

# **WELLCOME WITNESSES TO TWENTIETH CENTURY MEDICINE**

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## **HAEMOPHILIA: RECENT HISTORY OF CLINICAL MANAGEMENT**

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THE TRANSCRIPT OF A WITNESS SEMINAR HELD AT  
THE WELLCOME INSTITUTE FOR THE HISTORY OF MEDICINE,  
LONDON, ON 10 FEBRUARY 1998

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Volume Four – September 1999

WITNESS SEMINAR TRANSCRIPT EDITED BY:

E M TANSEY   D A CHRISTIE

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#### Key

##### Front cover photographs, L to R from the top:

Dr James Matthews

Professor Stuart Douglas (1921–98), Sir Christopher Booth

Dr James Matthews, Dr Lise Wilkinson, Mr Ross Dike

Professor Christine Lee (chair), Mr Clifford Welch

Professor Christine Lee (chair), Rev'd Alan Tanner

Professor Ilsley Ingram (1919–2004), Professor Robert Duthie (1925–2005)

Mr Clifford Welch, Dr Charles Rizza

Dr Peter Jones, Dr Ethel Bidwell (d. 2003)

##### Back cover photographs, L to R from the top

Dr Peter Jones, Rev'd Alan Tanner

Dr Gordon Cook, Dr David Tyrrell (1925–2005), Dr Lise Wilkinson

Dr Helen Dodsworth, Dr David Evans

Dr Sheila Howarth (1920–2000)

Dr Peter Jones, Rev'd Alan Tanner

Dr David Evans

Rev'd Alan Tanner, Professor Christine Lee (chair)

# CONTENTS

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**INTRODUCTION**

E M TANSEY

i

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**HAEMOPHILIA: RECENT HISTORY OF CLINICAL MANAGEMENT**

EDITORS : D A CHRISTIE AND E M TANSEY

TRANSCRIPT

1

INDEX

83

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## INTRODUCTION

Haemophilia is a rare disorder of the clotting mechanisms of the blood. Estimates of its prevalence in the United Kingdom range from 1 in 4000 to 1 in 10 000 of the male population. But haemophilia has achieved a prominence out of all proportion to its incidence. Several factors have contributed to the reputation of the disease: the idea that blood, the very life-carrying force itself, can cause pain, incapacity and eventually death, is in itself deeply shocking. So too is the vision of small boys suffering the tragic consequences of the disease, added to which is its 'hidden' transmission through unaffected mothers, and in particular its passage via descendants of Queen Victoria through European Royal families. The role of the notorious Siberian monk Rasputin, whose ability to 'cure' the Tsarevitch Alexey's bleeding led to his sinister involvement with the Russian Royal family, may even have contributed to the Russian Revolution.<sup>1</sup>

This Witness Seminar examined the changes that have occurred in the treatment and clinical management of haemophilia in the past half-century, by inviting scientists, haematologists, carers and haemophiliacs themselves to a meeting at which advances and some of the disastrous reversals of the past 50 years were discussed. At the end of the second world war, treatment for haemophilia had advanced little – immobilization of painfully swollen joints into which uncontrolled bleeding took place was the main treatment. Suffering children with a short life expectancy were condemned to lie in bed-ridden pain, and several Witnesses here recall wards of small boys with limbs in plaster. Therapies were limited. Some, like Russell's viper venom, offered limited relief, or like Timperley's egg white, held out the hope of relief. For many, the most reliable method of treatment was whole blood transfusion, and here one Witness, Clifford Welch, himself a sufferer of a mild form of haemophilia, recalls the extraordinary situation in which his triplet siblings, all haemophiliacs, frequently received life saving transfusions from their mother (page 40). As Welch emphasizes, the history of haemophilia during the past 50 years has seen 'an extraordinary transformation' (page 76).

That extraordinary transformation began in the 1930s, at a time when the life expectancy of a haemophiliac was only 20 years. Experimental research and laboratory investigations into clotting mechanisms lead to the 'cascade' hypothesis

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<sup>1</sup> See for example Orlando Figes (1996) *A People's Tragedy: The Russian revolution, 1891–1924*. London: Pimlico, 24–34.

of blood coagulation (see Appendix, page 79) and the identification of a number of different clotting factors. The development of blood transfusion services during the second world war lead to improvements in fractionation techniques and the production of therapeutic plasma for transfusion, although an ominous portent of things to come was the recognition of post-transfusion jaundice, transmitted through pooled plasma.

A major breakthrough was made in Oxford in the 1950s when Ethel Bidwell first prepared factor VIII concentrate, although its bespoke production meant that its availability was limited until the mid 1960s. In the present volume, Dr Bidwell and her contemporaries discuss those early days, and the seemingly primitive conditions in which blood was collected from local abattoirs, transported across Oxford, and then fractionated in poorly equipped labs. Photographs of this period (pages 48–51), generously provided by Mr Ross Dike, Dr Bidwell's assistant, emphasize not only the makeshift nature of this life-saving enterprise, but also the dedication and determination of those involved in this pioneering work.

Isolation of further factors and the involvement of commercial producers and the National Blood Transfusion Service all provided increased treatment options for haemophiliacs, and the wider availability of cryoprecipitate in the 1960s lead to a further revolution – home treatment pioneered in particular by Kathleen Dormandy at the Royal Free Hospital, often in the face of strong disapproval from medical colleagues. Home treatment opened up another door to a normal life for sufferers and their families. That door to normality was cruelly slammed shut by the tragedy, many here use the word scandal, of contamination of blood products, many imported because of economy measures, with hepatitis viruses, HIV, and even now the spectre of CJD haunts haemophiliacs and their families. Haemophilia and the rights of haemophiliacs moved from the purely medical arena into the political spotlight as issues of compensation, or recompense (see page 65), were successively debated and fought over by pressure groups. The effect of litigation against doctors, many of whom had warned Government and health authorities of the potential problems of relying on imported blood products, adds a particularly poignant flavour to the story, as does the tragedy of the devastation of the haemophilic community. One Witness speaks movingly of three generations decimated by HIV infection and AIDS (page 66). Haematologists and paediatricians had to become rapidly knowledgeable about virology and safe sex, the latter an uncomfortable subject to raise in a children's hospital (see page 27).

As well as the straight scientific and clinical advances, other important issues emerge from this meeting, some more obvious than others. The setting up of the United Kingdom Haemophilia Centre Directors Organization, so that those

treating this rare condition could benefit from shared experiences, emerged in a haphazard way, spearheaded by Rosemary Biggs, who was unable to come to the meeting, but who, in a pre-recorded interview told how she organized parties, believing that as a woman she could hold a party and not offend anyone, although if she called a formal academic meeting feathers might be ruffled.<sup>2</sup> A less obvious area for discussion was the impact of material technology, as plastic containers, disposable needles and catheters, and ready-made butterfly needles improved the preparation and administration of therapeutic products. Some here tell harrowing tales of resharpened needles, many so old that they became hooked, blocking in the middle of an injection into a deeply distressed child, and of a traumatized boy having to be sedated daily to receive life-saving treatment.

These are just a selection of the issues that are covered here by our Witnesses, to whom we are grateful for the time they gave us not only in planning and holding this meeting, but also during the editorial process, as we have sought to transform a spoken meeting into readable text, and to provide explanatory footnotes.

To date, the Wellcome Trust's History of Twentieth Century Medicine Group has held 21 Witness Seminars, most of which have been published, as listed in the Table below. For the Haemophilia meeting we are especially grateful to Professor Christine Lee for suggesting the subject, assisting us so enthusiastically in organizing the meeting, and chairing it so efficiently; Ross Dike kindly displayed a selection of his photographs at the meeting and has allowed us to reproduce some of them here; and Dr Huw Dorkins kindly read the edited transcript for general sense and understandability, and offered suggestions for glossary terms. As with all our meetings, we hope that even if the precise details of some of the technical sections are not clear to the non-specialist reader, the sense and significance of the events are understandable. We are grateful to our colleagues in the Wellcome Trust for their help in running these meetings, and wish to mention in particular the assistance of the Audiovisual Department, the Medical Photographic Library, and the Publishing Department, especially Julie Wood who has supervised the design and production of the published volume. Mrs Jaqui Carter is our transcriber, and Mrs Wendy Kutner and Mrs Lois Reynolds assist us in running the meetings. Finally we thank the Wellcome Trust for supporting this programme.

**Tilli Tansey**

**Wellcome Institute for the History of Medicine**

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<sup>2</sup> Tansey, E M. (ed.) (1998) Witnessing medical history: an interview with Dr Rosemary Biggs, conducted by Professor Christine Lee and Dr Charles Rizza. *Haemophilia* 4: 769–777.

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## History of Twentieth Century Medicine Witness Seminars, 1993–1999

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- 1993    **Monoclonal antibodies**<sup>3</sup>  
Organizers: Dr E M Tansey and Dr Peter Catterall
- 1994    **The early history of renal transplantation**  
Organizer: Dr Stephen Lock  
**Pneumoconiosis of coal workers**<sup>4</sup>  
Organizer: Dr E M Tansey
- 1995    **Self and non-self: a history of autoimmunity**<sup>3</sup>  
Organizers: Sir Christopher Booth and Dr E M Tansey  
**Ashes to ashes: the history of smoking and health**<sup>5</sup>  
Organizers: Dr Stephen Lock and Dr E M Tansey  
**Oral contraceptives**  
Organizers: Dr Lara Marks and Dr E M Tansey  
**Endogenous opiates**<sup>3</sup>  
Organizer: Dr E M Tansey
- 1996    **Committee on Safety of Drugs**<sup>3</sup>  
Organizers: Dr Stephen Lock and Dr E M Tansey  
**Making the body more transparent: the impact of nuclear magnetic resonance and magnetic resonance imaging**<sup>6</sup>  
Organizer: Sir Christopher Booth

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<sup>3</sup> Published in Tansey E M, Catterall P P, Christie D A, Willhoft S V, Reynolds L A. (1997) (eds) *Wellcome Witnesses To Twentieth Century Medicine*. vol. 1. London: Wellcome Trust, 135pp.

<sup>4</sup> P D'Arcy Hart, edited and annotated by E M Tansey. (1998) Chronic pulmonary disease in South Wales coalmines: An eye-witness account of the MRC surveys (1937–1942). *Social History of Medicine* 11: 459–468.

<sup>5</sup> Lock S P, Reynolds L A, Tansey E M. (eds) (1998) *Ashes to Ashes – The history of smoking and health*. London: Wellcome Trust, 198–220.

<sup>6</sup> Published in Tansey E M, Christie D A, Reynolds L A. (eds) (1998) *Wellcome Witnesses to Twentieth Century Medicine*. vol. 2. London: The Wellcome Trust, 282 pp.



- 1997**     **Research in General Practice**<sup>6</sup>  
Organizers: Dr Ian Tait and Dr E M Tansey
- Drugs in psychiatric practice**<sup>6</sup>  
Organizers: Dr E M Tansey and Dr David Healy
- The MRC Common Cold Unit**<sup>6</sup>  
Organizers: Dr David Tyrrell and Dr E M Tansey
- The first heart transplant in the UK**<sup>7</sup>  
Organizer: Professor Tom Treasure
- 1998**     **Haemophilia: recent history of clinical management**<sup>8</sup>  
Organizers: Dr E M Tansey and Professor Christine Lee
- Obstetric ultrasound: historical perspectives**  
Organizers: Dr Malcolm Nicolson, Mr John Fleming and Dr E M Tansey
- Post-penicillin antibiotics**  
Organizers: Dr Robert Bud and Dr E M Tansey
- Clinical research in Britain, 1950–1980**  
Organizers: Dr David Gordon and Dr E M Tansey
- 1999**     **Intestinal absorption**  
Organizers: Sir Christopher Booth and Dr E M Tansey
- The MRC Epidemiology Unit (South Wales)**  
Organizers: Dr Andy Ness and Dr E M Tansey
- Neonatal intensive care**  
Organizers: Professor Osmund Reynolds, Dr David Gordon and Dr E M Tansey
- British contribution to medicine in Africa after the second world war**  
Organizers: Dr Mary Dobson, Dr Maureen Malowany, Dr Gordon Cook and Dr E M Tansey

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<sup>7</sup> Tansey E M, Reynolds L A. (eds) (1999) Early heart transplant surgery in the UK. *Wellcome Witnesses to Twentieth Century Medicine*, vol. 3. London: The Wellcome Trust, 72 pp.

<sup>8</sup> Tansey E M, Christie D A. (eds) (1999) Haemophilia: Recent history of clinical management. *Wellcome Witnesses to Twentieth Century Medicine*, this volume.



# **HAEMOPHILIA: RECENT HISTORY OF CLINICAL MANAGEMENT**

The transcript of a Witness Seminar held at the Wellcome Institute  
for the History of Medicine, London, on 10 February 1998

Edited by D A Christie and E M Tansey

# HAEMOPHILIA: RECENT HISTORY OF CLINICAL MANAGEMENT

## Participants

Dr Derek Bangham	Professor Ilsley Ingram
Dr Ethel Bidwell	Dr Peter Jones
Sir Christopher Booth	Professor Christine Lee (Chair)
Dr Brian Colvin	Dr James Matthews
Dr Angela Dike	Mrs Riva Miller
Mr Ross Dike	Dr Charles Rizza
Dr Helen Dodsworth	Rev Alan Tanner
Professor Stuart Douglas*	Dr Tilli Tansey
Professor Robert Duthie	Professor Edward Tuddenham
Dr David Evans	Dr David Tyrrell
Dr Sheila Howarth	Mr Clifford Welch

Others present at the meeting: Dr Trevor Barrowcliffe, Ms Jacqui Marr,  
Dr J K Smith, Miss Rosemary Spooner

Apologies: Professor Jean-Pierre Allain, Dr Donald Bateman, Dr Rosemary Biggs, Mrs Peggy Britten,\*\* Professor Judith Chessells, Dr Audrey Dawson, Mr Ron Hutton, Professor Ralph Kekwick, Professor Sir David Weatherall

\*Deceased 15 November 1998

\*\*Deceased 1 March 1999

Professor Christine Lee:<sup>1</sup> I think haemophilia is one of the best areas of clinical medicine where we have seen a very rapid introduction of scientific discovery into clinical practice. All of us who work on haemophilia realize that this has gone on very much with cooperation between the patients and the scientists and the doctors. I first saw haemophilia in 1967 when I was a medical student in Oxford and we were doing our orthopaedics at the Nuffield Orthopaedic Hospital. I have a very clear memory of a ward of little boys with their legs strung up, their arms strung up, and I think there was a schoolroom nearby. It was with great pleasure that last week we were able to talk with Dr Rosemary Biggs,<sup>2</sup> who with Macfarlane, put haemophilia care on the map in Oxford from the late 1940s onwards.<sup>3</sup> Unfortunately, Dr Biggs wasn't able to be with us today, but I am hoping that throughout the discussions this afternoon I can interject some of her comments, and try and raise memories from you and our invited speakers. What I am going to try very hard to do – I do have a kind

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<sup>1</sup> Professor Christine Lee FRCP FRCPath DSc(Med) (b. 1943) qualified from the University of Oxford Medical School and has been Professor of Haemophilia and Director and Consultant Haematologist at the Haemophilia Centre and Haemostasis Unit, The Royal Free Hospital, London, since 1987 and is a member of the International Society of Thrombosis & Haemostasis. She has published many papers on the side-effects of blood product therapy in haemophilia, particularly hepatitis and acquired immune deficiency syndrome (AIDS).

<sup>2</sup> Dr Rosemary Biggs MD FRCP (b. 1912) first joined Gwyn Macfarlane in Oxford in 1945 in his studies on fibrinolysis. She is co-author on many papers including the seminal paper on Christmas disease (see for example notes 3, 17, 18, 23, 37 and 198). When the Medical Research Council Blood Coagulation Unit in Oxford closed in 1967, Dr Biggs became Director of the newly opened Haemophilia Centre. She was Secretary of the UKHCDO from 1968 to 1977. See Tansey E M. (ed.) (1998) Witnessing medical history: an interview with Dr Rosemary Biggs, conducted by Professor Christine Lee and Dr Charles Rizza. *Haemophilia* 4: 769–777.

<sup>3</sup> Professor R G Macfarlane CBE FRCP FRCPS FRS (1907–1987) qualified in medicine from St Bartholomew's Hospital in 1933 and in 1936 he became Clinical Assistant Pathologist at the Postgraduate Medical School Hammersmith. He was appointed clinical pathologist to the Radcliffe Infirmary, Oxford in 1940 and was Radcliffe lecturer in haematology in 1943. He was joined by Dr Rosemary Biggs (see note 2 above) and Dr Ethel Bidwell (see note 47 below) and together they collaborated closely on extensive studies of fibrinolysis and purification and concentration of the various blood-clotting factors. He became Director of the Blood Coagulation Research Unit in Oxford in 1959, Fellow of All Souls College, Oxford, in 1963, Professor of Clinical Pathology in the University of Oxford in 1965, and President of the Haemophilia Society in 1981. The Macfarlane Trust was established in his memory to administer funds to haemophiliacs infected with HIV through treatment with blood products. See Born G V R, Weatherall D J. (1990) Robert Gwyn Macfarlane. *Biographical Memoirs of Fellows of the Royal Society* 35: 211–239. Robb-Smith A. (1993) *Life and Achievements of Professor Robert Gwyn Macfarlane FRS Pioneer in the Care of Haemophiliacs*. London: Royal Society of Medicine Services Limited. See also Biggs R. (1967) Thirty years of haemophilia treatment in Oxford. *British Journal of Haematology* 13: 452–463.

## Haemophilia: Recent history

of programme here, but I am told by Dr Tansey that these things tend to go off in ways which nobody can predict – is to try by the end of the afternoon to have covered the introduction of treatment and the organization of haemophilia, and to talk a bit about some of the disastrous side-effects and the impact that that has had on us all. So without going on any more, I am going to start by asking Ilsley Ingram, who was Professor of Experimental Haematology at St Thomas' Hospital, and has an amazing history to tell us, and perhaps, Ilsley, you could begin a bit at the beginning and talk about when you first got into haemophilia.

Professor Ilsley Ingram:<sup>4</sup> I have made a note of some landmarks in the history of haemophilia.<sup>5</sup> The earliest known written reference to abnormal post-traumatic bleeding in maternally-related males is from rabbinical references from the second century to do with circumcision. The earliest clear medical description of haemophilia is probably in 1803, and the name 'haemophilia' is first found in a dissertation by Hopff in 1828. Haemarthroses were not clearly described in relation to haemophilia until 1890, because before that they were thought to be rheumatic manifestations. The first female haemophiliac, from a first-cousin marriage, is believed to be that recorded by Treves in 1886; and the diagnostic triad of lifelong, male bleeding, transmitted by females, is first really brought out in the monumental study of Bulloch and Fildes in 1911. They analysed the entire previous literature on abnormal bleeding and sorted out the reports they thought were probably to do with haemophilia, and published a large number of family trees. We all know about Queen Victoria, who had a haemophilic son, Leopold, born in 1853, and two carrier daughters who transmitted the abnormal gene to the Royal Houses of Spain and Russia. Defective blood clotting in haemophilia was first noted, I think, by Wardrop in 1835, yet haemophilic blood was normally clotted by thrombin by Addis in 1910 and the normal prothrombin time was recorded by Quick in 1935.

I always regard that as the beginning of the modern period in the study of haemophilia, because up to that time, although some plasma fractions were made in the laboratories, it was thought that it was the prothrombin that was abnormal in haemophilia. A globulin fraction of plasma was found to correct

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<sup>4</sup> Professor Ilsley Ingram FRCP FRCPath FLS (b. 1919) was Director of the Haemophilia Centre at St Thomas' Hospital from 1956 to 1979, and Professor of Experimental Haematology in the University of London at St Thomas's Hospital Medical School from 1972 to 1979.

<sup>5</sup> These early landmarks in the history of haemophilia are detailed and referenced in Ingram G I C. (1997) The history of haemophilia. *Haemophilia* 3: 5–15. *idem* (1976) The history of haemophilia. *Journal of Clinical Pathology* 29: 469–479.

the haemophilic blood-clotting defect by Patek and Taylor in 1937,<sup>6</sup> so in the 1930s the modern study had begun. The term ‘antihemophilic globulin’ (AHG) was coined by Lewis, Taylor and others in 1946.<sup>7</sup> In 1950 Merskey described mild haemophilia with a normal whole blood-clotting time in a glass tube.<sup>8</sup> This was of great clinical importance because up until then it was thought that if the clotting time was normal, the person could not have haemophilia. But we know that mild haemophiliacs do indeed have serious post-traumatic bleeding, for instance if they are inadvertently operated on without proper preparation.

From 1951 onwards there were early assay methods for factor VIII, particularly Merskey and Macfarlane [in Oxford], and Graham and others in America.<sup>9</sup> Roman numerals were first used to designate clotting factors by a committee chaired by Wright in 1962;<sup>10</sup> and the immunological detection of factor VIII was begun by Ratnoff and others in 1971,<sup>11</sup> who showed that haemophilic plasma, although it contained no factor VIII activity, reacted with a rabbit antibody to human factor VIII.<sup>12</sup> I expect that subsequent speakers will say more about the immunological side, because that has developed greatly since I retired in 1979. An international standard for factor VIII clotting activity was developed in the 1960s by the Biological Standards Division of the National Institute for Medical Research; and the Division began to distribute working standards to clinical laboratories.<sup>13</sup>

Von Willebrand’s disease was distinguished from haemophilia by von Willebrand in 1926 and by Minot in 1928, and was shown to affect both sexes

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<sup>6</sup> Patek A J, Taylor F H L. (1937) Hemophilia II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. *Journal of Clinical Investigation* 16: 113–124.

