding – a five-fold increase in survival into adulthood

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Russia – Increase in Factor VIII IU Per Capita



WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Source: Russian Hemophilia Society 1996-2007; 2008 est.

Haemophilia – new problems for wealthy countries

- New generation of young men with haemophilia who don't know what a bleed is
- How ‘normal’ should life be?
  - Sports restrictions?
- Transition of care in adolescence
- Prophylaxis – at birth? When should it stop?
- New problems to manage in old age
- Inhibitor management
  - Prevention
  - Treatment

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Haemophilia and bleeding disorders in the under-developed countries

- Availability of reliable diagnosis
- Availability of treatment products
- Low priority in comparison with other medical needs
- High importance of genetic diagnosis and counselling because of the more severe clinical problems faced with inadequate treatment
- Cultural issues

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Strategies to Improve Clotting Factors

Prolonged efficacy

- **PEGylation**
  FVIIa, FIX, FVIII: GlycoPEGylation (Novo)
  FVIII: Site-directed PEGylation (Bayer)
  FVIII, FIX: Random PEGylation (Baxter)
- **Hyperglycosylation**
  FVIIa: Maxy-7 (T106N - V253N) (Bayer)
  FVIII: Polysialylation ±vWF (Baxter)
- **Fusion proteins**
  FVIIa: FVIIa-albumin (CSL Behring);
  FIX-Fc (Biogen Idec)
- **FIX, FVIII polymorphism screening**
- **Liposome formulation (FVIIa, FVIII)**
- **Polymer-based delivery (FIX, FVIII)**

Higher potency

- **Higher specific activity**
  FVIIa: Novo NN1731 (V158D - E296V - M298Q)
  FVIIa: FVIIaVEAY, FVIIaDVQ
  FVIII: E113A
  FIX: R338A, Y1A, other muteins
- **Improved activation**
  FVIII: (FVIII/HCII hybrid)
- **Increased membrane affinity**
  FVIIa: Gla-domain (Maxy-7, other muteins)
- **Improved post-translational modifications**
  FIX: Gla, sulfation, phosphorylation, glycosyl.

Resistance to inhibitors

- **Protein sequence**
  FVIII, FIX: Change sequence to make it less immunogenic
- **Hybrid proteins**
  FVIII: Porcine-human hybrids

Higher production

- **Increase secretion**
  FVIII: A1 mutation (F309S)
  FVIII: B domain variants (226aa/N6)

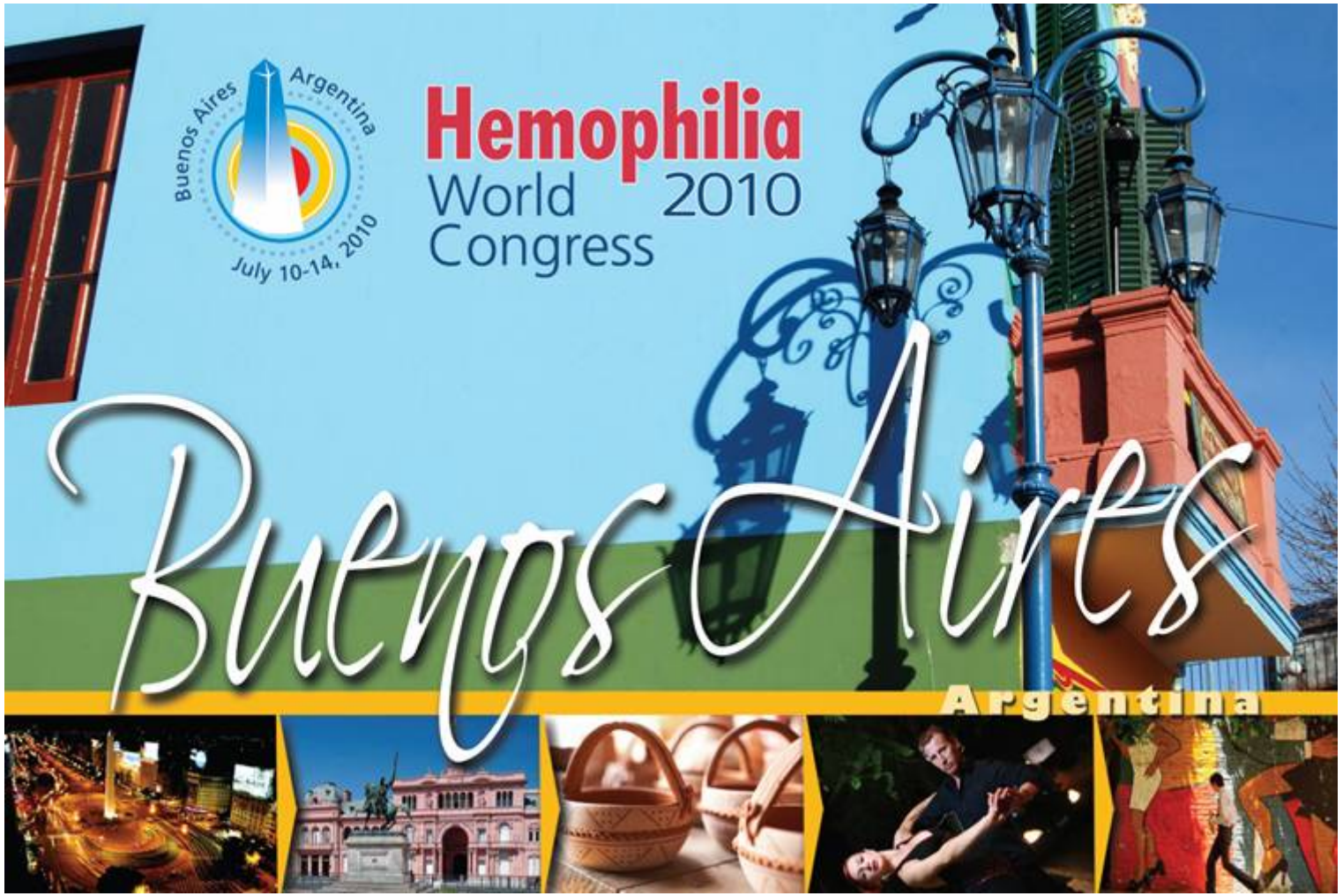
Resistance to inactivation

- **Stabilized protein**
  FVIII: IR8; Disulfide bond-FVIII
- **Hybrid protein**
  Porcine-human hybrids (D318G/M337R)

WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Assess risks of immunogenicity, thrombogenicity

Hope to see you there



WORLD FEDERATION OF
HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA