Peanuts to Gene Therapy, where to from here in improving outcomes?

Dr Liane Khoo

Haematologist

Director, Haemophilia Treatment Centre

Royal Prince Alfred Hospital

NSW Health Pathology

Sydney, Australia

Earliest references haemophilia - in 2nd century AD

Ruling of Rabbi Judah the Patriarch – exempts a woman's third son from being circumcised if his two brothers had died of bleeding after circumcision

1828, Friedrich Hopff, a student at the University of Zurich, and his professor Dr. Schonlein, are credited with coining the term "haemophilia"

1926 Finnish physician Erik von Willebrand published a paper describing a bleeding disorder affecting men and women equally. It was later named von Willebrand disease.

1947, Dr. Alfredo Pavlovsky, a doctor in Buenos Aires, distinguished two types of haemophilia in his lab—A and B

FIRST TREATMENT : 1840

- Boy named George Firmin – operation to relieve ‘squint’ – had past history of bleeding – not initially elicited.

- Operated - ‘nothing worthy of particular notice occurred… excepting that boy became faint and there was more bleeding than usual’

- Bleeding continued for 5-6 days and not responding to pressure
- Tried powdered gum tragacanth and beaver fur

- By day 6 – patient close to death – considered transfusion – direct

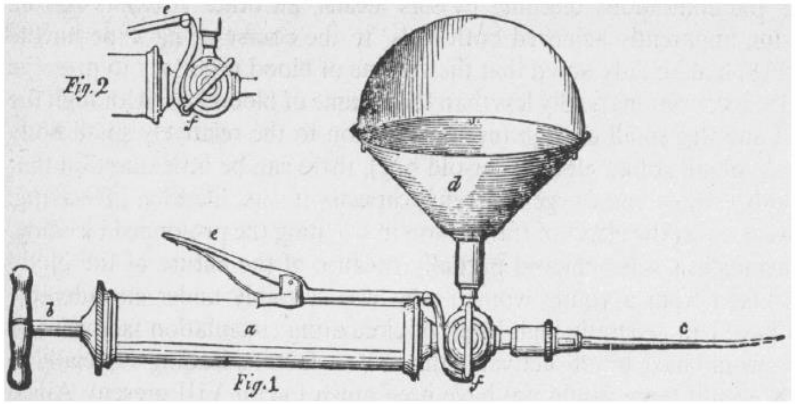


Figure 1. Lane’s transfusion syringe, 1840 (Reproduced from *Lancet*, 1840, i, 186)

- In course of an hour or two – boy sat up in bed and discharged after 3 weeks. No recurrence of bleeding

Slide courtesy of Dr John Rowell

No. 4711 February 13, 1960 NATURE

ANIMAL PHYSIOLOGY

A Peanut Factor for Hæmostasis in Hæmophilia

It is known that there are unpredictable apparent remissions of clinical symptoms enjoyed by hæmophiliacs; 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 'antihæmophilic factor' associated with classic hæmophilia has been attributed[1] to a hypothetical block during the metabolic synthesis of the factor resulting from the action of the mutant gene of hæmophilia,

Brit. med. J., 1967, 4, 453–456

Double-blind Experiments on the Effect of a Peanut Extract on the Bleeding Incidence in 92 Haemophiliacs*

M. VERSTRAETE,† M.D.; C. A. J. RUYS,‡ M.D.

Summary

The haemostatic value of an aqueous extract of raw ground and hexane-defatted peanut kernels was evaluated in 92 severely affected haemophilic patients during a six-months double-blind trial. With the criteria selected, no statistical proved benefit on the bleeding incidence could be demonstrated during the "active" treatment.