<sup>7</sup> Lewis J H, Tagnon H J, Davidson C S, Minot G R, Taylor F H L. (1946) The relation of certain fractions of the plasma globulins to the coagulation defect in hemophilia. *Blood* 1: 166–172.

<sup>8</sup> Merskey C. (1951) Haemophilia associated with normal coagulation time. *British Medical Journal* i: 906–912. See biographical note 35 below.

<sup>9</sup> Merskey C, Macfarlane R G. (1951) Female carrier of haemophilia: a clinical and laboratory study. *Lancet* i: 487–490. Graham J B, Penick G D, Brinkhous K M. (1951) Utilization of antihemophilic factor during clotting of canine blood and plasma. *American Journal of Physiology* 164: 710–715.

<sup>10</sup> Irving Wright, Professor of Internal Medicine at Cornell, New York, chaired the International Committee on Blood Clotting Factors, which later became the International Committee on Haemostasis and Thrombosis in 1965. See Wright I S. (1962) The nomenclature of blood clotting factors. *Thrombosis et Diathesis Haemorrhagica* 7: 381–388.

<sup>11</sup> Zimmerman T S, Ratnoff O D, Littell A S. (1971) Detection of carriers of classic hemophilia using an immunologic assay for antihemophilic factor (factor VIII). *Journal of Clinical Investigation* 50: 255–258.

<sup>12</sup> The patient’s plasma and the antibody diffuse in a gel: where they meet, an opaque line forms if the plasma contains a substance ‘recognized’ by the antibody.

<sup>13</sup> See Dr Derek Bangham’s contribution on page 20.

## Haemophilia: Recent history

and to have a long bleeding time.<sup>14</sup> Reduced levels of factor VIII were also found in von Willebrand's disease by Alexander and Goldstein in 1953, and by Larrieu and Soulier in 1953.<sup>15</sup>

In 1944 Pavlovsky described the mutual cross-correction of two haemophilic bloods<sup>16</sup> and this led to the identification of factor IX deficiency with identical clinical manifestations to haemophilia. Then Macfarlane and Biggs developed the thromboplastin generation test which allowed clinical laboratories to distinguish the two conditions.<sup>17</sup> It was largely on that basis, I understand, that the system of 'Haemophilia Centres' was set up in Britain, the initial purpose being to separate the diagnosis of haemophilia from that of Christmas disease (factor IX defect),<sup>18</sup> in readiness for the time when different specific treatments would be available. Topical treatment with Russell's viper venom [Stypven], which was found to clot haemophilic blood, at the dilution of one in a million, was identified by Macfarlane in 1934.<sup>19</sup> Use of blood transfusion, interestingly, dates back to the work of Lane in 1840,<sup>20</sup> who effectively administered the blood of someone he described as 'a stout young woman' to a boy, known to have bled abnormally, who had been inadvertently operated on, and bled and bled.

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<sup>14</sup> See Willebrand E A von. (1926) Hereditäre pseudohefili. *Finska Läkaresällskapets Handlingar* 68: 87–112. Minot G R. (1928) Familial hemorrhagic condition associated with prolongation of bleeding time. *American Journal of Medical Science* 175: 301–306.

<sup>15</sup> Alexander B, Goldstein R. (1953) Dual hemostatic defect in pseudohefili. *Journal of Clinical Investigation* 32: 551. Larrieu M J, Soulier J P. (1953) Déficit en facteur antihémophilique A chez une fille, associé à un trouble du saignement. *Revue d'hématologie* 8: 361–370. *idem* Differentiation of hemophilia into 2 groups: study of 33 cases. *New England Journal of Medicine* 249: 547–553.

<sup>16</sup> Professor Ilsley Ingram added: 'Both having prolonged clotting times but the mixture clotting normally, showing that the samples corrected each other and must therefore have had different deficits, each able to provide what the other lacked.' Letter to Dr Daphne Christie, 13 March 1999. See Castex M R, Pavlovsky A, Simonetti C. (1944) Contribución al estudio de la fisiopatogenia de la hemofilia. *Medicina Buenos Aires* 5: 16–24. Pavlovsky A. (1947) Contribution to the pathogenesis of hemophilia. *Blood* 2: 185–191.

<sup>17</sup> Macfarlane R G, Biggs R. (1953) Thrombin generation test: application in haemophilia and thrombocytopenia. *Journal of Clinical Pathology* 6: 3–8. Biggs R, Douglas A S. (1953) Thromboplastin generation test. *ibid.* 23–29. Biggs R, Douglas A S, Macfarlane R G. (1953) Formation of thromboplastin in human blood. *Journal of Physiology* 119: 89–101.

<sup>18</sup> See Biggs R, Douglas A S, Macfarlane R G, Dacie J V, Pitney W R, Merskey C, O'Brien J R. (1952) Christmas disease: a condition previously mistaken for haemophilia. *British Medical Journal* ii: 1378–1382.

<sup>19</sup> Macfarlane R G, Barnett B. (1934) The haemostatic possibilities of snake venom. *Lancet* ii: 985–987. *idem* On the relative potency of certain snake-venoms to coagulate haemophilic blood. *Proceedings of the Zoological Society* 4: 977–978. Macfarlane R G. (1965) Russell's viper venom, 1934–64. *Oxford Medical School Gazette* 17: 100–115.

<sup>20</sup> Lane S. (1840) Haemorrhagic diathesis. Successful transfusion of blood. *Lancet* i: 185–188. See also Ingram G I C. (1995) Mr Lane and the blood of a stout young woman. *Haemophilia* 1: 277–282.



In 1931 Macfarlane,<sup>21</sup> who reviewed the previous treatments offered for haemophilia, clearly recognized that human blood transfusion was the only effective systemic treatment. Freeze-dried fractions made from human blood were developed in the 1950s by Kekwick and Wolf, Soulier, Blombäck and others,<sup>22</sup> and then Dr Bidwell in 1954 introduced the fractions from ox and pig plasma.<sup>23</sup> In 1965 Judith Pool introduced cryoprecipitate.<sup>24</sup> This was a major clinical advance because of the convenience of the smaller volume for administration and because it could be stored frozen. Use of antifibrinolytic drugs to spare factor VIII doses was introduced by Walsh in 1971 in connection with dental extractions,<sup>25</sup> and the use of 1-deamino-8-D-arginine vasopressin (DDAVP) in mild haemophilia and von Willebrand's disease by Mannucci in 1977.<sup>26</sup>

I will add that in the UK the Haemophilia Society had its roots in the 1930s, curiously when Macfarlane and J B S Haldane worked together on the interesting parallel between the inheritance of haemophilia and red/green colour blindness.<sup>27</sup> That was probably the first time in Britain that haemophiliacs came together and so met one another. In 1950 the British Haemophilia Society, which had at first grandly been called the International Haemophilia

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<sup>21</sup> Macfarlane R G. (1931) Haemophilia: a short survey. *St Bartholomew's Hospital Journal* 39: 47–54.

<sup>22</sup> Kekwick R A, Wolf P. (1957) A concentrate of human antihemophilic factor – its use in six cases of haemophilia. *Lancet* i: 647–650. Soulier J P, Gobbi F, Larrieu M J. (1957) Séparation du fibrinogène et du facteur antihémophilique A. *Revue d'hématologie* 12: 481–496. Blombäck B, Blombäck M, Nilsson I M. (1958) Note on the purification of human antihemophilic globulin. *Acta Chemica Scandinavica* 12: 1878.

<sup>23</sup> Macfarlane R G, Biggs R, Bidwell E. (1954) Bovine antihemophilic globulin in the treatment of haemophilia. *Lancet* i: 1316–1319. Bidwell E. (1955) The purification of bovine antihemophilic globulin. *British Journal of Haematology* 1: 35 and 386.

<sup>24</sup> Professor Judith Pool reported that on slowly thawing frozen plasma, much of the factor VIII activity remained with the fibrinogen sludge which was slow to re-dissolve, the so-called 'cryoprecipitate'. This could be spun down, re-frozen for storage and finally reconstituted for administration in a small volume of saline. For details see Pool J D, Shannon A E. (1965) Production of high-potency concentrates of antihemophilic globulin in a closed bag system. *New England Journal of Medicine* 273: 1443–1447. See also Sibinga C S. (1996) Emile Rémigy and the discovery of anti-hemophilic activity in cryoprecipitate. *Haemophilia* 2: 56–60.

<sup>25</sup> Walsh P N, Rizza C R, Matthews J M, Eipe J, Kernoff P B A, Coles M D, Bloom A L, Kaufman B M, Beck P, Hanan C M, Biggs R. (1971) Epsilon-aminocaproic acid therapy for dental extractions in haemophilia and Christmas disease: a double blind controlled trial. *British Journal of Haematology* 20: 463–475.

<sup>26</sup> See Cash J D, Gader A M A, Da Costa J. (1974) The release of plasminogen activator and factor VIII to lysine vasopressin, arginine vasopressin, 1-deamino-8-D-arginine vasopressin, angiotensin and oxytocin in man. *British Journal of Haematology* 27: 263–264. Mannucci P M, Ruggeri Z M, Pareti F I, Capitanio A. (1977) 1-deamino-8-D-arginine vasopressin: a new pharmacological approach to the management of haemophilia and von Willebrand's disease. *Lancet* i: 869–872.

<sup>27</sup> See Bell J, Haldane J B S. (1937) Linkage between genes for colour-blindness and haemophilia in man. *Proceedings of the Royal Society B* 123: 119–150.

## Haemophilia: Recent history

Society, was registered as a charity; the World Federation of Hemophilia was started in 1963.

Haemophiliacs have always been very generous in giving their plasma for experimental work as a *quid pro quo* for being looked after. I think that this is a very interesting example of the way that affected people and their doctors worked together for mutual benefit.

Lee: I would like to pursue some of the things you brought up there. When we were talking with Dr Biggs last week,<sup>28</sup> she was laying great emphasis on the thromboplastin generation test<sup>29</sup> as the point at which diagnosis was possible. Would you agree with that?

Ingram: Yes, in Britain, I think that was of great importance. In America, at Chapel Hill, Brinkhous and Graham developed the partial thromboplastin time,<sup>30</sup> which wasn't so good at distinguishing deficiencies of factors VIII and IX, but could be adapted to do so by the use of appropriate plasmas. But the great thing about the thromboplastin generation test was that the reagents were made from normal plasma, so that you didn't have to have the haemophilic blood there to show whether or not it was corrected. I will go back to the time where the mutual correction of two apparently haemophilic plasmas led to the realization that there was more than one defect, because, after all, this is analogous to the general biological principle of identification from type specimens. There you had a type specimen of haemophilic blood and then you saw whether other bloods would correct it or not. Fortunately, the thromboplastin generation test side-stepped that and made it unnecessary for all laboratories to have samples of both haemophilic and Christmas disease plasma always on hand.

Lee: And that mutual correction, when we were talking with Dr Biggs,<sup>31</sup> she said was just done by accident.

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<sup>28</sup> See note 2 above.

<sup>29</sup> See note 17 above.

<sup>30</sup> Langdell R D, Graham J B, Brinkhous K N. (1950) Prothrombin utilization during clotting: comparison of results with 2-stage and 1-stage methods. *Proceedings of the Society for Experimental Biology and Medicine* 74: 424. Langdell R D, Wagner R H, Brinkhous K M. (1951)

Effect of antihemophilic factor on one-stage clotting tests: presumptive test for hemophilia and a simple one-stage antihemophilic assay procedure. *Journal of Laboratory and Clinical Medicine* 41: 637–647.

<sup>31</sup> See note 2 above.

Ingram: I think it was, yes. It was a bit of serendipity.

Lee: When the thromboplastin generation test was described and it was possible to differentiate, who was using it? Was it just the very specialized centres, or was it more widespread?

Ingram: I think it gradually spread, although perhaps people who hadn't seen it done found it rather fiddly to do from written instructions, but it was becoming more widely used.

Lee: I think it might be an appropriate time to talk about differentiation of factor VIII and factor IX. Dr Rizza, remind us about Christmas disease.

Dr Charles Rizza:<sup>32</sup> Can I go back to what Professor Ingram said? I think of the serendipity when Stephen Christmas first came to Oxford: I think it was John Poole<sup>33</sup> who did the mixing experiments. He took haemophilic blood and mixed it with Stephen Christmas's blood and, lo and behold, it was corrected, and they thought, 'What is going on here? There is something different'. That was how it all began. But Stuart Douglas, I think, was there at the time and that was what encouraged him to look further and use the thromboplastin generation test in 1951/52.

Professor Stuart Douglas:<sup>34</sup> I want to comment on the contribution of experiments on mixing of bloods from two haemophiliacs. We should

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<sup>32</sup> Dr Charles Rizza FRCPEd (b. 1930) was MRC Clinical Research Fellow at the Blood Coagulation Research Unit in Oxford between 1958 and 1961, working with Dr R G Macfarlane and Dr Rosemary Biggs. He was awarded an MD from the University of St Andrews in 1962 and received the University Gold Medal for his thesis 'Conditions affecting the level of antihemophilic globulin (factor VIII) in the blood.' He was Consultant Physician at the Oxford Haemophilia Centre from 1966 to 1993, and Director of the Centre from 1977 to 1993. He was Clinical Lecturer in Haemophilia at the University of Oxford between 1967 and 1993 and Chairman of the United Kingdom Haemophilia Centre Directors Organization from 1987 to 1990.

<sup>33</sup> John Poole was a registrar in Oxford in 1951. See also note 41.

<sup>34</sup> Professor Stuart Douglas FRCP FRSEd (1921–1998) qualified in medicine at Glasgow in 1944. He won a Medical Research Council fellowship to work in the Blood Coagulation Research Unit in Oxford where he and others devised the thromboplastin generation test (see note 17 above). His main interest was in the study of blood coagulation and bleeding, and later problems of thrombosis. He was Professor of Medicine in Aberdeen, from 1970 to 1985 (Emeritus).

## Haemophilia: Recent history

recognize Clarence Merskey,<sup>35</sup> a research fellow from South Africa working in Oxford in 1949, for introducing the habit of mixing blood from two haemophiliacs. He pointed out that there were at least two grades of haemophilia: one severe and one mild.<sup>36</sup> Addition of a small amount of plasma from the mild patient would give some correction of the plasma-clotting time of the severe haemophiliac, but not as effectively as normal plasma. This mixing became part of the laboratory 'work up' of a new suspected bleeder. A test for haemophilia was failure to correct the recalcification time of a known haemophilic plasma as effectively as normal plasma.<sup>37</sup>

I thought of the Oxford-taught investigators, John Poole was the first to find cross-correction.<sup>38</sup> I did not know that John O'Brien had found this at an earlier date.<sup>39</sup>

Ingram: I think even before the mixing in Oxford someone did it in South America.

Rizza: Pavlovsky.<sup>40</sup>

Douglas: I think if you look, John Poole didn't actually describe that phenomenon until the Christmas disease paper was published,<sup>41</sup> but I think if you talk to him, you'll find that he did it many years earlier. Ilsley Ingram in

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<sup>35</sup> Dr Clarence Merskey FRCP (1914–1982) worked with Biggs and Macfarlane from 1949 to 1951 at the Radcliffe Infirmary, Oxford, where he developed his coagulation expertise and made valuable contributions to the study of haemophilia. In New York he collaborated closely with Alan Johnson (mentioned later in the meeting) devising tests for measuring fibrin degradation products. See also notes 8, 9 and 36.

<sup>36</sup> Merskey C. (1950) The laboratory diagnosis of haemophilia. *Journal of Clinical Pathology* 3: 301–320. See also note 8 above.

<sup>37</sup> Small amounts of normal plasma and of the patient's plasma are added to citrated plasma from the known haemophiliac, and the clotting times after recalcification are recorded. Very small proportions of normal plasma will shorten the calcium-clotting time of haemophilic plasma almost to normal. If similar proportions of the patient's plasma fail to do so, he presumably has haemophilia. See Biggs R, Macfarlane R G. (1953) The coagulation defect in haemophilia. In *Human Blood Coagulation and its Disorders*, ch. XV. Oxford: Blackwell Scientific Publications, 227–231, 348.

<sup>38</sup> See notes 16 and 41.

<sup>39</sup> Professor Stuart Douglas wrote: 'I had thought the first assessment in Oxford of Stephen Christmas's blood was a sample collected by me from London at the request of John Dacie and Bob Pitney in 1952. I am willing to be proved wrong.' Letter to Dr Tilli Tansey, 24 July 1998.

<sup>40</sup> op. cit. note 16 above.

<sup>41</sup> Poole J C F. (1953) A haemorrhagic state resembling haemophilia. *Lancet* i: 122. op. cit. note 18 above.

his introductory remarks also mentioned Mannucci in relation to the use of DDAVP in mild haemophilia.<sup>42</sup> There was an important British contribution which led to the work by Mannucci in 1977. You [Ingram] showed that the level of factor VIII in normal blood could be raised by injections of adrenaline<sup>43</sup> and you [Rizza] showed a rise in factor VIII after exercise.<sup>44</sup> John Cash and his colleagues in Edinburgh showed that these responses could not be totally prevented by  $\alpha$  and  $\beta$  receptor blockers and the possibility was raised of an involvement of the hypothalamic-pituitary axis as a secondary pathway.<sup>45</sup> The only neuropeptide available for human prescription was vasopressin – antidiuretic hormone (ADH) – and they gave this to themselves, and found a factor VIII response; side-effects were too troublesome for clinical practice (vasoconstriction, and powerful contractions of the uterus and gastrointestinal tract). They found that the synthetic analogue desmopressin [DDAVP] was as active in raising factor VIII (and von Willebrand's factor) as the natural antidiuretic hormone. Clinicians in their Haemophilia Centre in Edinburgh had ethical doubts about trying this in haemophilia. The clinical value was then established by Mannucci.

Ingram: Desmopressin [DDAVP] is a synthetic analogue of vasopressin [antidiuretic hormone] from the hypothalamic/posterior pituitary axis; it has the advantage that it does not stimulate bowel contraction or raise blood pressure like the normal hormone, so that it can be given virtually symptomlessly, but it does raise factor VIII between two- and four-fold in the normal subject and proportionally in mild haemophilia but not in severe haemophilia. It has also found a place in treating von Willebrand's disease and thrombocytopenia.<sup>46</sup>

Lee: We still use it by preference in people with mild disease, rather than clotting factor concentrates, and recently there is a formulation which comes as a nasal spray which people are using for home treatment as well. Charlie, can we get back to Christmas disease and 1952?

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<sup>42</sup> op. cit. note 26 above.

<sup>43</sup> Ingram G I C. (1961) Increase in antihemophilic globulin activity following infusion of adrenaline. *Journal of Physiology* 156: 217–224.

<sup>44</sup> Rizza C R. (1961) Effect of exercise on the level of antihemophilic globulin in human blood. *Journal of Physiology* 156: 128–135.

<sup>45</sup> Ingram G I C, Vaughan Jones R. (1966) The rise in clotting factor VIII induced in man by adrenaline: effect of  $\alpha$ - and  $\beta$ -blockers. *Journal of Physiology* 187: 447–454. Gader A M, Da Costa J, Cash J D. (1974) The effect of propranolol, alprenolol and practolol on the fibrinolytic and factor VIII responses to adrenaline and salbutamol in man. *Thrombosis Research* 4: 25–33.

<sup>46</sup> Mannucci P M, Ruggeri Z M, Pareti F I, Capitano A. (1983) op. cit. note 26 above.

## Haemophilia: Recent history

Rizza: Dr Bidwell is here. She is the one to answer that.

Dr Ethel Bidwell:<sup>47</sup> I couldn't think what everybody was so interested in, in 1952, and they weren't at all interested in what I was doing. Then people slowly explained to me about this Christmas disease and then I realized.

Rizza: I think the trouble with Christmas disease in 1952 was that, as for haemophilia, there was no therapy. There was no treatment apart from plasma transfusion, giving moral support and holding the patient's hand. When the NHS began 50 years ago, that's just when I started to study medicine, there was no therapy, although as Ilsley said, the antihemophilic globulin had been recognized as being the important constituent of plasma which haemophiliacs lack. Since 1941, Cohn had been fractionating human plasma into its various constituents,<sup>48</sup> so rather than giving the patient the whole plasma the different patients were given only the fraction they required. It was soon shown that Cohn's fibrinogen fraction was contaminated with factor VIII and began to be used in a limited way in the late 1940s and early 1950s for the treatment of haemophilia.<sup>49</sup>

Bidwell: Certainly for a long time after that we weren't still sure that factor VIII and fibrinogen were not modified forms of the same thing. One of the few purely academic things that I was ever involved in was electrophoretic separation, not from the point of view of preparation of factor VIII, but just to show you could get them apart.

Lee: Dr Bidwell, tell us when you first got involved in making treatment for haemophiliacs.

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<sup>47</sup> Dr Ethel Bidwell (b. 1919), an experienced enzyme chemist, joined Macfarlane in Oxford in 1950 and in 1952 started a study of plasma concentration and selective extraction of factor VIII. By 1953 she was producing a concentrated bovine factor VIII 8000 times as strong as normal human plasma. In 1959 she held a full time MRC appointment in the newly opened MRC Blood Coagulation Research Unit in the grounds of the Churchill Hospital, Headington, Oxford, and concerned herself with the preparation of human coagulation factors. See *Report of the Medical Research Council for the Year 1958–1959*. London: HMSO, 111. Her research assistant, Ross Dike (see biographical note 177 below), joined the team in 1954. Dr Bidwell retired in 1981. See also notes 60 and 62 below.

<sup>48</sup> Cohn E.J. (1941) Properties and functions of plasma proteins with consideration of methods for their separation and purification. *Chemical Reviews* 28: 395–417. *idem* (1947) Separation of blood into fractions of therapeutic value. *Annals of Internal Medicine* 26: 341–352.

<sup>49</sup> Human factor VIII was first available in 1957, see note 3 above. For animal factor VIII, see page 13 below. Minot G R, Taylor F H L. (1947) Hemophilia: the clinical use of antihemophilic globulin. *Annals of Internal Medicine* 26: 363–367. Alexander B, Landwehr G. (1948) Studies of hemophilia. II. The assay of the antihemophilic clot promoting principle in normal human plasma with some observations on the relative potency of certain plasma fractions. *Journal of Clinical Investigation* 27: 9–18.

## Haemophilia: Recent history

Bidwell: I went to Oxford in 1950, not because I had an interest in blood coagulation, but because Macfarlane worked on gas gangrene. I worked for seven years for the Wellcome Foundation, during the war, on toxins of anaerobic bacteria involved in gas gangrene and later on tetanus toxin. Macfarlane wanted someone to work on nothing to do with blood coagulation. I got pretty browned off to find nobody was interested in what I was doing [they were involved in the discovery of factor IX deficiencies]. They realized that I was restless, because I didn't want to work all on my own in a corner doing something nobody was interested in. So he said to me, 'Well we have got nothing to treat these haemophilic patients with, would you like to have a go at seeing if you can make something from animal blood?'. So that's how I got started in 1952.

Lee: Which animals did you choose first of all?

Bidwell: Animals that were slaughtered in a slaughterhouse. I think the first thing was the bovine blood. When I got involved, it was done by the slaughterhouse men and they were very helpful, very kind. They wanted the very best for me. They wanted me to have the animals that had won all the rosettes at the shows, but ancient old cows were much better. I went down to the slaughterhouse on my Vespa motorbike and I came back with a large glass container. I got concerned lest I tipped off my motorbike and tipped blood on the floor.

Lee: How much blood would you be collecting?

Bidwell: About a gallon. People don't realize that plastics were only just coming in. It cost me about the equivalent of a week's wages to buy a plastic container to put the blood in so that it wouldn't break on the road to Oxford.

Lee: What year are we talking about?

Bidwell: 1952. As I say, I had worked on gas gangrene toxins, *Welchii* toxins, at the Wellcome Foundation and I put that sort of knowledge to use, but I was a very pure chemist, who went round bleating, 'What is a cell?' to my colleagues. I just had to make use of what was available. There were no refrigerated centrifuges. We had to cool them with dry ice and so on. The Blood Transfusion Centre was three miles away and they didn't even have a centrifuge

## Haemophilia: Recent history

to spin their bottles. They used to have to come to us if they wanted to prepare blood. People just don't realize the things that weren't there.

One of our major problems was sterilization, because the properties of the factor VIII were such that it wouldn't go through the usual filter media, and that's why in the beginning we used to just hopefully give it a high-speed spin and put it in a quartz tube and irradiate it; it wasn't really sterile.

Lee: When did you have the first lot of treatment material that you actually were prepared to use?

Bidwell: It was about 1954 when we started to use it for patients requiring tooth extraction, knowing that they were likely to bleed to death if we failed. Then in the autumn of 1954, we were called to Norwich for a patient who worked in a gun shop and he had got shot by mistake by a customer who was trying out a gun! So we went up there and to our horror when we tried the bovine factor VIII, the patient had the most awful anaphylactic reactions. We couldn't understand this; we hadn't had this sort of reaction before. I am not medical myself, so I was chatting away to the technicians while the medical people were having talks at a distance and the technicians whispered to me that this patient about ten days earlier had been given an Italian preparation which I vaguely thought was from bovine material. So I went to Macfarlane and whispered, 'Can I speak to you?' and I told him about this and of course his face changed because he realized the significance – the patient had been sensitized to the bovine material. Macfarlane and Biggs had to go back to Oxford, and I and a Canadian called Danny Bergsagel, a medical man who was working with them, stayed behind and eventually the patient was moved to Oxford in an RAF plane. That was the first time I had flown and I was sitting on the floor of this plane while a nurse was putting a drip up. I got back to Oxford, the patient continued to have reactions to the bovine material and I can remember at the end of that week going to Macfarlane and saying, 'There's nothing I can do, can I try pig?' and he said, 'Well, go on'.

The first pig we used was from an animal that was being slaughtered in the next village on the Sunday morning. Ross Dike<sup>50</sup> had just joined me and I rang him up. That's when we started work and by Wednesday we were treating that patient with a course of porcine antihæmophilic globulin. They wouldn't let you do that these days.

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<sup>50</sup> See Ross Dike's contributions later in this meeting and biographical note 177 below.



Lee: No, that's right. One of the things that I hadn't quite understood, and it came out when we were speaking with Dr Biggs<sup>51</sup> and again here, is why did people push to use animal plasma. I think I am right in saying that Macfarlane had made the calculation of how much plasma was needed from human blood in the United Kingdom to treat the people with haemophilia and he came up with the calculation that it was absolutely impossible; so he therefore said we must use animals. Isn't that right?

Ingram: Yes, that's right.

Bidwell: Not only that. Again I emphasize this was before the advent of plastic, which made all the difference practically.

Dr Peter Jones:<sup>52</sup> If we can put this into context, this discovery and the large scale manufacture, I think later by Maws,<sup>53</sup> of the animal products brought treatment particularly to people who had to have major surgery. In the 1960s, when I started in haemophilia care, the major operation wasn't reconstructive surgery, it was for peptic ulceration with partial gastrectomies, and pyloroplasties and vagotomies. There was simply not enough human factor VIII in the United Kingdom to treat more than one patient at a time, and so we had to turn to the animal products and they were terrific. We used to go for pig first, because we thought it was least antigenic and least likely to cause thrombocytopenia. The antihaemophilic effect lasted for something like five, six, seven, and if you were lucky, eight days, and then we used to change to bovine and that would last a similar period. We watched the platelet count but never had a clinical problem. Last of all we'd top up with human factor VIII if the patient hadn't healed. But that was the position. We used to have to ring round to Oxford and to Edinburgh, and to our colleagues in London to get enough human factor VIII for one major surgical operation at a time. So the animal products were life-saving very early after their introduction.

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<sup>51</sup> op. cit. note 2 above.

<sup>52</sup> Dr Peter Jones FRCP (b. 1937) is Consultant Paediatrician at the Royal Victoria Infirmary, Newcastle upon Tyne. He is Director of the Newcastle Haemophilia Centre and an Executive Member of the World Federation of Hemophilia. In 1981 he received the Gold Medal (Macfarlane Award) of the Haemophilia Society. He has published extensively on haemophilia and on AIDS, and is the author of *Living with Haemophilia*, 4th edition. Oxford: Oxford University Press.

<sup>53</sup> It had been arranged that the firm of Maws & Son Ltd should take over the responsibility from Bidwell (see note 47 above) for preparing concentrates of animal factor VIII.

## Haemophilia: Recent history

Ingram: I have here a copy of the surgical course of a patient who had an abdomino-perineal excision in October 1959 and who had treatment with ox and pig, and human factor VIII.<sup>54</sup>

Lee: Another point that Dr Biggs made was that you [Bidwell] didn't use sheep and there was a reason for that.

Bidwell: There were two reasons. One was that sheep were very woolly, so it would have been extremely difficult to collect blood that didn't clot as fast as you looked at it.<sup>55</sup> The other is that the relationship between sheep and cows was close enough to get a cross reaction.

Rizza: Dr Bidwell mentioned the horrendous reaction that the man in Norwich had,<sup>56</sup> but of course patients nearly always had reactions as the course of therapy went on and you had to watch for this and the patients told some lovely stories. 'Why is it, doctor, I always see stars in front of my eyes when this stuff goes in?' and we didn't know why they were seeing stars. In retrospect the suggestion is that it may have been platelet clumps going through the retina, because the AHG clumped the platelets and the platelets disappeared from the blood as a consequence. One ended up sometimes with the patient at risk of bleeding from thrombocytopenia, although his haemophilia was better. It was very, very interesting. James Matthews<sup>57</sup> and I had many a worrying time with patients going on to second courses of treatment and wondering what would happen to them.

Bidwell: Do you remember the terrible cysts that the patients used to have? As I say, I am not medical, I was told that according to strict anatomy they shouldn't have had those, because there shouldn't have been a track but there obviously were and they were frightful.

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<sup>54</sup> Copy prepared for the meeting by Ilsley Ingram, taken from Christie T H, Graham-Stewart C W, Ingram G I C. (1960) Abdomino-perineal resection of the rectum in a haemophiliac. *Thrombosis et Diathesis Haemorrhagica* iv: 224–234, page 229.

<sup>55</sup> The blood on the wool would coagulate very quickly.

<sup>56</sup> This refers to the anaphylactic reaction after treatment with bovine factor VIII of the patient with a gun shot wound described earlier by Ethel Bidwell.

<sup>57</sup> Dr James Matthews contributes later in the meeting, see biographical note 110.

RIZZO: This is the awful thing with haemophilia bleeding of course. It can track anywhere. It can destroy soft tissue, it can destroy even bone, because of the pressure it can exert in a confined space.

Your [Bidwell] factor VIII was excellent material and so was the Maws material and the Crookes, but the problem we had was getting it into solution. It took an hour sometimes or more, shaking bottles, and you had to be careful not to shake too hard, because if you got a froth the powder would never dissolve, because the factor VIII would sit in clumps on the bubbles and wouldn't go into the water. This is one of my recollections, sitting for two or three hours shaking. In fact, all of the department used to be involved in this. If it was major surgery which was being undertaken, you made up numerous bottles and you passed them round to technicians, secretaries, research workers and they'd all sit there at tea time drinking their tea and shaking their bottles.

Dr Brian Colvin:<sup>58</sup> I want to add a little bit to what Peter [Jones] said about peptic ulceration and haemophilia. I still look after a patient who had, I think, bovine or porcine factor VIII in 1961 in Oxford and it's important to appreciate that people not only got hold of this material, but also referred patients to Oxford. For many years, even after my interest began, people were being referred to Oxford for treatment and to have their lives saved. It's significant perhaps that 40 years later some of these people are still walking the planet, who certainly wouldn't be doing so otherwise.

Perhaps while I have the microphone, I could add a little tiny anecdote to Professor Ingram's presentation. Treves's description of the haemophilia scene in 1886 in the *Lancet*<sup>59</sup> relates to an East End family and concerns a young girl called Florence. I never saw her, but her daughter, Edith, broke her hip in a strike in 1978 and couldn't be accommodated at The London so she was sent to the Royal Free to be operated on. This lady was also probably a true haemophiliac and had four sons, all of whom had haemophilia, and the last of those sons died last month. So we have a direct link to Treves's description in 1886. Some years ago our district treasurer asked me how long we had been treating haemophilia at the Royal London Hospital and I was able to tell him that it was since 1886, which dealt with the argument.

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<sup>58</sup> Dr Brian Colvin FRCP FRCPath (b. 1946) is Assistant Warden at St Bartholomew's and The Royal London School of Medicine and Dentistry. He has been Consultant Haematologist and Haemophilia Centre Director at The Royal London Hospital since 1977 and Director of Postgraduate Medical and Dental Education at the Royal Hospitals Trust since 1996. He is a Member of the British Society for Haematology and has published many papers on the management of haemophilia.

<sup>59</sup> Treves F. (1886) A case of haemophilia, pedigree through five generations. *Lancet* ii: 533-534.

## Haemophilia: Recent history

Lee: Dr Rizza, we just heard then how people were sent to Oxford to have treatment. Tell us about the little boy.

Rizza: Oh, the little boy with Christmas disease. I think he was the first person to receive Dr Bidwell's factor IX.<sup>60</sup> I was lucky enough to be working with Dr Macfarlane and Dr Biggs in 1959–60 and I used to write home to friends and colleagues, telling them episodes about my personal life as well as my working life. I told them what I was up to and what was happening at the Centre, what was being done in the way of research. It's a thing you daren't do nowadays. You keep your notebooks shut; nowadays you must not tell anyone what you are doing. Everything was so relaxed in those days, you didn't mind telling people what you were doing in the way of research. You didn't expect them to steal your ideas or results. I wrote and I said that Dr Bidwell was being successful with the factor IX concentrate and that Dr Biggs had made an assay, and that soon this concentrate would be available. Promptly, Dr Biggs got a telephone call from Dundee where I had come from, asking if she could take on the care of a little boy of four, who had had a venepuncture in the antecubital fossa and for some reason or other had developed a haematoma at the site of puncture. It got huge. It got infected and he ended up with osteomyelitis of the radius and he was in a very bad way. He was obviously very frightened, in great pain. He was referred to Oxford to be looked after by Professor Trueta,<sup>61</sup> who was Professor of Orthopaedic Surgery then, a paediatrician called Dr Victoria Smallpeice and Dr Biggs. I remember when we unwrapped his hand, his thumb fell off, because his thumb was gangrenous. As soon as he was admitted Trueta said, 'This [forearm] must come off, he's very ill, he's infected', and this was done. I remember the first dose being given. You, Dr Bidwell, were there watching. Dr Bidwell liked to see what the junior doctors got up to with her material, so that she knew whether it was the doctor's mishandling of the material, rather than the material that caused the problems. The child was taken to theatre and given factor IX, and he had to be sedated with rectal pentothal every day because he was so frightened. But the operation went very well, the factor IX caused no [side] reactions whatsoever, and he healed very well. I know that boy well, because when I was up in Scotland last year I went to see him. He's now 42 years old, he's an architect, and he tells me that he likes to play

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<sup>60</sup> See Rizza C R. (1995) The first patient to receive factor IX concentrate in the UK: a recollection. *Haemophilia* 1: 201–212.

<sup>61</sup> Professor Joseph Trueta FRCS DSc (1897–1977). Following a distinguished career during the Spanish Civil War was surgeon in charge of the accident service at the Radcliffe Infirmary in Oxford in 1942 and Nuffield Professor of Orthopaedic Surgery at Oxford from 1949 to 1965. He was succeeded by Professor Robert Duthie (see biographical note 106). See Strubell M, Strubell M. (1980) *Trueta: Surgeon in war and peace*. (Translated memoirs) London: Victor Gollancz Ltd.

golf. He has only one hand, of course. He did away with his prosthesis very early on, because he found the artificial arm more of a nuisance than a benefit, and he plays one-handed, right-handed golf.

Bidwell: I remember his ginger hair, bright, bright. I had been putting together enough factor IX for some sort of cold operation such as tooth extraction on an adult, when you [Rizza] came to me with this story, and, of course, having worked with gangrene organisms, it put terror into me. I have never been so frightened in my life.

Rizza: It's sad to say that the man you were saving the factor IX for had haemorrhoids and had to have his operation postponed for several months.

Bidwell: I didn't know what he suffered from.

Rizza: It's a bit sad, because he was the man who came and gave us blood every month for Dr Biggs to develop the factor IX assay, so he thought he was getting the assay developed for himself and you were making factor IX for his surgery. He, in fact, was a very understanding man. The only point that we haven't mentioned is that the development of factor IX went hand in hand with the development of good assays, because you didn't know what you were making without good assays and you can't do anything without good assays.

Bidwell: We didn't have access to human plasma for a good long while after that and it was decided to see if we could get any factor IX from what they were throwing away at Elstree,<sup>62</sup> at the end, when they had taken out albumin and gammaglobulin, and factor VIII, which was everything they made. Of

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<sup>62</sup> At that time, the large-scale fractionation of plasma was carried out at the Blood Products Laboratory of the Lister Institute at Elstree by the ether process of Kekwick and Mackay (Kekwick R A, Mackay M E. (1954) The separation of protein fractions from human plasma with ether. *Medical Research Council Special Report Series* No. 286. London: HMSO). This yielded, as a by-product, a yellowish, green, greasy residue which was rich in factor IX and it was with this that Dr Bidwell and her assistant, Ross Dike, used to extract factor IX. Dr Bidwell wrote: 'I am not sure why Kekwick and Mackay did not use Cohn's fractionation method using ethyl alcohol, but it is possible a patent covered the latter. It is a great tribute to the skills of the early Blood Products Laboratory staff that the place did not explode or burn down. ...I mention in the meeting that my earliest starting material for preparing factor IX was the final residue from this process. But the first fraction from the process was a concentrate of factor VIII, which was supplied from Elstree to clinicians in need. ...Leon Vallet worked at Elstree in getting this into production and Dr Snape who worked with me at Oxford, is in charge there now.' Letter to Dr Daphne Christie, 28 March 1999.

## Haemophilia: Recent history

course, there was a mess with what they threw away, and that was what we used for our factor IX, the first type of factor IX.

Lee: You were just talking about the importance of good assays and you are talking now about making the concentrates really rather more formalized. When did standardization start, and having standards for assays? When did standardization become used either for assays themselves or for assaying the material that was being made? When was it realized that that was important?

Dr Derek Bangham:<sup>63</sup> During the 1960s we [in the Division of Biological Standards, National Institute for Medical Research] were constantly on the lookout for biological substances which needed standards [reference materials] for measurements of macromolecules in human physiology and pathology (although not necessarily needed for legal control). Peter Walton, who had done a PhD with Ralph Kekwick on factor VIII assays,<sup>64</sup> was working with us, and was, perhaps, the first person to prompt us that a standard was needed. He left in the early 1960s and the Division was for some years without a haematologist. During those years splendid papers by Macfarlane, Rosemary Biggs, Ken Denson and others showed the variability of factor VIII concentrations during conditions of physical activity, and variability in different people.<sup>65</sup> This was a striking example where a standard was needed, for comparisons of assay results.

In 1966 I went to Oxford and introduced myself to Rosemary Biggs and Gwyn Macfarlane. In Rosemary's office I asked her what she used as a standard. She turned and pointed to a glass-stoppered sweet jar full of freeze-dried bovine factor VIII preparation, and said, 'That's it'.<sup>66</sup> I am a medical, but was then innocent of knowledge of blood clotting, and Rosemary, being a rather forthright person, was a little taken aback by my proposal for a proper standard. But when I'd described the MRC's work on biological standards, and the possibility of establishing a WHO international standard, she immediately

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<sup>63</sup> Dr Derek Bangham FRCP (b. 1924) was Head of the Division of Biological Standards at the NIMR from 1961 to 1972. He was later Head of the Hormones Division of the National Institute for Biological Standards and Control (NIBSC), from 1972 to 1987.

<sup>64</sup> Walton P L. (1962) Studies on the proteins of the blood coagulation mechanism in the human. PhD thesis, University of London.

<sup>65</sup> op. cit. note. 44 above. See also Denson K W. (1973) Molecular variants of haemophilia B. *Thrombosis et Diathesis Haemorrhagica* 29: 217–219.

<sup>66</sup> Dr Ethel Bidwell wrote: 'I would like to record that my seven years with the Wellcome Foundation at Beckenham had ensured that when I had available freeze-dried bovine factor VIII, I had at least done accelerated degradation tests showing that the material would be sufficiently stable to serve as a standard. It was a great improvement on "pooled normal plasma".'  
Letter to  
Dr Daphne Christie, 28 July 1998.

agreed, and from then on was tremendously helpful. It was the start of a very good collaboration with her, Ken Denson, Charlie Rizza and Ethel Bidwell in setting up several standards for this field of haematology.

Some citrated plasma was freeze-dried, within four hours of its collection at the Edgware Transfusion Centre, in ampoules in the fastidious conditions used for biological standards. Ampoules were labelled with code numbers with the year in which they were filled and sealed. It was first necessary to determine, using accelerated degradation studies, if factor VIII had long-term stability. An international collaborative study was organized to compare this with a concentrate preparation supplied by Alan Johnson of the New York Medical Center, freeze-dried at NIMR in ampoules coded 67/19. Each participating laboratory was asked to assay the coded ampoule against their own standard, or fresh human blood.<sup>67</sup> The results revealed that what people called '1 ml of normal blood' varied from pools of blood, with or without various dilutions of citrate. One chap simply used his own blood, day by day. It was a very large and complex study, and probably the first international study of factor VIII assays involving the world's expert laboratories. It was a problem to sort out the huge number of results.

By then we had been joined by a young Yugoslavian haematologist, Dr Milica Brozovi\_. She helped Joyce Skegg, our statistician, to analyse and interpret the results, also helped by Rosemary [Biggs]. The draft report of the study was circulated to the participants for agreement. Eventually, in 1970, the final report was sent to the Expert Committee on Biological Standardization of WHO, which in 1970 formally established the preparation 67/19 as the First International Standard for factor VIII.<sup>68</sup> That was a significant step because International Units of WHO have legal importance in all countries. Any preparation for sale claiming to have factor VIII activity was obliged by law to be labelled with those international units. Fortunately, that standard was established just in time for the first commercial products that were licensed in the UK, and were formally controlled in proper units.<sup>69</sup>

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<sup>67</sup> As many as 20 laboratories participated in the study. See Bangham D R, Biggs R, Brozovi\_ M, Denson K W E, Skegg J L. (1971) A biological standard for the measurement of blood coagulation Factor VIII activity. *Bulletin of the World Health Organization* 45: 337–351.