Slide courtesy of Dr John Rowell

Cryoprecipitate

1965 – Judith Pool reported that on slowly thawing frozen plasma much FVIII activity remained with the fibrinogen sludge which was slow to dissolve

TABLE 3. *Comparison of Costs to Patients of Currently Available Sources of Antihemophilic Globulin.*

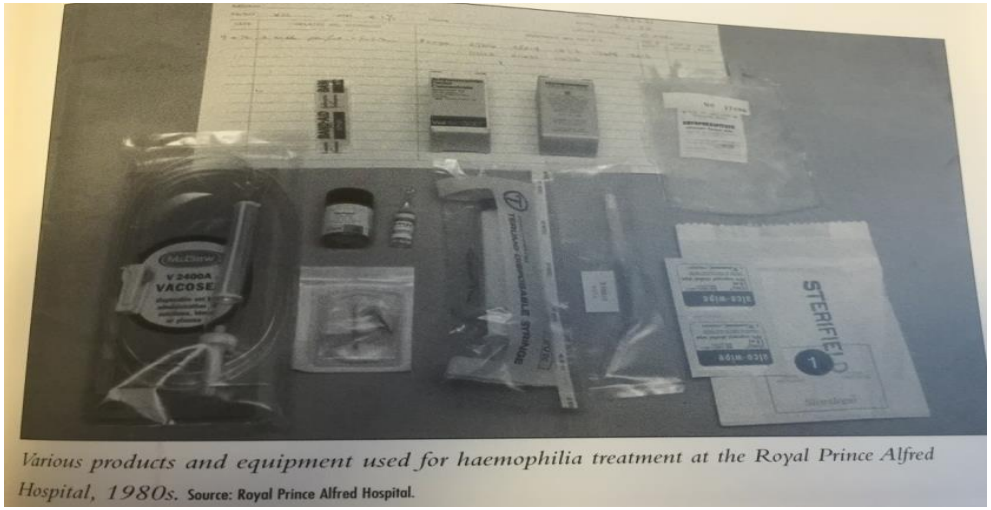
SOURCE	ACTIVITY OF ANTIHEMOPHILIC GLOBULIN X PLASMA (AT EQUIVALENT PROTEIN CONCENTRATIONS)	COST FOR 250 UNITS OF ANTIHEMOPHILIC GLOBULIN†	
	%	$	*ml. of donated blood*
Fresh-frozen plasma*	0.65	19.30	770
Pooled lyophilized* commercial "antihemophilic plasma"	1.0	1.00	500
Commercial "AHG-rich fibrinogen"	6.8	43.75	—
Cryoprecipitates*	19.8	—	272

*Rates established at Peninsula Memorial Blood Bank, Burlingame, California.

†1 unit = amount in 1 ml. of average fresh normal plasma.

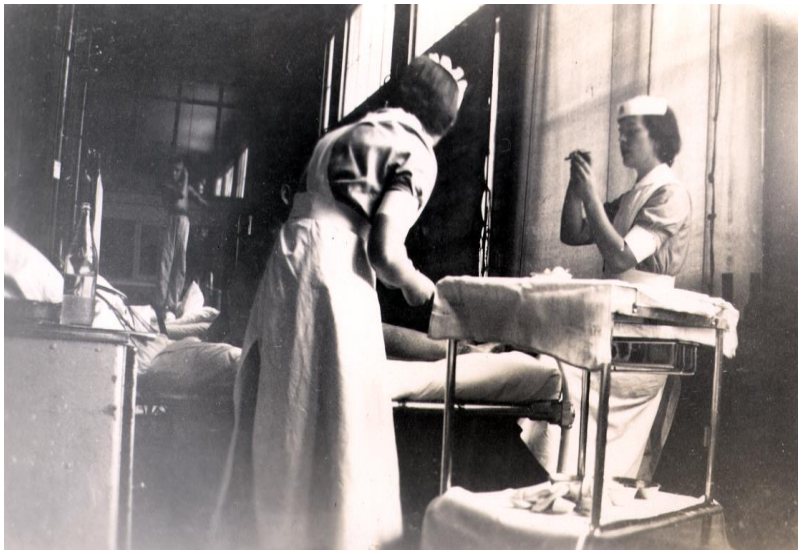
Pool, J.G.; Shannon, A.E.: Production of high-potency concentrates of antihemophilic globulin in a closed-bag system: assay in vitro and in vivo. New Engl. J. Med. *273:* 1443-1447 (1965).