<sup>68</sup> Dr Derek Bangham wrote: 'When tests for hepatitis became available, the concentrate (the International Standard) was found to be contaminated and was promptly replaced with another preparation established as the Second International Standard, calibrated in International Units against the First International Standard.' Letter to Dr Daphne Christie, 27 July 1998.

<sup>69</sup> See *British Pharmacopoeia* (1973) Dried human antihæmophilic fraction, 64–65. *ibid.* H. Biological assay of human antihæmophilic fraction, A114–A115.

## Haemophilia: Recent history

I should add, another preparation of freeze-dried whole plasma, included in the study, was established as the British Working Standard, made available to Haemophilia Centres all over Britain.<sup>70</sup> It proved to be enormously useful, and the twentieth (replacement) working standard is now being distributed.

Lee: It's very interesting to hear how long ago it was that standardization, which is so much part of our life, began. I want to try and change tack a little bit, and think about the children who were having treatment. One of the things that was said early on was that nobody really thought about what was going to happen when these children grew up, because nobody expected them to grow up, and it wasn't until they started having treatment that people started organizing haemophilia care. We've got some patients in the audience and relatives of patients, and we have also got Dr Evans and Dr Jones here, paediatricians. Would you like to just try and take us back as far as you can and tell us about the children and how treatment came in and the issues?

Dr David Evans:<sup>71</sup> I thought my brief was actually to continue with a bit of the history after Ilsley left off. So I have got a two-part talk really. One is a little bit of personal ramblings, which I hope will set ideas off in individuals' minds, and perhaps get them remembering things which they may otherwise have forgotten, and secondly, more a sort of brief run-down of things that happened year by year afterwards. But let's start with the first bit.

I was an undergraduate at Cambridge in the early 1950s at Downing College at a time when Sir Lionel Whitby was Master of Downing. He was, of course, the first President of the Haemophilia Society and had an enormous fund of information on blood disorders, which he published in his book.<sup>72</sup> It would be nice for me to be able to say to you that as a result of this marvellous experience of meeting Sir Lionel I was inspired with a desire to become a haematologist, but it would not be true. All I remember about Sir Lionel was that he'd come back from the First World War minus one leg, and with a crate of whisky and we all respected him for that. Later in the 1950s, I was a student

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<sup>70</sup> Brozovi\_ M. (1977) Physiological mechanisms in coagulation and fibrinolysis. *British Medical Bulletin* 33: 231–238.

<sup>71</sup> Dr David Evans FRCPEd (b. 1930) trained in paediatrics at hospitals in Carshalton and Lewisham and in pathology at Guy's Hospital, London, before going to Booth Hall and the Royal Manchester Children's Hospitals in Manchester where in 1966 he developed a regional service for children with blood diseases. In 1972 he set up a Haemophilia Centre at the Royal Manchester Children's Hospital. He retired in 1992.

<sup>72</sup> Whitby L E H, Britton C J C. (1935) *Disorders of the Blood: Diagnosis, pathology, treatment and technique*. London: J & A Churchill.



at St Thomas' where Ilsley Ingram and Roger Hardisty<sup>73</sup> were lecturers in clinical pathology. I remember Ilsley Ingram giving me a tutorial, which I can't remember much about. But he did talk about von Willebrand's disease and that made an impression upon me, but alas it did not inspire me to become a haematologist either.

Now, I am going to talk a little bit about blood transfusion at Manchester, because of what we probably regard now as blood banking, which of course is still terribly important for the early days of haemophilia care. Blood banking was really started in the Spanish Civil War by a Basque, Dr Frederick Duran-Jorda. He originally worked in the Public Health Department in Barcelona and in 1936 he organized a blood transfusion service for the Catalan army during the days of the Spanish Civil War. And this was the first time, in 1936, that civilian blood donors had been used and their blood was stored to form a blood bank, and this was what was original about Dr Jorda's work.<sup>74</sup> In 1937 it was extended to the whole of the Spanish Army and Dr Duran-Jorda was appointed Director of Blood Transfusion, and he gave lectures in France, Switzerland and Czechoslovakia. In 1939 he was invited by the Red Cross to come to England. He went to the haematology department of the Postgraduate School and lectured to the Royal Society of Medicine. I remind you that other Basques left Spain at the same time and that Professor Trueta,<sup>75</sup> who has already been mentioned, who was later Professor of Orthopaedic Surgery at Oxford, was another one.

In the same year, 1939, in the expectation of masses of civilian casualties from bombing, the National Transfusion Service in the UK was set up. In 1940, the following year, Dr Duran-Jorda came to Manchester. In 1950 he was appointed Director of Pathology at Booth Hall Children's Hospital and this is really why I mention him, because it was the same post that I took over from his successor in 1966. In Manchester he would have been in touch at the Royal

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<sup>73</sup> Professor Roger Hardisty FRCP FRCPath (1922–1997) qualified at St Thomas' Hospital, London, in 1944 concentrating on haematology and particularly the bleeding disorders. In 1957 he was appointed honorary consultant haematologist to the Hospital for Sick Children, Great Ormond Street, London, and over 30 years built up one of the first paediatric haematology departments in Britain. He was Professor of Paediatric Haematology at the Institute of Child Health, London, from 1969 to 1987, and Professor Emeritus of Haematology at the Royal Free Hospital School of Medicine, London, from 1987 to 1997. He served as president of several haematological societies and was Editor of the *British Journal of Haematology*.

<sup>74</sup> Dr Frederico Duran-Jorda was Clinical Pathologist to the Public Health Department in Barcelona in 1934. In 1936 he organized a blood transfusion service for the Catalan army using civilian blood donors. Duran-Jorda F. (1937) El servicio de transfusión de sangre de Barcelona. *Revista de Sanidad de Guerra* 1: 307–321.

<sup>75</sup> See biographical note 61 above.

## Haemophilia: Recent history

Infirmery with Dr Wilkinson,<sup>76</sup> who was Director of the Department of Clinical Research there, which actually developed from a study of gastric function into one in pernicious anaemia and is now a department of haematology. Dr Wilkinson organized the blood transfusion services in the north-west. He is now over 100 years old<sup>77</sup> and is a vice-president of the Haemophilia Society. It is fair to say that Dr Duran-Jorda had an original mind, but I regret to have to tell you that he published one of his original ideas in *Nature* in 1947 and it was that red blood cells originate from the granules of eosinophils.<sup>78</sup>

I want to talk a little bit about my early contacts with the use of factor VIII concentrate, because in 1957, which was when I qualified, Kekwick and Wolf reported on the use of a factor VIII concentrate in the treatment of six cases of haemophilia.<sup>79</sup> Two years later I was a Registrar at Lewisham, and Peter Wolf was still pouring these dreadful soups and thick creamy stuff into individuals with haemophilia.<sup>80</sup> I was very concerned that they were going to go into cardiac failure because he was putting in this stuff so fast, but fortunately they were predominantly young men with good cardiovascular reserves and I think that apart from a tachycardia and a shortness of breath, we didn't have any complications. Dr Holman was the haematologist at Lewisham in those days, and I think it is quite appropriate that we remember that haematologists as we know them now did not exist. The patients were all under the care of general physicians and a haematologist was a specialist in the laboratory who got interested in aspects of blood and blood management. There were very, very few clinical haematologists.

I went to Manchester in 1965 and that was the year in which Judith Pool described cryoprecipitate.<sup>81</sup> We didn't get cryoprecipitate in Manchester until much, much later. We used fresh, so-called 'snap-frozen' plasma. Dr Stratton was the Director of the Blood Transfusion Service in Manchester at the time and he was a very autocratic individual. He really believed that all people wanted from a blood transfusion service was what he called 'the pint', and he would hold up a bottle of blood, because the blood came in bottles with a

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<sup>76</sup> Dr John Wilkinson (1897–1998) was Director of the Department of Haematology at Manchester Royal Infirmary from 1947 to 1962 and set up the first blood transfusion service in Manchester. He was cofounder of the British Society of Haematology, President of the European Haematology Society and a Life Councillor of the International Haematology Society.

<sup>77</sup> Dr Wilkinson died shortly after the meeting, on 13 August 1998. See biographical note 76.

<sup>78</sup> Duran-Jorda F. (1947) Secretion of red blood corpuscles. *Nature* 159: 293–294.

<sup>79</sup> See Kekwick R A, Wolf P. (1957) op. cit. note 22 above.

<sup>80</sup> At that time the concentrates came in bottles as an opaque thick creamy juice.

<sup>81</sup> See note 24 above.

waist in those days, and he'd say, 'Look at that, doc, that's the pint, that's what you want'. And all the doctors in the Transfusion Service were called 'Doc' by the workers, and by Fred [Stratton] himself. He provided a very good service, but he never thought it was a business of his department to provide blood fractions.

So very shortly after arriving in Manchester when I had a baby with a cerebral haemorrhage, I couldn't get anything other than plasma to treat him with. In fact I managed to get some cryoprecipitate which was being made for the first time in Manchester by Dr Watson-Williams at Manchester Royal Infirmary. It seemed to work, the child recovered, but subsequently died, but it inspired us to buy a large vacuum flask and we made our own cryoprecipitate. But whereas in London there had been no difficulty in obtaining blood donors, because there was a Red Cross panel, you phoned up the Red Cross and they sent somebody along, any hour of the day or night, Manchester had never developed that concept. There were special donors, but they all had individual and particular blood groups and they were called up when a funny blood group was needed, not when you wanted blood in a hurry. So we had extreme difficulty in getting donors to provide us with blood from which you could make the cryoprecipitates. I remember we had to buy the blood bags and we got them from Tuta (Australia), because they were cheaper than from Baxter,<sup>82</sup> and that caused problems because the hospital hadn't had to buy blood bags before and they wouldn't authorize the purchase because they thought that was the job of the Blood Transfusion Service and, of course, as I told you, the Blood Transfusion Service wouldn't do it. Eventually we got cryoprecipitate from the Blood Transfusion Service and continued to use it for a very long time, because there were no funds to buy imported concentrate.

Actually, this proved to be a benefit, because as a result only a rather small percentage of our boys developed human immunodeficiency virus (HIV), because they had been treated with British cryoprecipitate, rather than imported [contaminated] American concentrate. When cryoprecipitate did become available Dr Stratton wouldn't provide it to outlying hospitals, and he insisted that the patients be referred either to me at Manchester if they were children, or adults to the MRI (Manchester Royal Infirmary). That led to our setting up our own Centre in the children's hospital in 1972. That's a little bit about my personal involvement.

What I want to do now is to run through a sort of annual summary of the way things developed. In the 1970s we were starting to use much more freeze-dried concentrate in the UK and gradually amounts were beginning to become

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<sup>82</sup> Manufacturers Tuta (Australia) and Baxter (UK) supplied plastic blood bags to the English National Blood Authority and Scottish National Blood Transfusion Service.

## Haemophilia: Recent history

available. The Bethesda assay for inhibitors was developed in 1975 which helped standardize assays round the world.<sup>83</sup> Lots of the methods, I think, were very good, but they weren't used everywhere and, I think, standardization, as we have just mentioned, was very important. I think the Bethesda assay was helpful in that.

In 1976 the Department of Health published HC-76/4, recommending three-tier arrangements for haemophilia care.<sup>84</sup> By that time a large number of hospital laboratories were able to do factor VIII assays and a lot of haematologists were being appointed because the College of Pathologists was well under way by then and the concept of having a small centre came into being. I think it was a mistake, because the Haemophilia Society and those people who deal with a large number of patients feel that it is better to concentrate patients in a larger unit where there can be a depth of expertise rather than in a small unit. The problem with the small unit has always been you have an enthusiastic haematologist leading it, but when he goes on holiday there is nobody to take his place and the surgeons don't know anything about it and the system falls down. That's just a personal view.

In 1978 fetal blood sampling *in utero* [in the second trimester] enabled us to check the sex and the factor VIII or IX level, and to offer termination of pregnancy to those women who wanted it.<sup>85</sup> My experience was that only a minority of women wanted termination.

In 1982 the gene for factor IX was cloned.<sup>86</sup> Factor IX was cloned before factor VIII because it is a smaller molecule, not so complicated and was easier to work on. In the same year, eight individuals with haemophilia and acquired

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<sup>83</sup> A meeting was held in November 1974, sponsored by the Division of Blood Diseases and Resources, National Heart and Lung Institute, USA, to address the problem of non-uniform inhibitor measurement. It was agreed to standardize inhibitor measurements and to describe a 'Bethesda unit' to be used in the measurement of inhibitors arising in haemophiliacs. See Kasper C K, Aledort M, Aronson D, Counts R B, Edson J R, Fratantoni J C, Green D, Hampton J, Hilgartner M, Lazerson J, Levine P, McMillan C, Pool J G, Shapiro S, Shulman N R, van Eys J. (1975) A more uniform measurement of factor VIII inhibitors. *Thrombosis et Diathesis Haemorrhagica* 34: 869–872.

<sup>84</sup> Department of Health. (1976) *Arrangements for the Care of Persons Suffering from Haemophilia and Related Conditions*. HC-76/4. London: HMSO. The three-tier system comprised Reference Centres (which later became Regional Centres), Haemophilia Centres and Associate Haemophilia Centres.

<sup>85</sup> Rodeck C H, Campbell S. (1978) Sampling pure fetal blood by fetoscopy: in second trimester of pregnancy. *British Medical Journal* ii: 728–730. Mibashan R S, Rodeck C H, Thumpston J K, Edwards R J, Singer J D, White J M, Campbell S. (1979) Plasma assay of fetal factors VIIIc and IX for prenatal diagnosis of haemophilia. *Lancet* i: 1309–1311.

<sup>86</sup> Choo K H, Gould K G, Rees D J H, Brownlee G G. (1982) Molecular cloning of the gene for human anti-haemophilic factor IX. *Nature* 299: 178–180.

immunodeficiency syndrome (AIDS) were reported in the United States.<sup>87</sup> In 1983 parvovirus was found to be spread by concentrates.<sup>88</sup> Factor VIIa – that's plasma-derived factor VIIa – was first used in 1983 to treat inhibitor patients and the first two British cases of haemophilia and AIDS were reported.<sup>89</sup> In 1984 the gene for factor VIII was cloned. I think the initial hope was that because we could clone factor VIII, we would be able to make an instant diagnosis, but because it's such a large and complicated molecule there were an enormous number of defects, and hopes that antenatal diagnosis based on genetic testing with both factor VIII and factor IX would be easy, proved to be quite the reverse.

In 1985 tests for HIV were introduced to the Blood Transfusion Service and in fact tests for HIV became generally available. We were all asked by the parents of the children we were looking after, 'Please test our children' and that's what we did. But we read the message wrongly. What they were asking us, without saying so, was, 'Please find my boy is negative'. In those days when the first test came out, the concept of counselling was really not very well understood, and certainly we didn't understand it. We told the parents the results and then an enormous flood of anxieties and queries came in and people came and talked to us. It was a topic of enormous interest to patients at the time. The north-west group of the Haemophilia Society had its annual general meeting in Manchester. Peter Jones was invited to come and give a talk about HIV, and 400 people came to hear him. We had to move into a larger lecture theatre. It was a larger number than any attendance at a general meeting of the whole Haemophilia Society in London.

But we did have a lot of problems with HIV, not so much dealing with the individual cases of treatment, but in dealing with children through their parents. When the test was first introduced, a large number of our boys were quite small, but as time went by, little boys of 12 became big boys of 16 or 17 and it became time for them to know. In a children's hospital, it is very difficult to inquire into the sexual habits of your patients. It is just not in the ethos of a children's hospital, and we thought that all these boys should know their HIV status. Whether or not they would actually modify their behaviour we very much doubted, although we did have condoms available in the Haemophilia Centre. I

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<sup>87</sup> Evatt B L, Gomperts E D, McDougal J S, Ramsey R B. (1985) Co-incidental appearance of LAV/HTLV-III antibodies in haemophiliacs and the onset of the AIDS epidemic. *New England Journal of Medicine* 312: 483–486.

<sup>88</sup> Mortimer P P, Luban N L C, Kelleher J F, Cohen B J. (1983) Transmission of serum parvovirus-like virus by clotting factor concentrates. *Lancet* ii: 482–484.

<sup>89</sup> Jones P. (1983) Acquired immunodeficiency syndrome, hepatitis and haemophilia. *British Medical Journal* 287: 1737–1738.

## Haemophilia: Recent history

should not think that many children's hospitals in this country would have condoms available. It proved very difficult to get them to talk and it proved impossible to persuade their parents to tell them. Eventually we came to an agreement that if the boys asked, we would tell them. Various ways and means were found to raise the topic so the boys actually asked us, so they could be told. One father came to my office at eight o'clock in the morning and he said, 'I hear what you are planning to do. On no account should my son be told, it will destroy him'. Eventually the boy found out and said he was grateful to be told because it was all hushed up so much at home that he thought something much more serious must be afoot. You will all remember how dreadful it was at the time with the television advertisements showing rolling waves and talking about HIV and safe sex, and so forth.<sup>90</sup> When this happened in a haemophilia household the television was turned off. People just could not bear up to it, they had to turn their heads away. So our problem with HIV was really as much dealing with the parents as actually treating the boys who were positive.

Back to the sort of sequence of events. In 1988 recombinant factor VIIa was introduced for treating inhibitor patients<sup>91</sup> and that year was also the first time that the recombinant factor VIII concentrate was used. 1989 was another milestone year – hepatitis C was identified.<sup>92</sup> In 1990 the Macfarlane Trust was set up to distribute funds to people with haemophilia and HIV. In 1992 a setback came when people realized that solvent-detergent-treated concentrates could spread virus infections in the form of hepatitis A.<sup>93</sup> By 1993 the Health Services Guidelines (93/30) came with the recommendation of a two-tier system of Haemophilia Centres.<sup>94</sup> They recommended what services should be available, but made no recommendations whatsoever about what physical facilities, what buildings, clinics and so forth should be made available, and that I think has led to certain problems for some Centres. In 1994 the

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<sup>90</sup> In the 1980s bold television advertisements were used for public education on AIDS. See Berridge V. (1996) *AIDS in the UK. The Making of Policy, 1981–1994*. New York: Oxford University Press, 113–114.

<sup>91</sup> Hedner U, Glazer S, Pingel K, Alberts K A, Blombäck M, Schulman S, Johnsson H. (1988) Successful use of recombinant factor VIIa in a patient with severe haemophilia A during synovectomy. *Lancet* ii: 1193.

<sup>92</sup> Choo Q L, Kuo G, Weiner A J, Overby L R, Bradley D W, Houghton M. (1989) Isolation of a cDNA clone from a blood-borne non-A non-B viral hepatitis genome. *Science* 244: 359–362.

<sup>93</sup> Mannucci P M, Gdovin S, Gringeri A, Colombo M, Mele A, Schinaia N, Ciavarella N, Emerson S U, Purcell R H. (1994) Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. *Annals of Internal Medicine* 120: 1–7.

<sup>94</sup> This replaced the three-tier system HC-76/4, see note 84 above. Department of Health. (1993) *The Provision of Haemophilia Treatment and Care*. Health Services Guidelines HSG (93)30. London: HMSO. The two-tier system comprised Comprehensive Care Centres and Haemophilic Centres.

UKHCDO [United Kingdom Haemophilia Centre Directors Organization]<sup>95</sup> was set up and registered as a charity and by 1997 things were working very nicely until Creutzfeldt–Jakob disease (CJD) raised its head and produced a lot of anxiety, not so much for haemophilia but for blood transfusion services in general.

Other things which have come up, related to haemophilia and which I have not actually dated, are the use of a continuous infusion of a concentrate.<sup>96</sup> What has been extremely important, but often ignored, is the introduction of small needles and butterfly needles and later, in-dwelling venous catheters and Port-a-Caths for the management of haemophilia care;<sup>97</sup> and another topic which is covered very little in the UK is radiosynovectomy<sup>98</sup> which has been perhaps more popular in parts of the world where concentrate has been less readily available.

Dr Helen Dodsworth:<sup>99</sup> I used to work at St Mary's Hospital, London, after working in Manchester, alongside Dr David Evans.<sup>100</sup> May I say briefly something about the availability of factor VIII concentrate? Although the manufacturing process was discovered in the early 1950s,<sup>101</sup> there was never adequate provision for manufacture of factor VIII concentrate in this country

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<sup>95</sup> See also Rizza's contribution on page 53 below.

<sup>96</sup> Giving concentrate by continuous infusion was first reported in 1970. See McMillan C W, Webster W P, Roberts H R, Blythe W B. (1970) Continuous infusion of factor VIII in classic haemophilia. *British Journal of Haematology* 18: 659–667. Bona R D, Weinstein R A, Weisman S J, Bartolomeo A, Rickles F R. (1989) The use of continuous infusion of factor concentrates in the treatment of hemophilia. *American Journal of Hematology* 32: 8–13.

<sup>97</sup> Dr Jones remembers how, when he worked as a junior doctor with Dr William Walker (later first Professor of Haematology in the University of Newcastle upon Tyne), he had to make the devices that later emerged as butterfly needles and intracaths. Hypodermic needles were cut off their hubs with pliers and either threaded by, or attached to, thin plastic tubing. The results were used in the treatment of babies with haemolytic disease of the newborn. Letter to Dr Daphne Christie, 1 July 1999.

<sup>98</sup> See Pietrogrande V, Dioguardi N, Mannucci P M. (1972) Short-term evaluation of synovectomy in haemophilia. *British Medical Journal* 2: 378–381. Kay L, Stainsby D, Buzzard B, Fearn M, Hamilton P J, Owen P, Jones P. (1981) The role of synovectomy in the management of recurrent haemarthroses in haemophilia. *British Journal of Haematology* 49: 53–60.

<sup>99</sup> Dr Helen Dodsworth FRCP FRCPath (b. 1938) was Honorary Consultant Physician at St Mary's Hospital Medical School, London, from 1970 to 1993 and Founder Member of the British Blood Transfusion Society in 1983. She was a Member of the British Society of Haematology from 1972 to 1993 and has published several papers on blood transfusion-related topics including: Dodsworth H. (1996) Blood transfusion services in the UK. *Journal of the Royal College of Physicians of London* 30: 457–464. Gunson H H, Dodsworth H. (1996) 50 years of blood transfusion. *Transfusion Medicine* 6: 1–88.

<sup>100</sup> See biographical note 71 above.

<sup>101</sup> op. cit. note 23 above.

## Haemophilia: Recent history

until the early 1970s.<sup>102</sup> In 1972–73, a unit dedicated to the production of plasma fractions and managed by the MRC was built on the Elstree site.<sup>103</sup> At about this time the anticoagulant into which donor blood is taken was changed from acid-citrate-dextrose (ACD) to citrate-phosphate-dextrose with adenine (CPD-Ad). ACD has a pH of 5.0 rising to 6.8 after the addition of blood. Factor VIII, however, is stable over only the narrow pH range of 7.1–7.2, the final pH achieved when blood is added to CPD. Although the introduction of CPD-Ad increased the potential for factor VIII production, facilities at Elstree were inadequate to produce the quantities which were needed.

In 1976 Pat Mollison,<sup>104</sup> for whom I was working at the time, asked me to represent him on a committee convened to advise the Department of Health on how much factor VIII concentrate and albumen were needed to treat patients in the UK. Our spokesman, Dr Tovey,<sup>105</sup> the Director of the Bristol Transfusion Centre, had been through a similar exercise for the World Health Organization in Geneva. He persuaded us that if we wanted to treat our patients adequately, it would be necessary to fractionate at least 80 per cent of the blood that was donated. At this point the Government decided that money was available for neither extending the fractionation unit at Elstree nor for equipping the transfusion centres to separate yet more plasma from donor units. So this is really why we found ourselves buying large quantities of factor VIII concentrate from America, and why we infected so many of our patients with HIV.

Professor Robert Duthie:<sup>106</sup> I was interested in what Dr Evans has said about a small unit in a big department. This tends to lead to difficulty in the admission of haemophilic patients, and the follow-up organization, as well as educating members of the team. Oxford has been unique, in that haemophilia

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<sup>102</sup> Anon. (1974) Factor VIII concentrates made in the United Kingdom and treatment of haemophilia based on studies made during 1969–72. Report of the Medical Research Council's Blood Transfusion Research Committee Working Party on the cryoprecipitate method of preparing AHF concentrates. *British Journal of Haematology* 27: 391–405.

<sup>103</sup> *op. cit.* note 62 above.

<sup>104</sup> Professor Patrick Mollison FRCP FRCOG FRCPath FRS (b. 1914) has been Honorary Consulting Immunohaematologist to the South East Regional Service since 1983 and Professor Emeritus of Haematology, St Mary's Hospital, London, since 1979. He was Director of the MRC Experimental Haematology Unit from 1960 to 1979 and Consultant Haematologist at St Mary's Hospital, London, from 1960 to 1979.

<sup>105</sup> Dr Geoffrey Tovey FRCP FRCPath (b. 1916) was Director of the South West Regional Blood Transfusion Centre from 1946 to 1978 and President of the International Society of Blood Transfusion from 1973 to 1976. He was also Consultant Adviser on Blood Transfusion at the Department of Health and Social Security from 1979 to 1981.

<sup>106</sup> Professor Robert Duthie CBE FRCS (b. 1925) was Professor and Orthopaedic Surgeon in charge of orthopaedic surgery at the University of Rochester Medical Center, Rochester, New York, from 1958 to 1966 and Nuffield Professor of Orthopaedic Surgery, University of Oxford, and Nuffield Orthopaedic Centre, from 1966 to 1992, Professor Emeritus since 1992.



has always been a separate and large department run as a multidisciplinary specialty with good staffing in all disciplines, e.g. nurses, doctors, teachers, social workers, physiotherapists, etc. and in the supply of orthopaedic beds for those haemophiliacs who have musculo-skeletal bleeds, i.e. 85 per cent. I am afraid that this may be an old argument but I think that one of the real advances made in Oxford was when the Haemophilic Unit consisted of a full team, including your *sic* 'uneducated surgeons' who, with further training can provide a learning experience for others. HIV, with its biological problems, introduced an ethical one. Professional people were very much concerned about their degree of risk and the infectivity of materials from operations. Indeed, in America, surgeons used this as a new indication for doing or not doing surgery. Because of the additional risk of HIV, pathologists were refusing to do *post mortems* or handle operative material. This ended a very fruitful number of years in which a much more accurate definition of the local pathology of haemophilia had been worked out. People were scared of using local tissues for analysis, e.g. by spectroscopy, and so this form of research ceased. So, HIV had a much greater impact than just on immunology or infectivity. For example, although HIV was one of the indications for using synoviorthrosis, this was limited because of the discovery of chromosomal breakages identified in the patients undergoing radiosynovectomy. Obviously, in many places in the world where factor VIII is scarce this is a preferred method, but in England we continue to undertake surgical synovectomy because of the availability of factor VIII and because of the knowledge of outcome.<sup>107</sup>

One of the reasons why I returned to England from the United States was the privilege of being able to work in the Oxford Haemophilic Unit, after having set up a small Orthopaedic Centre in the University of Rochester, New York. Oxford has provided a large grouping of patients of all ages without the artificial division of being a child one day and an adult the next. Obviously haemophilic patients were living much longer, well into adulthood and old age, with the development of degenerative processes requiring to be operated upon. This was common until HIV appeared. Suddenly we lost between one-third and two-thirds of our haemophilic patient population. Indeed, there are now

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<sup>107</sup> Professor Robert Duthie wrote: 'We discovered that only 10 per cent of haemophilic patients with chronic synovitis required surgery; the remainder responding to conservative management by factor replacement, compression bandaging and subsequent careful physiotherapy. The complications of ongoing haemorrhaging into the musculo-skeletal tissues were controlled and dealt with in our Centre by conservative treatment. This then allowed further development in elective orthopaedic surgery: management of severely damaged joints by replacement; the management of progressive haemophilic cyst formation, by internal fixation systems in order to prevent pathological fractures, with the increased mortality rates; the prevention of fixed flexion contractures, caused by muscle haemorrhages, by dynamic splinting, etc. All giving marked improvement in the musculo-skeletal tissues of mobility, reduction in deformities and improved function.' Letter to Dr Daphne Christie, 24 July 1998.

## Haemophilia: Recent history

two main areas in the epidemiology of haemophilia, pre- and post-HIV infection. This is of particular importance when it became necessary to examine our surgical and conservative treatment modalities. A lot of epidemiological studies have yet to be carried out on the effect of surgery upon the immunology status of HIV patients.

Lee: Can you talk a little about when you first started doing elective surgery in these patients and what it really involved for you as a surgeon, and the team work involved? Can you remember the first elective surgery that you did on these patients?

Duthie: Very, very clearly. Charles [Rizza] is smiling as well, because, of course, the usual discussion which we carried out was about the availability of factor material, the actual quantity required for the operation, for healing to take place, and whether or not there was enough. The golden rule was that there had to be enough on the shelves before we embarked upon any surgery. Then one changed the surgical attack because of the availability of sufficient factors, and also because we began to understand the pathology and subsequent healing of haemophilic tissues which were, and are, different. However, what we had learnt from poliomyelitis patients all added to the knowledge required to rehabilitate a haemophiliac after surgery.<sup>108</sup> The simpler the operative technique the better, because the healing of the tissues would be less demanding upon factor supply. The development of the factor VIII antibodies was very critical because with antibodies elective surgery was contraindicated. Actual operating techniques were modified by use of electrocautery, compression post-operatively, and fibrin injection into haemophilic cysts and their walls. We devised a type of sterile air operative enclosure in Oxford in order to reduce, to the lowest level possible, surgical infection rates in the haemophilic patient, with great success. It became even more important when we were operating on HIV patients (up to two a week), in being able to isolate and reduce the surgical team with more control

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<sup>108</sup> Professor Robert Duthie wrote: 'This aspect of rehabilitation is highly specialized and carried out by many committed individuals, e.g., nurses, physio-occupational therapists and social workers. The aim is to restore the patient back to school or to work, by overcoming muscle weakness, stiffness and joint immobility, negative attitudes towards educational, daily living and recreational activities. Working under haemostatic control by factor replacement, dynamic splintage, orthotics, compression air splints, new skills of proprioceptive neuromuscular facilitation (TENS – transcutaneous electrical nerve stimulation) are now available to improve the results of surgery and the treatments of bleeds.' Letter to Dr Daphne Christie, 22 March 1999.

in the numbers around the patient, handling the patient, materials and instruments.<sup>109</sup>

Lee: Dr Matthews, could I try and encourage you to talk a bit about the beginnings of treatment for patients, regular home treatment for patients, and maybe we can draw out of you a bit about needles and the changes that came in with decent needles and things like that.

Dr James Matthews:<sup>110</sup> I came to Oxford in 1961 and before that time transfusion equipment was rather unreliable. The rubber and glass drip sets sometimes came apart in the middle of a transfusion and created havoc. Needles and syringes in 1961 were still of a type that had been used for many decades. Needles were all steel, sterilized by autoclaving after use and resharpened in a machine similar to that used for sharpening gramophone needles. They were sometimes blunt or even had a hooked point! They were packed for use in glass tubes and the size was identified by a twist of coloured cellophane which closed off the end of the tube. The syringes were of glass and sometimes stuck whilst drawing blood or giving an injection, usually at the worst possible time, particularly if you were dealing with a child. For some time after I came syringes were autoclaved in aluminium canisters. Blood sample tubes for coagulation studies were prepared in the laboratory, as were pipettes and many of the test reagents.

When dealing with bleeding patients in the early days, one of the main problems was shortage of treatment material. The material most commonly used was fresh-frozen plasma. This was a material which was relatively easy to obtain and became more plentiful as the blood transfusion organizers allocated more for the treatment of haemophilia. We were very fortunate in Oxford in having Dr Jean Grant as Director of the Blood Transfusion Service. She was one of many consultants who cooperated closely with the Haemophilia Centre. It was a time when the clinicians at the Haemophilia Centre had access to the key of the Blood Transfusion Centre and could obtain plasma out of hours without delay. Plasma was used for the treatment of many of the common bleeding

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<sup>109</sup> Professor Robert Duthie wrote: 'Because of having sufficient numbers going through our specialized operating facilities the discipline and the efficiency of the team were readily worked out, and indeed there was no further need to use HIV as an excuse or as another indicator of whether surgery was indicated.' Letter to Dr Daphne Christie, 24 July 1998.

<sup>110</sup> Dr James Matthews (b. 1930) was Clinical Research Fellow at the MRC Blood Coagulation Research Unit, Churchill Hospital, Oxford, from 1962 to 1965, with a special interest in the clinical management of haemophilia and other bleeding disorders. He remained at the Oxford Haemophilia Centre as an Associate Specialist until his retirement in 1991.

## Haemophilia: Recent history

episodes which responded to the limited factor level achievable with the material. Allergic reactions were not uncommon and the volume of infusion required was a disadvantage particularly in children who might be upset and restless at the time. A few years passed, and more of the human and animal factor VIII concentrates became available and treatment became easier in terms of the volumes used and the factor levels which could be achieved. Home treatment was not used for some time as the materials were in short supply and those which were available were not really suitable for using at home.

Lee: Was it right to think that cryoprecipitate was a thing that really pushed home treatment?

Matthews: It did make a big difference, because it was easily made. It still wasn't the ideal material because it was a liquid plasma product stored in the frozen state but many Centres found it a very useful material for home treatment.

Lee: In our own Centre, Katharine Dormandy<sup>111</sup> really made a major contribution. I think I am right in saying that she made cryoprecipitate in the old hospital at Lawn Road in the labs there,<sup>112</sup> and that the patients were actually started on home treatment with cryoprecipitate. In fact, if you go back and look through the notes of some of our older patients, the social work contribution was to raise the money to buy the deep freezers enabling them to have it at home.

Rizzo: I think Katharine Dormandy was one of the few to start using cryo [precipitate] for home therapy. I remember having a discussion with her about the problems of fridges without alarms on them, because if the patients were going to keep cryoprecipitate at home, deep frozen, then they had to know if the fridge had gone off, when they went away for the weekend. They had to have an alarm system fitted and those were very expensive at that time.

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<sup>111</sup> Dr Katharine Dormandy FRCP (1926–1978) qualified at the Royal Free Hospital School of Medicine in 1951 and was appointed Senior Lecturer in Haematology in 1964 and Reader in Haematology in 1970. She developed the Haemophilia Centre at the Royal Free Hospital, London, raising money personally and campaigning tirelessly for better treatment for people with haemophilia and better educational opportunities for haemophilic boys. She was a pioneer of home treatment. In 1977 she was awarded the first gold medal of the Haemophilia Society. The Centre named in her honour was opened in 1978. See also notes 114, 125, 170 and 171 below.

<sup>112</sup> See note 171 below.

Lee: There's a sort of interesting twist in that tale, which Ted [Tuddenham] might throw a bit of light on. In our Centre we were a bit slow to use large full clotting factor concentrate, because it wasn't really until you and Peter Kernoff came that people were started on this treatment, because Katharine had been so taken up with the cryoprecipitate. Is that fair?

Matthews: I think it is probably fair to say that we used the freeze-dried pooled plasma concentrate in preference, because it was available to us and seemed a suitable material for home treatment.

Professor Edward (Ted) Tuddenham:<sup>113</sup> Katharine had a wonderful relationship with her patients. It was maternal in some ways, because she knew them all very well and their social circumstances, she put a very great deal of effort into ensuring that they would have the best possible circumstances for home treatment.<sup>114</sup> She was a pioneer in that area and obtained, as you mentioned, money for them to have freezers in their own homes in which they kept cryoprecipitate. I would say that, to be fair to Katharine, it was difficult, as other speakers have mentioned, to obtain adequate supplies of higher-purity concentrates other than for surgery, and the Centre's treatment relied very much on cryoprecipitate produced through local blood transfusion centres. Things changed, of course, when Peter Kernoff and I came in after Katharine tragically died, and the concentrates were brought in progressively through battles against the controllers of the finances. Although to do them justice, they did progressively increase the fraction of local capital that was being expended on imported concentrates until they reached towards the dizzying heights of today. So it was a transitional phase. Katharine was a pioneer and it undoubtedly changed the lives of our patients at that time to have their own freezers filled with locally produced cryoprecipitate.

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<sup>113</sup> Professor Edward Tuddenham FRCP FRCPath (b. 1944) was Co-director of the Haemophilia Centre, The Royal Free Hospital, London, from 1978 to 1986, and Director of the MRC Haemostasis Research Group at Northwick Park Clinical Research Centre from 1987 to 1994. He has been Director of the Haemostasis Research Group, Clinical Sciences Centre, Imperial College Medical School, London, since 1994 and Honorary Consultant Haematologist at the Hammersmith Hospital, London, since 1994. He is a Member of the World Federation of Hemophilia, the International Society on Thrombosis and Hemostasis, and the British Society of Hemostasis and Thrombosis.

<sup>114</sup> See for example Le Quesne B, Britten M I, Maragaki C, Dormandy K M. (1974) Home treatment for patients with haemophilia. *Lancet* ii: 507-509. Ingram G I, Dykes S R, Creese A L, Mellor P, Swan A V, Kaufert J K, Rizza C R, Spooner R J, Biggs R. (1979) Home treatment in haemophilia: clinical, social and economic advantages. *Clinical and Laboratory Haematology* 1: 13-27.

## Haemophilia: Recent history

Jones: Yes, just to go back to cryo [precipitate]. Judy Pool discovered cryo [precipitate]<sup>115</sup> – it was another case of serendipity really. She was looking at the various bits of concentrate and she was going to throw away the gunge. I think it was Shannon who decided to test the gunge for factor VIII and discovered all the factor VIII was in the gunge and that was cryoprecipitate. Judy came to Newcastle in the mid-1960s and the day after her visit the blood transfusion service made the first pack of cryoprecipitate. The introduction of cryo [precipitate] revolutionized the care of children, because previously we had to give so much fresh-frozen plasma, particularly to patients with factor IX deficiency because of their poor response, that they used to go into heart failure. So they were all on digitalis and diuretics and they lay in bed on the dreaded drip, and it was hardly surprising that they never wanted to come to hospital again. But if they bled sufficiently they had to! My first patient was in hospital 27 times before his fifth birthday and, worse than that, he saw 17 different doctors. Nobody was interested in haemophilia. Haemophilia was ‘a bloody nuisance’ and kids with haemophilia were ‘bloody nuisances’. Only one in 16 000 of the population has severe transfusion-dependent haemophilia, and so it’s easy to see where the resistance came from. There was great resistance, particularly from the Blood Transfusion Service of this country and certain of its directors, to treating haemophilia at all, except as a hospital disease. There was great resistance to home therapy. There were letters in the medical press and the lay press,<sup>116</sup> suggesting that people with haemophilia were not capable of treating themselves, that their parents should not take responsibility for them at home, that it was dangerous and unethical and immoral to put treatment into their hands. In two European countries, Italy and, I think, Spain at the time, it was illegal for patients to inject themselves with any medication, including factor VIII or factor IX. So there was an enormous inertia to overcome. The other feature of medicine in those days that we tend to forget was its paternalistic nature; the doctor always knew best, nurses really didn’t come into it, and it was thought that it was not right to educate patients. It sounds terrible

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<sup>115</sup> See note 24 above

<sup>116</sup> The difficulties in implementing home therapy because of the shortage of concentrates are reported in the *Lancet* in 1974. See for example Biggs R. (1974) Supply of blood-clotting factor VIII for treatment of haemophilia. *Lancet* i: 1339. Lay articles about the shortage and the difficulties for both patients and staff, including comments opposing home therapy, were published in the *Yorkshire Post* in 1975 and 1978. Dr Jones was Chairman of the UK Home Therapy Working Party at the time, and reported the situation in the UK in the *British Medical Journal*. See Jones P, Fearn M, Forbes C, Stuart J. (1978) Haemophilia A home therapy in the United Kingdom 1975–1976. *British Medical Journal* i: 1447–1450. Mr Clifford Welch’s recollections of home treatment for haemophiliacs at that time are written in a letter to Dr Daphne Christie, 5 July 1999, and will be deposited with the records of this meeting in the Contemporary Medical Archives Centre of the library of the Wellcome Institute for the History of Medicine.

to say that now, but we are talking about 30 years ago. It was for the doctor to say when patients needed treatment. That's one of the reasons the children of that generation grew up crippled with haemophilic arthritis.<sup>117</sup>

There wasn't enough plasma being collected. When cryo [precipitate] came in there was just enough to be able to perform outpatient treatment, there wasn't enough for home therapy. There wasn't enough plasma going through to the new Elstree site to make concentrate and that was one of the reasons why the Government decided to bring in concentrate, particularly from the United States of America. This decision should be seen against the background of a very, very rare disorder in the multitude of medical conditions, and the resistance that there was to the treatment which had been developed in Oxford, and to allowing patients to start treating themselves.

Mrs Riva Miller:<sup>118</sup> I am from the Royal Free and I very much appreciated Dr Evans's talk, because it certainly reminded me that in 1958 I was at the Manchester Royal Infirmary and worked on the Leukaemia Unit, so I had some connections back there. Let us come back to Dr Dormandy and home treatment. She employed me in 1966 to look into the home circumstances of all the patients, particularly the children and how much they missed school, to see whether we could start to think about home treatment. That was an enormous survey which really had quite an impact.<sup>119</sup> It was Dr Tuddenham's foresight and persistence that secured a position to look into all the other needs of people, that helped me to stay there until today, although that position is being dismantled now.

EVANS: I want to contradict Peter Jones, because I worked in a children's hospital and I think actually it's very different in children's hospitals. At the time we were introducing home treatment, we were positively encouraged by

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<sup>117</sup> Dr Peter Jones wrote: 'There was no treatment at home and the parents were usually very reluctant to take them to hospital'. Letter to Dr Daphne Christie, 5 July 1999.

<sup>118</sup> Riva Miller (b. 1935) is a social worker and a trained family therapist with particular interests in HIV/hepatitis and close involvement in orthopaedic clinics, and has worked in the Royal Free Hospital Haemophilia Centre since 1966. Her main interest has been in integrating the social, psychological and medical aspects of the lives of people with haemophilia and their families into the day-to-day work of the Centre, particularly in busy clinics. She currently runs the AIDS Counselling Unit at the Royal Free NHS Trust and has a consultancy at the Blood Service in North London. She has worked for the World Health Organization running workshops for haemophilia and AIDS.