Slide courtesy of Dr John Rowell



Various products and equipment used for haemophilia treatment at the Royal Prince Alfred Hospital, 1980s. Source: Royal Prince Alfred Hospital.

x factors : A history of haemophilia in Australia(Crockett,2003)



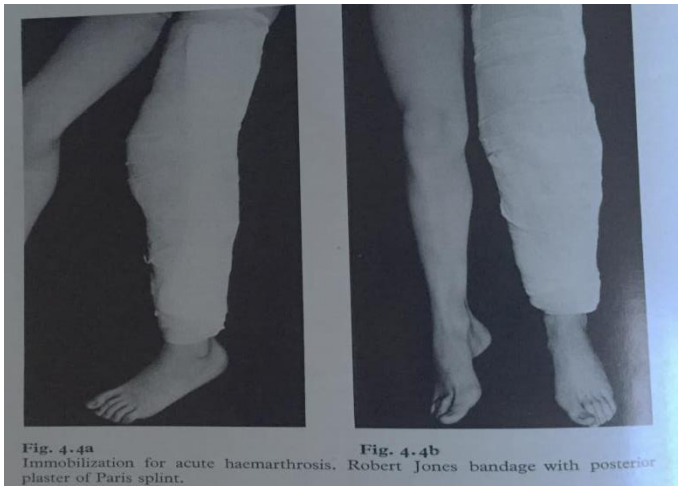


Fig. 4.4a
Immobilization for acute haemarthrosis.

Fig. 4.4b
Robert Jones bandage with posterior plaster of Paris splint.

The Management of Musculo-skeletal Problems in the Haemophilias (Duthie *et al* 1972)

What we have now : 2019

Recombinant products available to all patients (recombinant products since 2004)

- **Factor VIII**
  1. Advate (Shire/Takeda)- recombinant FVIII
  2. Xyntha (Pfizer) – recombinant FVIII
  3. Adynovate (Shire/Takeda)– Extended Half Life FVIII (limited interim agreement)
  4. Eloctate (Bioverative/Sanofi) – Extended Half Life FVIII (limited interim agreement)