<sup>119</sup> Rizza C, Spooner R J D. (1977) Home treatment of haemophilia and Christmas disease: five years' experience. *British Journal of Haematology* 37: 53–66. *idem* (1983) Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976–80; report on behalf of the directors of haemophilia centres in the United Kingdom. *British Medical Journal* 286: 929–933.

## Haemophilia: Recent history

everyone to do so. We were appointing nurses to look after children with cystic fibrosis at home, nurses to look after children with diabetes at home, and as soon as I wanted to introduce a home treatment programme I was encouraged to do so and I was provided with a nursing sister to help do it. I think that was the difference between adult centres and the children's hospitals, which were quite independent. The second thing, of course, about cryoprecipitate for home treatment is that little children only need little doses, so it was much easier for the parents to be trusted to draw up a few bags of cryoprecipitate rather than the enormous number of bags that you have to do for an adult.

Colvin: I wanted to say a couple of words in support of what Riva [Miller] was saying, and to mention Katharine Dormandy's influence on trying to provide comprehensive care for all the children, and indeed, adults, in the North-East Thames region. When Professor Jenkins<sup>120</sup> was Director of the London Hospital Haemophilia Centre, he and Katharine got together in the early 1970s and organized a haemophilia nurse to go round the whole of our huge region, seeking out people with haemophilia and that was really the beginning for us of the idea of having a home treatment programme on a large basis. I think it is important to know that Katharine, just before she died, made a really big impact on finding out just exactly who'd got haemophilia in our region and set up the possibility of treating them all, instead of just some of them.

Lee: In my room in the hospital I found a book which has got the minutes of those meetings and what is so amazing is that there is an account of the number of bottles of concentrate that were being issued in the region: they are minuscule amounts. One of the things that Charlie [Rizza] was talking about the other day, was that you got as many bottles as your local transfusion centre provided the plasma for.

Rizza: Yes, there was a time when the factor VIII produced by Elstree was delivered *pro rata* to the different Haemophilia Centres, so that if a region put in large amounts of plasma centrally to be fractionated, it got large amounts of factor VIII back to the Haemophilia Centre. If the region put in only a small amount of plasma to be fractionated centrally, then that region got a very small amount of factor VIII. That made difficulties for some large centres which had Blood Transfusion Centres which were not giving large amounts of plasma

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<sup>120</sup> Professor George Jenkins FRCP FRCPath (b. 1927) was Consultant Haematologist at the Royal London Hospital from 1965 to 1992 and President of the British Society of Haematology in 1988.



through central organizations for fractionation. I think that system has now fallen into disrepute.

Lee: We have heard so far this afternoon only from the people who were giving out the care. We haven't really heard much of the history of things from the people who were receiving the care. I wonder if I could encourage some comments about that?

Reverend Alan Tanner:<sup>121</sup> I am very interested in the saying of Gwyn Macfarlane, 'One has to remember what it was like not to know things which now seem self-evident', because, I think, testifying from the point of view of a father of a patient, it is worth remembering the change in attitude and lifestyle which took place at these various stages. I was very interested to hear the mention of 'comprehensive care', which was one of the major advances in treatment, care management and so on. But going right back to the beginning, some have heard me testify before about my introduction to haemophilia with Professor Hardisty,<sup>122</sup> because my own son was diagnosed at Great Ormond Street. Then, as I have said many times, there was no treatment except Russell's viper venom.<sup>123</sup> Russell and the viper have been much maligned in the past, but were of great comfort in moments of crisis.

Lee: We are talking about 40 years ago, aren't we?

Tanner: Yes I am going right back – 40 years. The facilities provided were minimal. Russell's viper venom for crises, plasma, a pat on the back, tender loving care and all that. So we need to remember the transformation which came with the introduction of cryoprecipitate. I am a Royal Free Hospital supporter, so I can speak again about Dr Katharine Dormandy. One of the things we haven't mentioned yet is that Dr Dormandy introduced boys to treating themselves at a very, very early age. When parents thought they were taking over the management of injecting cryoprecipitates, Dr Dormandy was very firm: the boys were going to exercise that sturdy independence, and begin to treat

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<sup>121</sup> The Reverend Prebendary Alan Tanner (b. 1925) was Chairman of the Haemophilia Society from 1976 to 1997, Chairman of the World Federation of Hemophilia from 1973 to 1995 and Chairman of the Macfarlane Trust since its foundation in 1988. He has three daughters and one son who was diagnosed with haemophilia at the age of five in 1960 and died in October 1998, as a result of HIV infection and hepatitis C virus (HCV) through the use of contaminated blood products.

<sup>122</sup> See biographical note 73 above.

<sup>123</sup> *op. cit.* note 19 above.

## Haemophilia: Recent history

themselves and that was when they began, as it were, to wean themselves from centres, doctors, and all that. So that's cryo [precipitate] for a start.

It was round about that time that we obviously looked to Oxford for the kind of academic support in these endeavours, and at the same time I have to pay tribute to Professor Ingram who was my mentor in those days. I often remember he was the one whom I asked, 'How do you say amniocentesis?' He told me and explained what it meant, and that was another part of my tutoring in the whole endeavour. And then, as we have mentioned, with the introduction of concentrates, that was where comprehensive care came in. Dr Jones won't mind my mentioning the transformation that took place at his centre when he took over Newcastle. He was one of the first to introduce comprehensive care with a team which included an orthopaedic surgeon, a dental surgeon, physiotherapists, social workers and so on. He developed what we used to call the 'heavy gang' in Newcastle, which, I think, he took on tour to show how it could be done. So then again, it's a transformation taking place, not only in a physical sense, but in that development of independence, and in emotional maturity, because for the boys and men, when they were introduced to these new concepts of treatment and management, their lives were transformed. Where they had previously been tied to a centre, they then began to travel. I speak from experience of those who came to the World Federation of Hemophilia;<sup>124</sup> they were released, made free, and there was a tremendous sense of liberation.

We then go onto the other stages with the introduction of HIV infection and hepatitis, and now possibly CJD. That's a sad part of the drama, but up to that stage there was that very, very significant transformation of life. I could speak forever about that, but I think that's probably enough to emphasize the points.

Mr Clifford Welch:<sup>125</sup> I was born in 1925 and haemophilia was diagnosed when I was a year old by my falling out of my highchair and tearing the fraenum in my upper lip. Thereafter, very fortunately, I had a perfectly normal life, having only mild haemophilia, so I enjoyed my school days, but life at home was really severely shook up when, at the age of five, my mother produced triplets who also had haemophilia and it was that which brought us into contact with Professor Macfarlane, Dr Macfarlane as he then was, at Bart's. It was in 1934 when one of my brothers was admitted to Bart's with a severe

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<sup>124</sup> For an account of the history of Haemophilia Societies and the World Federation of Hemophilia, see note 5 above, 12–13 and note 169.

<sup>125</sup> Mr Clifford Welch CBE FIM (b. 1925) trained as a materials engineer. He also pursued a career in scientific and technical publishing, and served on the Design Council from 1993 to 1998, latterly as Chairman. He has been associated with the Katharine Dormandy Trust for over 20 years and Chairman for the majority of that time.

haemorrhage and, I think, two of them were treated there for long periods. We also used to go up and see Gwyn Macfarlane regularly every few months while he took blood tests. After he retired I remember getting a letter from him in which he said how he watched his delicate apparatus in his small room at Bart's, most of which was constructed from Meccano,<sup>126</sup> being crawled over by my three brothers like monkeys, wondering whether it was all going to get torn to pieces or not. But he was really a wonderful supporter to my mother, because at that time in the 1930s there really was, as Alan Tanner has said, no treatment other than the Russell viper venom. I can remember cycling to John Bell and Croyden in Wigmore Street<sup>127</sup> on a Sunday to get Russell viper venom for one of my brothers with a serious external bleed. But apart from that the real miracle was Macfarlane introducing the concept of blood transfusions from my mother to the boys, which, of course, in the late 1930s saved their lives on a number of occasions.<sup>128</sup> Then in 1941, or 1942, we came into contact with Frank Smith<sup>129</sup> who was one of the early members of the Haemophilia Society. He had a flat off Baker Street and I can remember going to one of the first meetings of the Society with my mother in an air raid and listening to him explaining that the only sure treatment was Dr Timperley's egg white<sup>130</sup> and this was very seriously propagated by him for many years afterwards. It was a tragedy because despite his deep concern that Dr Timperley's work did not meet with success, Frank Smith made a major contribution to getting the Haemophilia Society going. But as far as I was concerned I had a charmed life really, and the only time I was seriously injured I was cared for in Bart's, during the war, when Dr Black and Charles Fletcher looked after me with advice, I gather, from Dr Macfarlane, who by then was at Oxford.

Lee: Last week when we went to interview Dr Rosemary Biggs,<sup>131</sup> I asked, 'What was Macfarlane doing all the time? Was he locked up in the laboratory,

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<sup>126</sup> Macfarlane devised a number of apparatus, in part made of Meccano. See for example Robb-Smith A. (1993) op. cit. note 3 above, 51. Macfarlane R G, Tomlinson A H. (1961) An apparatus for measuring the tensile strength of blood clots. *Journal of Clinical Pathology* 14: 320–323.

<sup>127</sup> John Bell and Croyden was a well-known pharmacy in London.

<sup>128</sup> op. cit. note 20 above.

<sup>129</sup> Frank Smith was one of Macfarlane's haemophilic patients and main organizer of the International Haemophilia Society.

<sup>130</sup> That is treatment with a bromide extract of egg white. Timperley found that if egg white is incubated at 37°C with potassium bromide for several days it was possible to extract a substance which on intravenous or intramuscular injection reduces the clotting time of blood and controls haemorrhage in haemophiliacs. See Timperley W A, Naish A E, Clark G A. (1936) A new method of treatment in haemophilia. *Lancet* ii: 1142–1149. See also page 53 below.

<sup>131</sup> op. cit. note 2 above.

## Haemophilia: Recent history

or did he get involved with the patients at all?'; and Dr Biggs replied, 'No, he didn't really get into our first patients. There were one or two patients he remembered from St Bartholomew's Hospital. One I remember was a set of triplets with haemophilia (that is, Clifford's brothers)'. And then I went on to explain what has happened to them since and she rounded off the conversation, '...They weren't angels, they were absolutely all over the place. I know Professor Macfarlane had them in Bart's when they were three or four and he said they were absolute menaces about the laboratory'. But it's interesting that you talk about the Meccano, because I have another patient who remembers Macfarlane from Bart's and keeps talking about this Meccano that was presumably shaking the tubes for the tests.

Douglas: Since you returned to Dr Biggs' earlier recollections, it is appropriate to give my reminiscences of Oxford between 1951 and 1953 at this stage. My time in Oxford preceded the major later endeavours to treat haemophilia. I had the enormous privilege of working with Gwyn Macfarlane, Rosemary Biggs and Ethel Bidwell. This experience shaped my academic interest in haemostasis and thrombosis after I left Oxford. My initial ignorance was a shock to Rosemary and Ethel, but after a few months of their training I was ready to do experiments. In the work which followed my name appears on several papers;<sup>132</sup> my name is there because I helped to do a lot of experiments but the ideas for these came from Dr Macfarlane and Rosemary Biggs. I arrived in Oxford at a time when there was about to be a breakthrough from their previous experimental work, especially their study of thrombin generation from whole blood.

I had some earlier interest. In 1944, on my first day as a house physician after graduation, a teenage haemophiliac had a single tooth extracted and the socket bled for three weeks after. Three years later a severe haemophiliac, who had been under my care, died from coronary thrombosis. This taught me that thrombosis was not entirely due to blood clotting.

I have quoted reminiscences here. I still remember a lot of things Macfarlane said, such as, 'Reminiscences are only really of interest to those who are telling them,' but more importantly, and it's already been quoted today, 'One has to remember what it was like not to know things which now seem self-evident'.<sup>133</sup>

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<sup>132</sup> See for example Biggs R, Douglas A S, Macfarlane R G. (1953) The initial stages of blood coagulation. *Journal of Physiology* 122: 538–553. Douglas A S, Biggs R. (1953) Consumption of some components involved in physiological blood coagulation. *Glasgow Medical Journal* 34: 329–342. See also note 17 above.

<sup>133</sup> See also Reverend Alan Tanner's recollections on page 39 above.

And in 1951 we did not know much. We knew using Quick's one-stage prothrombin time test that citrated or oxalated plasma clotted on the addition of tissue extract and calcium.<sup>134</sup> Some years later Quick noted when oxalated plasma was left standing on the bench, the clotting time of this plasma in his test lengthened; he assumed this to be a 'labile factor'.<sup>135</sup> Working in Norway during the war, Owren described a genetic coagulation defect with a prolonged one-stage test not due to prothrombin deficiency.<sup>136</sup> This was called factor V and was the same as Quick's 'labile factor'. We also knew at around that time that there was another factor involved and that was factor VII.<sup>137</sup> It had been shown in the late 1940s that normal serum (containing no prothrombin nor factor V) shortened the one-stage test of coumarin plasma.<sup>138</sup> This led to the discovery of factor VII.

Up to 1951 coagulationists had been mainly concerned with the action of tissue which produced rapid coagulation of blood. However, it was known that blood collected by clean venepuncture without tissue contamination did coagulate, albeit more slowly. This unknown intrinsic pathway for clotting had been neglected too long and its time came in Oxford in 1952. Previous studies had shown that normal blood delivered to a glass tube coagulated in five to ten minutes and that prothrombin was rapidly consumed. In haemophilia and thrombocytopenia, prothrombin consumption was defective and the plasma factor missing in haemophilia (so-called antihæmophilic globulin), and platelets were likely to be two components of an intrinsic pathway.<sup>139</sup>

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<sup>134</sup> According to the classical theory of coagulation, prothrombin was converted to thrombin and thrombin clotted fibrinogen (see Appendix). Quick A J. (1935) The prothrombin in hemophilia and in obstructive jaundice. *Journal of Biological Chemistry* **109**: lxxiii–lxxiv. Quick A J, Stanley-Brown M, Bancroft F W. (1935) A study of the coagulation defect in hemophilia and in jaundice. *American Journal of the Medical Sciences* **190**: 501–511.

<sup>135</sup> Quick A J. (1943) On constitution of prothrombin. *American Journal of Physiology* **140**: 212–220.

<sup>136</sup> Owren P A. (1947) Coagulation of blood: investigations on a new clotting factor. *Acta Medica Scandinavica* **128**: 1–327.

<sup>137</sup> de Vries A, Alexander B, Goldstein R. (1949) Factor in serum accelerates conversion of prothrombin to thrombin: its determination and some physiologic and biochemical properties. *Blood* **4**: 247–258. Koller F, Loeliger A, Duckert F. (1951) Experiments on new clotting factor (factor VII). *Acta Haematologica* **6**: 1–18.

<sup>138</sup> Fahey J L, Olwin J H, Ware A G. (1948) Effect of dicoumarol on Ac-globulin and prothrombin activity. *Proceedings of the Society for Experimental Biology* **69**: 491–494.

<sup>139</sup> Dr Charles Rizza wrote: 'Blood coagulation can proceed by the intrinsic or extrinsic system, two separate but interlinked routes. In the intrinsic system only the plasma coagulation factors are involved. In the extrinsic system tissue factor plays an important role (see Appendix). In haemophilia the intrinsic system is defective because of lack of factor VIII, an essential component. The fact that hæmophilic tissue (brain) when added to hæmophilic blood brought about normal clotting was evidence that hæmophilic tissue was normal and that the hæmophilic-clotting defect was due to a failure of the intrinsic system.' Letter to Dr Daphne Christie, 3 July 1999.

## Haemophilia: Recent history

Before I arrived in Oxford I had worked in Glasgow Royal Infirmary, where the brain from a patient who had died of haemophilia was as powerful as normal brain in clotting haemophilic plasma. The extrinsic pathway in haemophilia was intact.

Early in 1952 another important patient was studied, and in my way of thinking was more important than the Christmas factor-deficient patient, studied five months later. The patient was under the care of Professor L J Witts in Oxford.<sup>140</sup> He was a 26-year-old man who had an acquired coagulation defect with bruising epistaxis [nose bleed], gum bleeding and haematuria. He had a one-stage prothrombin time of 18–22 seconds compared to a normal plasma result of 14 seconds. When brain was added to his plasma and this then recalcified, thrombin developed immediately, but it was very little compared to that from a normal plasma. Rosemary [Biggs] had the foresight to do critically important experiments on this plasma, and I can still remember her doing these experiments. She diluted this plasma, recalcified it and then took aliquots using them *in lieu* of brain in a one-stage prothrombin time and finding as powerful thromboplastic activity as brain, developing after four to five minutes incubation. At the same time she subsampled on to fibrinogen and found no important amounts of thrombin. On 20 February 1952 she posted a letter to *Nature* which records her personal contribution to the enormous discoveries that were made in that year and launched a whole new era of blood coagulation research.<sup>141</sup>

Two simple plasma fractionation procedures were in use.<sup>142</sup> When alumina was added to plasma this removed prothrombin and factor VII leaving, after centrifugation, factor V and antihæmophilic globulin in the supernatant 'adsorbed plasma'. After centrifugation, elution from alumina precipitate recovered prothrombin and factor VII. A second fractionation method was ammonium sulphate precipitation producing crude preparations of factors V and antihæmophilic globulin. Platelets were prepared by differential centrifugation. Rosemary made a preparation of antihæmophilic globulin from ammonium sulphate precipitation of adsorbed normal plasma and a factor VII preparation from adsorption of serum, and when she incubated these three with calcium a powerful thromboplastin was formed.

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<sup>140</sup> Professor Leslie J Witts (1898–1982) was Nuffield Professor of Clinical Medicine at Oxford from 1938 to 1965 and a Fellow of Magdalen College. From 1963 to 1968 he was a member of the Committee on Safety of Drugs and Chairman of the Subcommittee on Adverse Reactions.

<sup>141</sup> Biggs R. (1952) Plasma thromboplastin. *Nature* 170: 280.

<sup>142</sup> Details of the plasma fractionation procedures are given in Biggs R, Macfarlane R G. (1953) *op. cit.* note 37 above, 71 and 343.

Following the findings described in *Nature* in early 1952, we used diluted adsorbed normal plasma as a source of antihaemophilic globulin, diluted normal serum as a source of factor VII and washed platelets with calcium to make a powerful thromboplastin. This became the work-up of the thromboplastin generation test.

In June 1952 we submitted a manuscript on the formation of thromboplastin in human blood to the *Journal of Physiology*.<sup>143</sup> It was published early in 1953 by which time we knew that the property of serum was not due solely, if at all, to factor VII.

The early features of the thromboplastin generation test were the abnormality present in the adsorbed plasma in haemophilia, and the abnormal behaviour of coumarin serum (initially attributed to factor VII). Also circulating anticoagulants could be detected, and abnormal platelet function in 'thrombasthenia' demonstrated.

Then one day in July 1952, I was asked to apply the thromboplastin generation test to two haemophiliacs where Merskey's 'plasma mixing experiments'<sup>144</sup> had shown cross-correction. One of the blood samples came from John Dacie and Bob Pitney at the Hammersmith Hospital [the patient was Stephen Christmas] and the second was an Oxford patient previously studied by John Poole.<sup>145</sup> Their adsorbed plasma behaved normally in the test but their serum was abnormal.

The test therefore provided a method for telling the two 'haemophilias' apart and provided immediately a worldwide reference to help differentiate the two disorders. When seven patients had been collected, from amongst previous postgraduate students at Oxford, including Clarence Merskey, the 'new' disorder was published in the *British Medical Journal* in December 1952.<sup>146</sup> One of the families described revealed a sex-linked recessive type of inheritance, making the two disorders not only clinically but genetically similar.

The thromboplastin generation test became important not only in the laboratory diagnosis of clinically suspected bleeding disorders, but was modified to produce assay techniques for antihaemophilic globulin (factor VIII) and Christmas factor (factor IX), these being essential in the therapeutic endeavours which developed later. We published two other papers on the

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<sup>143</sup> Biggs R, Douglas A S, Macfarlane R G. (1953), op. cit. note 17 above.

<sup>144</sup> op. cit. notes 35 and 36 above.

<sup>145</sup> See biographical note 33 above and Sir Christopher Booth's contributions below.

<sup>146</sup> op. cit. note 18 above.

## Haemophilia: Recent history

intrinsic pathway in the *Journal of Physiology*.<sup>147</sup> Factor V as well as factor VIII in the adsorbed plasma were shown to be needed. Dr Macfarlane often talked about an amplifier and we did some experiments realizing that all the known components (factors V, VII, VIII, IX and platelets) were unlikely to react together simultaneously. Our reagents were too impure to make significant progress and it was not until ten years later that Gwyn Macfarlane recognized his amplifier to be an enzyme cascade.<sup>148</sup>

Sir Christopher Booth:<sup>149</sup> I think I should, as a historian of the Hammersmith Hospital, inject two of Hammersmith's contributions into this. The first is that after Gwyn Macfarlane went to work at Hammersmith, from 1935 until the war, he wrote his thesis on disorders of the clotting mechanism for which he obtained a gold medal of the University of London.<sup>150</sup> I found that thesis when I was writing my own thesis in the 1950s and I modelled my thesis on his. I am happy to say that I got a gold medal too. But that isn't what I wanted to say. The point about the Christmas case was that the original case was a patient of the late Sir Graham Bull,<sup>151</sup> who attended at Hammersmith with bleeding of the tongue, this boy having bitten his tongue. And it was that patient, referred to Professor John Dacie's department, on whom W R Pitney<sup>152</sup> did a thromboplastin generation test<sup>153</sup> which came out wrong, and he couldn't understand it. So he went down to see John Dacie and it was Dacie, who knew

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<sup>147</sup> Biggs R, Douglas A S, Macfarlane R G. (1953) op. cit. notes 17 and 132.

<sup>148</sup> Macfarlane R G. (1964) An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. *Nature* 202: 498–499. *idem* (1966) The basis of the cascade hypothesis of blood coagulation. *Thrombosis et Diathesis Haemorrhagica* 15: 591–602.

<sup>149</sup> Sir Christopher Booth Kt FRCP (b. 1924) trained as a gastroenterologist and was Director of the Clinical Research Centre of the Medical Research Council, from 1978 to 1988. He was the first Convenor of the Wellcome Trust's History of Twentieth Century Medicine Group, from 1990 to 1996, and Harveian Librarian at the Royal College of Physicians from 1989 to 1997.

<sup>150</sup> Macfarlane R G. (1938) The normal haemostatic mechanism and its failure in the haemorrhagic states. MD thesis, University of London.

<sup>151</sup> Sir Graham Bull Kt FRCP (1918–1987) joined the Postgraduate Medical School in Hammersmith in 1947. He was appointed to a lectureship in the Department of Medicine and later was in charge of the renal unit where he developed a treatment that became renowned for its use in the acute phase of renal failure. He served as a member of the Medical Research Council from 1962 to 1966 and was appointed director of the Medical Research Council's Clinical Research Centre at Northwick Park in 1966. He was second Vice-President of the Royal College of Physicians from 1978 to 1979.

<sup>152</sup> Professor W R Pitney ('Bob' mentioned on page 45) (1921–1986) carried out research into blood disorders at the Royal Postgraduate Medical School in Hammersmith, London, and was Dean of the Faculty of Medicine at the University of New South Wales from 1984 to 1986, and President of the 21st International Congress of Haematology in 1986. Much of his research work focused on coagulation factors (see also notes 18 and 39).

<sup>153</sup> op. cit. note 17 above.



the literature extremely well, being a great scholar, and knew about the South American paper<sup>154</sup> and said, 'Go and do it again'. Following that they got in touch with Rosemary Biggs and Macfarlane and that resulted in the original Christmas paper in the Christmas issue of the *British Medical Journal* in 1952.<sup>155</sup> And it was interesting also that people like Dacie, Rosemary Biggs and Gwyn Macfarlane were not the sort of scientists who fought with each other for priority. If they had a problem they got together and that's exactly what happened over Christmas disease. It's a very good message to us all.

Lee: I think there's another twist of the tale of Mr Christmas. Rosemary Biggs<sup>156</sup> told me that nobody believed that his name was Christmas for a start, because it happened to appear in the Christmas edition of the *British Medical Journal*<sup>157</sup> and they thought it had all been made up. The rather sad thing, which probably summarizes what we have been talking about in the first part of this afternoon, is that I recently was participating in a meeting with a physician from Canada, called Jerry Teitle, who looked after Mr Christmas in his last years. Mr Christmas died a few years ago of HIV and I think that really illustrates what a short time span we are considering: first the disorder was described, the treatment was evolved, and the poor man actually died from the side-effects of that treatment. We are going to have to break for tea now in the next room, where there are some amazing photographs of Dr Bidwell in her younger days with her assistant Ross Dike (Figures 1–8). It's due to Mr Dike that we have these beautiful photographs, because when the laboratory was being tidied up at Oxford, he rescued them and put them in his loft.

Ingram: Just before we go may I finish the story about the name of Christmas disease? A gentleman from Leeds wrote to protest at this, and so Biggs and Macfarlane wrote back in the next *British Medical Journal*<sup>158</sup> to say that if they hadn't used that name they would have made up an enormously long name<sup>159</sup> which was much less easy to deal with, but they gave an undertaking that if they found a precursor factor they would not call it Christmas Eve factor!

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<sup>154</sup> See note 16 above.

<sup>155</sup> op. cit. note 18 above.

<sup>156</sup> op. cit. note 2 above.

<sup>157</sup> op. cit. note 18 above.

<sup>158</sup> See Collins D H. (1953) Christmas disease. *British Medical Journal* i: 97. Kemp P R. *ibid.* Biggs R, Douglas A S, Macfarlane R G. *ibid.* 221.

<sup>159</sup> Hypoprothromboplastinogenaemia.

## Haemophilia: Recent history

Evans: I also wanted to make one little comment, to remind some of the people who aren't as old as the rest of us, that in those days when you had to go to the slaughterhouse to get reagents to do laboratory work, you also had to make your own apparatus. You couldn't go and buy an amino-acid analyser, or a gas chromatograph off the shelf, you had to get the parts yourself and put it together and that's what the bits of Meccano were referring to.<sup>160</sup> If you wanted to make a chromatograph, you had to go to the workshop and get a tube, and cut it to the length you required, and that I think is worth remembering.

Lee: Can we now look at more of the organizational aspects of haemophilia both from the healthcare delivery side, the UK Haemophilia Centre Directors Organization, its beginnings, and the Registry at Oxford. Also the Haemophilia Society and how it grew up and how it interrelated with the Haemophilia Centre Directors Organization, and the delivery of care. Although we are primarily thinking about haemophilia in the context of Britain, we have to think a little bit about the influences that Britain had on the World Federation of Hemophilia, because they were quite significant. We are also going to discuss what we really don't like to think about too much, but sadly have to think about a lot, and that is the contamination that blood products have brought upon the haemophilic population and the enormous change in so many ways that that has influenced. Then, finally, because I think it would be so sad to end this afternoon

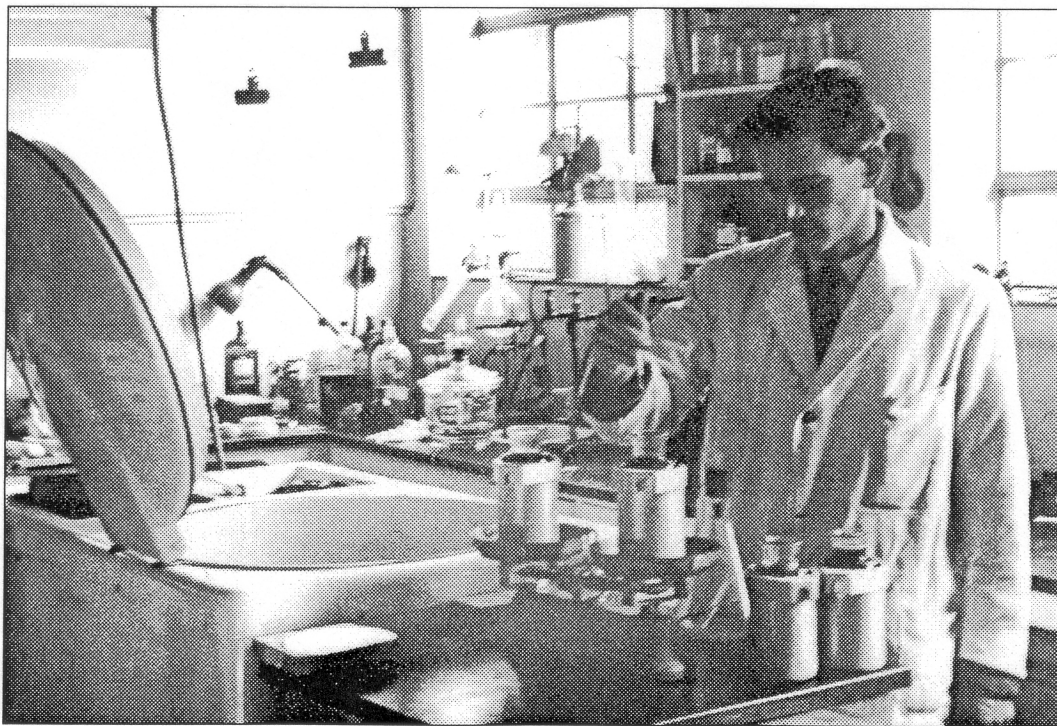
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<sup>160</sup> See note 126 above.

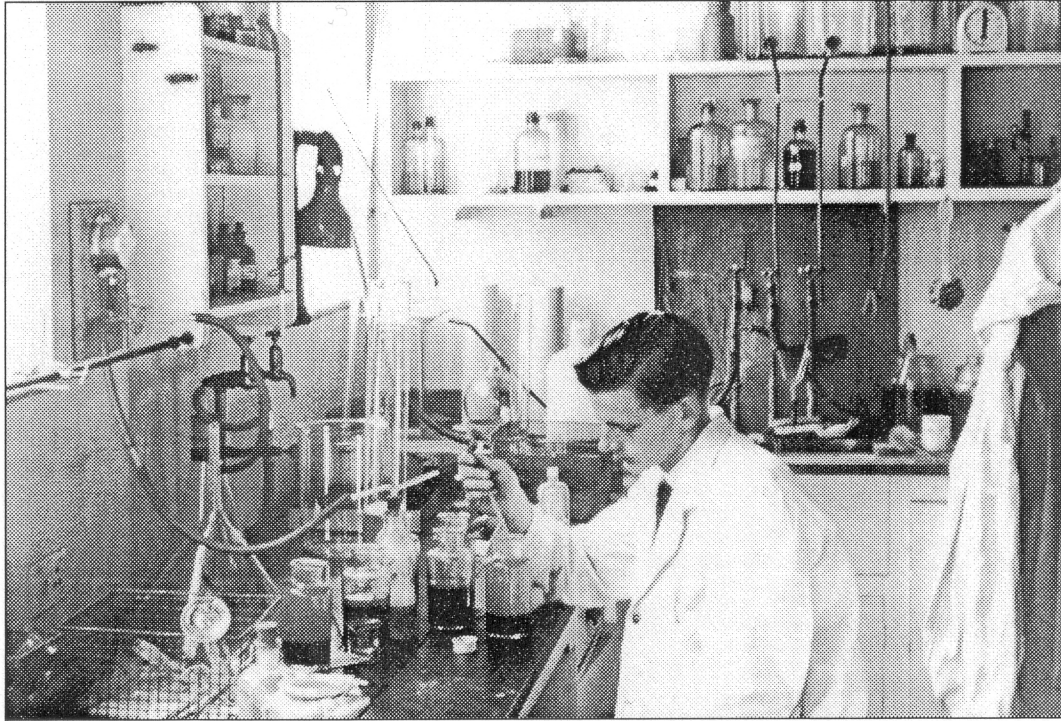
Figures 1–8. Preparation of animal antihaemophilic globulin in 1955



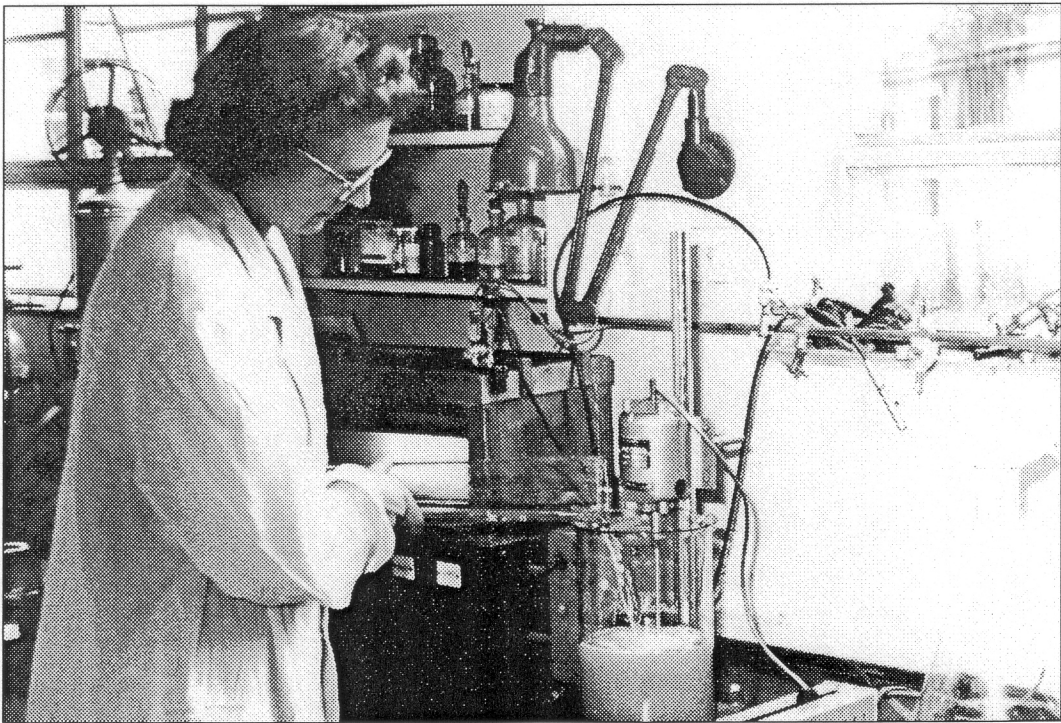
1. Animal blood is collected at the slaughterhouse and brought to the laboratory by Ethel Bidwell and her assistant Ross Dike.



2. The blood is centrifuged to separate plasma from the red cells.



*3. Plasma is removed by suction.*



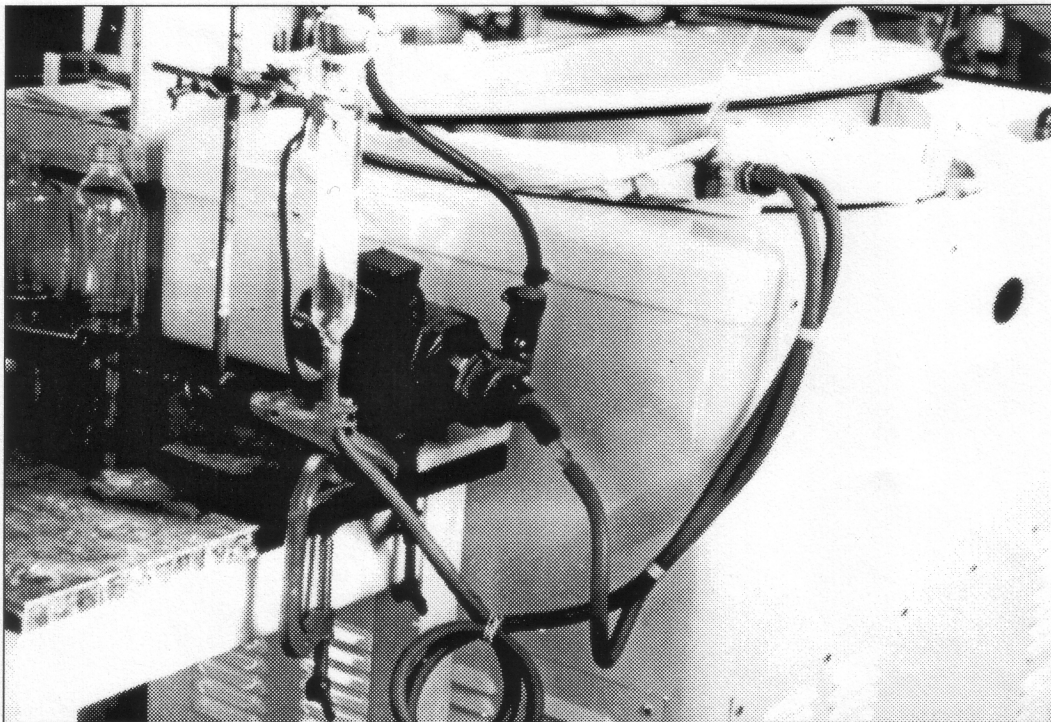
*4. The plasma is again separated by centrifuging. It is cooled and the active factor is precipitated by adding phosphate buffer.*



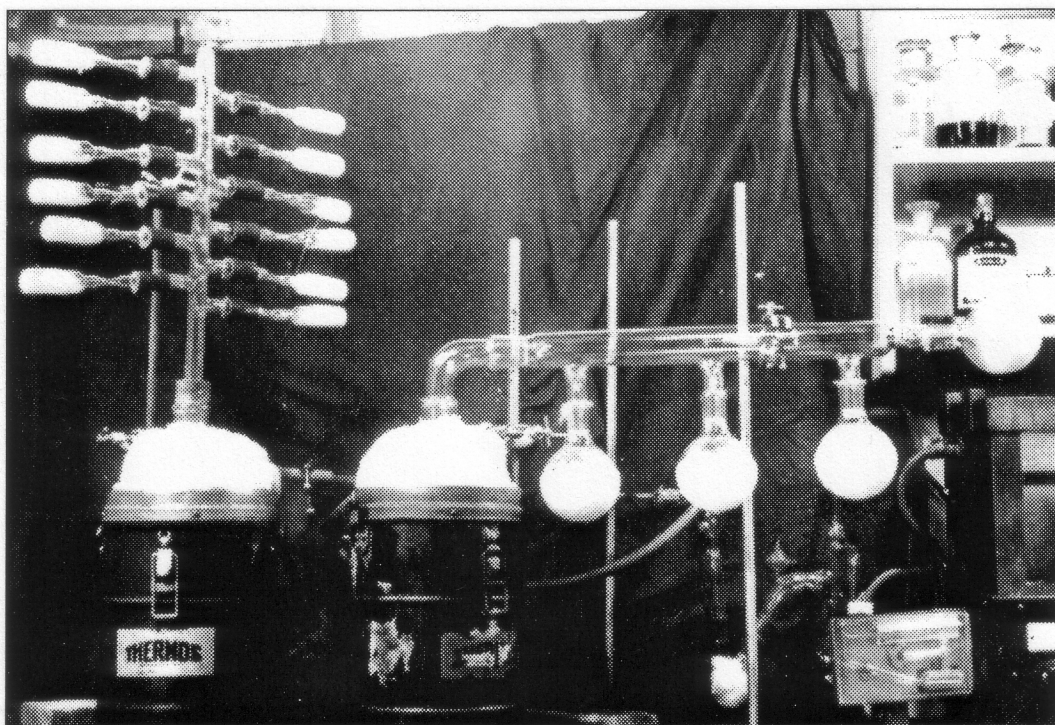
5. The purification is carried a stage further by another precipitation, with sodium citrate.



6. The precipitate is collected by centrifuging and the supernatant fluid containing impurities is discarded. The precipitate is dissolved in saline.



7. Most of the added salts must be removed by dialysis. Owing to the instability of material, this must be done rapidly. The apparatus is shown.



8. Preservation by freeze-drying.

Photographs kindly provided by Mr Ross Dike, processed and mounted by him. Permission granted to reproduce photographs, Dr Ethel Bidwell and Mr Ross Dike, 1999. ©Mr Ross Dike, 1999.

on a dismal note, I want to focus a little bit of attention on the early development of recombinant products which, of course, is what we all want to treat our patients with in 1998. I am going to ask Dr Rizza to try and set the scene. How did the Haemophilia Centre Directors Organization come about?

RIZZA: Before tea Clifford Welch talked about treatment as it was in the 1930s and the 1940s and he mentioned Timperley's egg white and a patient called Frank Smith.<sup>161</sup> Timperley's egg white were little tablets, these [holding some] the date of which, I think, was 1949. A bit out of date now. I am going to be provocative and suggest that, in fact, this is to some extent important in the development of haemophilia care, because Mr Frank Smith, and some other haemophiliacs at that time, were very conscious of a lack of treatment or any support for haemophilia. I know Mr Smith made a nuisance of himself – he wouldn't mind me saying that – by going to the Ministry of Health on many occasions, and to the Medical Research Council, asking them to make this very important material [i.e. Timperley's egg white]. But they could never find any scientific evidence for putting any effort into that, so he began to make it in his kitchen at home. My recollection is that this material required fuming hydrobromic acid for its manufacture from egg albumin and on one occasion it blew up in his face in the kitchen and he was scarred for life thereafter because of his acid burns. But I think the consequence of the inception of the National Health Service, and people like Frank Smith constantly asking for help, was that Sir Weldon Dalrymple-Champneys,<sup>162</sup> who was a Deputy Chief Medical Officer, wrote to Professor Macfarlane in Oxford and to Dr Wilkinson<sup>163</sup> in Manchester suggesting that something should be done for haemophiliacs. The time had come to sit down and make plans. So they had a little meeting, a very informal meeting in early 1950, and thereafter several meetings were held with other interested doctors. They wrote around to find out who was interested in haemophilia and they got a small group together and they began holding more formal meetings to discuss what could be done. And of course in those days there was nothing that could be done really. There weren't even diagnostic tests, or at least reliable ones. So they agreed that they should give advice to the patients on how best to help themselves, advice to the GPs on how best to help the patients and also to educate the general public, and in particular employers,

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<sup>161</sup> *op. cit.* notes 129 and 130 above.

<sup>162</sup> Sir Weldon Dalrymple-Champneys FRCP (1892–1980) was President of the Haemophilia Society for 27 years. He joined the medical staff of the Ministry of Health in 1927 and became Deputy Chief Medical Officer in 1940.