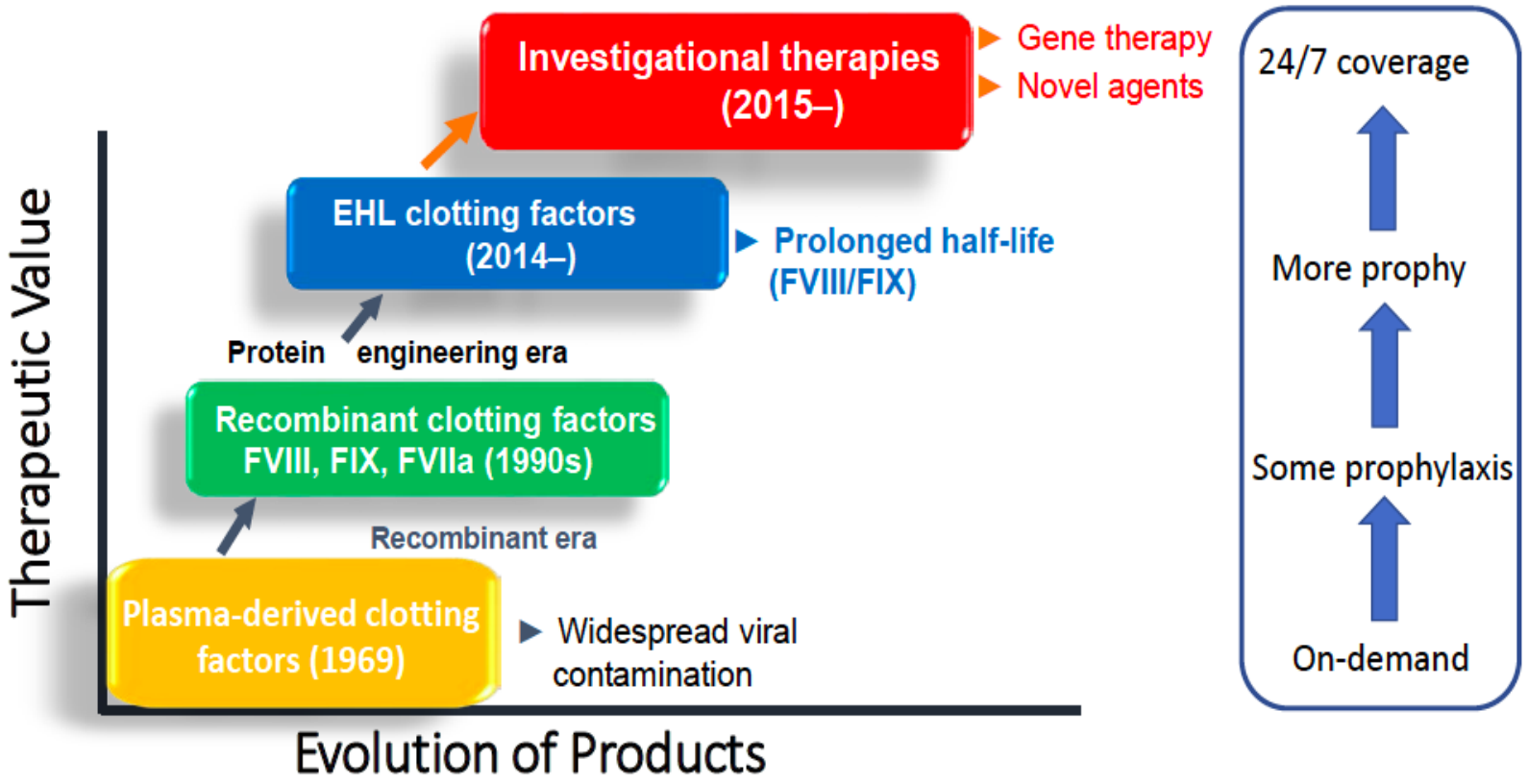
- **VWF containing FVIII concentrates**
  1. Biostate (CSL) – plasma derived. Contains Both FVIII and VWF (1:2.4)

- **Factor IX**

1. BeneFIX (Pfizer) -– recombinant FIX
2. Rixubis (Shire/Takeda) – recombinant FIX
3. FIX MonoFIX (CSL) – plasma derived FIX
4. Alprolix (Bioverative/Sanofi) – EHL FIX (limited interim agreement)

- **Bypassing agents:**
  1. rVIIa Novoseven (NovoNordisk)
  2. FEIBA –(Shire/Takeda)

Impact of Technology on Hemophilia Treatment



Slide:Glenn Pierce; WFH Board of Directors, WFH 2018 Congress

What can we look forward to:

Haemophilia Treatment has NOW just got more interesting……

Haemophilia Treatment ……

- **Extended Half-Life concentrates**

- Antibodies : Emicizumab
- Rebalanced haemostasis : Fitusiran (siRNA to ATIII), anti-TFPI ….

- Gene therapy

Comprehensive Care

Nurses

Doctors

Physiotherapists

Social Workers

Musculoskeletal Experts

- Rheumatologist
- Orthopaedic surgeons

Patient Support Organisation and Advocacy Groups

Patients and their families

Government Funders

Laboratory Scientists

Hospitals

General Practitioners

Psychologists

Liver Specialists

Industry

HIV Specialists

Chronic Pain Specialist

Dentists

Research