<sup>163</sup> *op. cit.* note 76 above.

## Haemophilia: Recent history

about the needs of haemophiliacs. And that's how it started and I like to think that it probably started because of the insistence by some patients on the value of this material, egg white.

Thereafter, the organizing group became larger, and it was agreed that certain regions should have centres to look after haemophiliacs. The MRC got involved in the early 1950s and promoted and funded work on the manufacture of factor VIII. Thereafter, the Ministry of Health took over the organization of care, but all the time there was a nucleus of centres in regions throughout the country who were offering care of a kind. It was mainly supportive, there was no therapeutic material available, but they were getting together the core of an organization.

As time went on and factor VIII became available more widely, especially by 1972 when the first large pool concentrates began to come into the country, it was seen then that there was a need to formalize the organization of the care a little more. In 1968 the first meeting of doctors who were interested in haemophilia met in Oxford. There were 26 doctors who turned up and we had an afternoon party and, I think, there were one or two lectures given, a lot of exchange of ideas, and exchange of worries about haemophilia care, and the feeling was that really this was so useful that we should meet every year thereafter to discuss the problems of haemophilia. Simple things like how many staff you require to look after 100 patients or 50 patients, what services, what nurses do you require. This is how it started in 1968 and since then, yearly, the Directors of the Haemophilia Centres up and down the country have met at different places around the UK just to do what I have said: discuss problems, learn from each other and from people from abroad. Eventually scientific sessions were built in so that foreign experts could come and tell us what was happening in other parts of the world, and this was the way the organization of haemophilia care in this country started.

Lee: Can you tell us when the Registry first came about?

Rizzo: In 1968, right after the first meeting. After the first meeting it was felt that without information on the numbers of patients, what kind of treatment was being used up and down the country, what kind of complications were being met, how many cases were dying, it would be very difficult to promote better care and better organization and so on. So from the very early days annual returns (Rosemary Spooner is here, she helped to set it up) were received from



all the Haemophilia Centres in the country.<sup>164</sup> They were analysed, reports were written, and those reports were sent back to the different Haemophilia Centres, as well as to the Department of Health and to the fractionation laboratories. The fractionation laboratories had to know the size of the problem as they were going to be manufacturing the concentrates necessary for treatment. The Registry has been going for 30 years now.

Lee: In the interview with Dr Biggs last week, she described in vivid detail this first meeting and she said, 'Well I decided to have a party. Everybody likes to come to a party. And I invited to this party everybody who knew anything about haemophilia at that time. I was a lady, and ladies were allowed to organize parties.' And the other thing was when we went on to talk about the organization and having a chairman and things, she said, 'I was never the chairman, I don't think there is any point in being a chairman. Chairmen don't have any power. The power resides in the person who writes the minutes, and I write very good minutes.'<sup>165</sup> Now can you perhaps, Alan, tell us when the two, the Haemophilia Society and the Organization, interacted.

Tanner: Yes, that was at the beginning as Dr Rizza says. He mentioned the name of Sir Weldon Dalrymple-Champneys<sup>166</sup> who was a key person in encouraging people with haemophilia to come together to meet for mutual support, sharing views about treatments or the paucity of treatments, to help each other in terms of financial support if that seemed to be necessary. Those small beginnings in the 1950s were mostly in people's houses, just a small number getting together. It began to expand and eventually in the 1960s they thought about looking for some kind of base where they could congregate much more frequently and have an office from which they could operate. So the older members, the old hands, will recall the famous fire station in Southwark. It was surplus to requirements, let me add, it was a building which was made available, and that was the beginning of an organization for the Haemophilia

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<sup>164</sup> Rosemary Spooner (b. 1937) was Secretary to the MRC Blood Coagulation Research Unit from 1961 to 1967 and Secretary/Research Assistant to Dr Rosemary Biggs, at the Oxford Haemophilia Centre from 1967 to 1977. Since 1977 she has had an NHS appointment as Research Assistant/Data Analyst at the Oxford Haemophilia Centre and has been Honorary Administrative Secretary to the United Kingdom Haemophilia Centre Directors Organization since 1988. She is co-author to several publications including Biggs R, Spooner R J D. (1977) Haemophilia treatment in the United Kingdom from 1969 to 1974. *British Journal of Haematology* 35: 487–504. *idem* Haemophilia Centre Directors' annual statistics for 1975. *ibid.* 36: 447–449. *idem* (1978) National survey of haemophilia and Christmas disease patients in the United Kingdom. *Lancet* i: 1143–1144.

<sup>165</sup> *op. cit.* note 2 above, 770.

<sup>166</sup> See biographical note 162 above.

## Haemophilia: Recent history

Society, manned entirely by volunteers and that was a very, very important aspect of the whole organization. It was done by volunteers supporting each other and beginning to become rather aggressive in their style in relating with their doctors and dealing with the Government and so on. They began to organize one or two campaigns, and now the society is well organized as a campaigning body.

One of the first campaigns they ran was to do with the provision of transport. There was some deadly mechanism which some will recall. It was a tricycle which was made available for those who were disabled and it was lethal. They managed to get none other than Graham Hill, who was quite famous as a racing driver then, who took his life in his hands by testing it. They assembled together MPs and Graham Hill drove this erratically so that it overturned and so he was able to demonstrate that it was not suitable for people with haemophilia. That was the beginning of that kind of campaigning movement. Volunteers were operating from this old fire station, which was a good place to meet and to lodge papers, because by then they began to accumulate a certain amount of files and papers and so on.

The next move was when the lease of that dilapidated building expired, and they moved into much more palatial surroundings in Trinity Street in Southwark, which many will remember, again run entirely by volunteers. But the Organization was developing to such a degree there in the 1960s that they found it was no longer satisfactory for people to be keeping papers at home; letters got lost and were never answered, so they managed to recruit a part-time secretary, Irene Watson, who came in two mornings a week to deal with the correspondence. Then, moving on quite rapidly to the end of the 1960s, beginning of the 1970s, they felt that they were in need of some kind of full-time assistance. But still pre-eminently, it was a volunteer organization and they could not see their way to appointing a general secretary or administrator. The first full-time person appointed was a social worker, Victoria Stockford, who operated from 1975 to 1980. It was the first sign of the introduction of professionalism into the society. All this is keeping pace with the development of medical care. Because now, towards the end of the 1960s, cryoprecipitate was available but not in sufficient quantities, so they began again to adopt that lobbying stance, pressing their centres, which were being established by then, pressing the Government and so on, and then all that led into the development of the concentrates. Again, a major lobbying function.

In the 1970s I was invited into the presence of the Minister of State for Health, Dr David Owen, because one of our points for lobbying at that stage was the disquiet about the purity of the blood products that were coming from America. We had seen stories on the television of blood donors in the

United States being recruited from Skid Row and we spoke very forcibly to Dr David Owen to let him know that we were not prepared to accept the risk of hepatitis coming from the blood products issued from the United States. All this was rather prophetic when you think back on those days and the ways in which things have changed.

From then on, the society having got its first taste of a professional administrator, found it wasn't so dangerous after all: they could still not see their way to appointing an executive secretary or a general secretary who would take over the organization, they still had the thought of volunteerism in mind, so they appointed a coordinator, one who would not be too firm, to the point of excluding them from running the society, but would coordinate the efforts of the volunteers. The person appointed was David Watters who came into the office in 1981 and served with us until 1993 with great distinction. I think when we come to write the history of the Haemophilia Society, a very, very significant contribution will be shown to have been made by David Watters who really did introduce that note of professionalism that was required to pull the whole organization together. From then on, it began to be recognized by Government departments, by centre directors and so on, as the instrument by which the voice of people with haemophilia could be expressed.

I'll go on later perhaps to say something about the way in which we have continued campaigning with the society, the way in which we have dealt with the Government in matters like HIV infection, with the supply of blood products and so on. But the society has also been very keen to be involved in the whole matter of the designation of centres, and the facilities provided by centres. At the same time they have had their eye not only on the people with haemophilia themselves, but those within the family, because there was an increasing concern for the sisters in the family, with the whole matter of genetic counselling. That has been again a very major contribution made by the society. Fund-raising came into it very emphatically, of course, because all this required money. So we've moved from those early days with a part-time secretary to now quite a substantial organization where there are specialists attached to it. There is an HIV worker appointed by the society and a hepatitis worker. That is the state where we are today.

Lee: Can you just very briefly talk a little bit about the contribution that has been made towards the World Federation of Hemophilia from a British perspective?

## Haemophilia: Recent history

Tanner: I was thinking it's a pity Peggy Britten<sup>167</sup> is not with us at this seminar. She really is the doyenne of all supporters of the World Federation of Hemophilia. She was responsible for generating an immense amount of enthusiasm in the national society for people to play a full part in the World Federation of Hemophilia. The history of that is: at the first meeting in 1963 in Copenhagen there were six national societies represented. Again, they got together for mutual support, they wanted to know, now that people were beginning to travel abroad, where they could get treatment, because what was available was very, very patchy in those days. They wanted to know about the kinds of treatment available, how to relate with the Government and how to develop friendships with people with haemophilia in other countries. From that beginning in 1963, it has now expanded to the point where practically every country of note has a national member organization which is represented in the World Federation of Hemophilia, so it's something like 88 on the present count. There was a particular parallel with the national society. The World Federation of Hemophilia started in a very amateur way, but was inspired by the founder, Frank Schnabel<sup>168</sup> who himself was a person with haemophilia and motivated his peers in the other national organizations. At that time, again, volunteerism was the key note, but now it is a highly professional organization which is concerned not only with sharing information but having a particular eye on the developing countries, which Peter Jones will be able to speak about.<sup>169</sup> That is mutual support *par excellence* in seeing that facilities are provided in those countries which are much less fortunate than ourselves in the provision of treatment and management.

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<sup>167</sup> Peggy Britten (1912–1999) was unable to attend the meeting and died shortly afterwards. She had two brothers who died of haemophilia. Her son, Tony, also a haemophiliac, trained as a doctor in Johannesburg and later became Medical Director of a large transfusion centre in New York and Head of the Blood Programme of the League of Red Cross and Red Crescent Societies in Geneva. In 1965, Tony put her in touch with Katharine Dormandy to help with surveys into the problems of young haemophiliacs. She later became involved with the Haemophilia Society and World Federation of Haemophilia. She held the position of London Secretary and travelled extensively to many World Federation meetings. See Britten P. (n.d.) Living beside haemophilia in the 20th Century [unpublished manuscript] and note 170 below. Copies of the tapes and transcript of an interview with Peggy Britten, conducted by Professor Christine Lee on 19 March 1998, will be deposited with the records of this meeting in the Contemporary Medical Archives Centre of the library of the Wellcome Institute for the History of Medicine.

<sup>168</sup> Frank Schnabel (1926–1987), a severe haemophiliac, was a Founder of the Canadian Haemophilia Society and also Founder and First President of the World Federation of Hemophilia in 1963 when he convened the first meeting of six national societies in Copenhagen.

<sup>169</sup> Dr Peter Jones wrote: 'The World Federation of Hemophilia is a unique international organization, administered jointly by people with haemophilia and their relatives, and by doctors and scientists with an interest in the inherited bleeding disorders. Much of the present thrust of their work is targeted at helping people with haemophilia in low economy countries.' Letter to Dr Daphne Christie, 5 July 1999.

Lee: Yes, maybe I could mention a little bit about Peggy Britten. Unfortunately, she wasn't able to come today because she has got a terrible cold, but we are hoping to interview her subsequently.<sup>170</sup> She had a son with haemophilia who subsequently became the Head of the Transfusion Service in Canada and she also suffered the death of a brother with haemophilia when she was quite young. So she was really very involved. She worked as Katharine Dormandy's research assistant, to research into the educational needs of the children of the south of England and to that end the Haemophilia Society paid money for a caravan which was put on the Lawn Road site.<sup>171</sup>

Before we move onto what we will spend most of the rest of the time talking about, and that's contamination, we should hear something from Dr Sheila Howarth about the MRC and the provision of concentrates.

Dr Sheila Howarth:<sup>172</sup> I was very surprised that in the course of the afternoon credit was not given where credit was due, because much of the work that has in fact been described was supported by the Medical Research Council, and pretty lavishly considering the budget of the time. The MRC Blood Coagulation Research Unit in Oxford, which was directed by Gwyn Macfarlane, ran from 1959 until Macfarlane retired in 1967, and the work was then continued under MRC auspices by Dr Rosemary Biggs. It trained a lot of the people who were seeded out throughout the country; and the Council gave fellowships for people to go and train there, as some people here will know.

But to go back before that. I moved into the headquarters office of the MRC in 1964, and there was a haemophilia committee, the MRC Haemophilia Committee, chaired by Dr J F Wilkinson of Manchester, of which Professor Ilsley Ingram was a member and could probably tell you much more about it than I could. When this was disbanded in 1966, its work was taken up in the main by the MRC Blood Transfusion Research Committee, chaired by Pat Mollison, which included representatives from England and Scotland and directors of centres and also representatives of the services. It took haemophilia on board when the Wilkinson committee was wound up. It hasn't been mentioned that the MRC actually managed the Blood Products Laboratory for

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<sup>170</sup> op. cit. note 167 above. See also Britten M I, Spooner R J D, Dormandy K M, Biggs R. (1966) The haemophilic boy in school. *British Medical Journal* ii: 224–228. Dormandy K M, Gandy R H, Britten M I. (1966) Problems of management of children with coagulation disorders. *Bibliotheca Haematologica* 26: 171–175. Britten M I. (1967) Haemophilia and its problems. *District Nursing* 10: 120–122.

<sup>171</sup> The caravan was parked at the old Lawn Road Hospital in 1964, on the site of the present Royal Free Hospital in Pond Street, Hampstead. It was replaced by the purpose-built Katharine Dormandy Haemophilia Centre and Haemostasis Unit in 1978.

<sup>172</sup> Dr Sheila Howarth FRCP (b. 1920) joined the staff of the headquarters office of the Medical Research Council in 1964. She retired as Principal Medical Officer in 1980.

## Haemophilia: Recent history

the Department of Health, and there was a Managing Committee, which again was chaired by Professor Mollison. This was a difficult committee because it had to point out endlessly to the Health Department the increasing need for blood products, and that really they ought to get on with increasing the accommodation at Elstree<sup>173</sup> and with the proposed new building. The Department of Health almost invariably dragged its feet. They were disastrous meetings. Dr Dodsworth has described very politely what went on. I can remember one occasion when Dr Biggs and I had to take Professor Macfarlane as an expert witness from Park Crescent [the MRC Headquarters], where he was briefed, by Tube, to a meeting at Elephant and Castle [the Department of Health and Social Security]. He had claustrophobia. We had the greatest difficulty in getting him down the escalator and onto the Tube, and having got him into the building at the Elephant, he stood at the bottom of the lift, dug his heels in and said he wasn't going to get in the lift. Anyway, we finally got him to the meeting, and he was our leading witness, so to speak. But the Department in England did drag its feet, and it was a disastrous period.

In Scotland, they took notice of the advice which was given by the committees of the MRC and phase 1 of the redevelopment of the Royal Infirmary in Edinburgh included the fractionation laboratory,<sup>174</sup> so they were prepared when nemesis came. My information [which came from the office of the Haemophilia Society] was that in 1990, at the time when my haemophilic nephew died HIV positive in this country [England], of the 600 known haemophiliacs in Scotland, only 27 were known to be HIV positive, and most of these were suspected of having acquired the infection by association with the drug fraternity in Edinburgh.<sup>175</sup>

The other point perhaps I should pick up – I don't want to go on – is the Haemophilia Register. When I went to the MRC in 1964, one of the first things that happened to me was that two card-index files arrived on my side table, covered with dust, and there they continued to accumulate dust. This was called the Haemophilia Register and it had been set up by the MRC. People used to submit cards to the relevant section of the office about additional cases of

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<sup>173</sup> See note 62 above.

<sup>174</sup> The Scottish National Plasma Fractionation Centre was housed in the Edinburgh Royal Infirmary. See Girdwood R H. (1990) Fifty years of an organized blood transfusion service in Scotland. *Scottish Medical Journal* 35: 24–28.

<sup>175</sup> Dr Charles Rizza wrote: 'Is it being suggested that those Scottish haemophiliacs were drug users? Or is it being suggested that the infected drug users gave blood which infected the plasma supply used for fractionating factor VIII in Edinburgh? I wonder how many drug users are volunteer blood donors. I think the source of infection in Scotland was probably no different from that in England. Even if the evidence is cast-iron that drug users were the source of infection, I think it should be made clear that the haemophiliacs themselves were not "drug users".' Communication with Dr Daphne Christie, 3 July 1999.

haemophilia as they were diagnosed. We tried to get the Health Department to put this on a more regular footing and we met with intense resistance. Finally we managed to get it handed over in 1966, when at Park Crescent [MRC headquarters] we had a party, as it had been such an uphill battle. I may add that the Register having sat on my side table, the Department then regarded it as something that had security risk implications, and they were said to have taken it down to the basement at the Elephant and Castle and locked it in the safe. I don't know what happened to it after that.

Anyway, you can see that, in fact, the MRC was extremely active in this field, in not a passive but an active role. If we failed I think it was due to the fact that we could not push the Elephant [Department of Health], which has a period of gestation anyway of about 18 months, into any urgent action. I think perhaps the history of the MRC's part in this ought to be gone into in more detail, because it's a long time ago. I retired in 1980 and I am totally out of touch with what went on after that.

Lee: Before we go to Dr Dodsworth, this Register, did it come into your hands, Charlie?

Rizzo: No, no. It must be locked away somewhere.

Howarth: It's probably still locked away in the safe at the Elephant and Castle!

Dodsworth: I wonder if I can make a slightly sympathetic comment with respect to the British Transfusion Service. The Fractionation Centre at Elstree never had control over its own plasma supply until the National Blood Authority was founded in 1993.<sup>176</sup> Consequently, although the facilities for making factor VIII were available, there was never enough plasma with which to make it. The situation was always somewhat easier in Scotland where the main concentration of population, and thus of blood donors, is close to the country's main transfusion centre [in Edinburgh]. When I was working in Manchester in the late 1960s we had no factor VIII at all and were aware that there seemed to be plenty in Scotland: we were very jealous.

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<sup>176</sup> A history of blood transfusion services in the UK is given in Dodsworth H. (1996) op. cit. note 99 above.

## Haemophilia: Recent history

Mr Ross Dike:<sup>177</sup> I would just like to make a further comment about the support we had from the Medical Research Council which is not often realized. Nearly all the advances, both in biochemical research and also in fractionation processes, are also consequent on the advances in the equipment that's used. In other words, the design and the building of novel equipment or the modification of commercial equipment. In this way when we moved up at the end of 1958 from the Radcliffe Infirmary, Oxford, into the MRC Blood Coagulation Research Unit at the Churchill Hospital, Oxford, we were very strongly supported by the MRC Central Workshops which occupied a building in the same hospital [the Churchill Hospital], and this led to a lot of advances, including such things as the successful separation of factor VIII from fibrinogen,<sup>178</sup> the equipment in which the first column fractionation of DEAE-cellulose factor IX was carried out,<sup>179</sup> etc. I could go on for half an hour enumerating these things. But it was in this way that part of the success of our research was due to the proximity of this workshop. This was proved later on after the retirement of Professor Macfarlane. We separated into three distinct units, one of them being a plasma fractionation unit, which I worked in. We did not have adequate engineering or electronic facilities after the MRC Central Workshop was closed, so we built and staffed our own workshops for the design, development, commissioning and modifying equipment and services, and the provision of a planned preventive maintenance programme. I think that the importance of this should be acknowledged.

Bangham: I'd like to point out again that all the biological standards contributing to the field were made in the Division of Biological Standards at

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<sup>177</sup> Mr G W R Dike (b. 1932) started working as Dr Bidwell's assistant in Dr Macfarlane's Haematology Research Unit, Radcliffe Infirmary, Oxford, in 1954 – in time to be involved in preparing the first dose of bovine antihæmophilic globulin which was successfully administered to a hæmophilic patient. The Unit was taken over by the MRC (in April 1959) as the MRC Blood Coagulation Unit, and moved to the Churchill Hospital, Oxford, when Dike became an MRC Technical Officer. On Professor Macfarlane's retirement in 1967, Dike was involved in the planning and supervision of the subsequent building of the Plasma Fractionation Laboratory on the same site, and then its subsequent expansion. Dike was Safety Officer from 1974 and retired in 1992 as a Higher Professional and Technological officer (MRC) and had also been on secondment to the NHS since 1969.

<sup>178</sup> Bidwell E, Dike G W R, Denson K W E. (1966) Experiments with factor VIII separated from fibrinogen by electrophoresis in free buffer film. *British Journal of Haematology* 12: 583–594.

<sup>179</sup> Dike G W R, Bidwell E, Rizza C R. (1972) The preparation and use of a new concentrate containing factor IX, prothrombin and factor X and of a separate concentrate containing factor VII. *British Journal of Haematology* 22: 469–490. Mr Ross Dike wrote: 'This paper has an illustration of the original large-scale chromatography column, and the refractometer that was invented and built for this work since no suitable commercial columns or in-line equipment were available.' Letter to Dr Daphne Christie, 22 March 1999.



the National Institute for Medical Research until 1974. That was all work under the MRC.

DOUGLAS: Dr Howarth has mentioned the relatively low incidence of HIV infection amongst the Scottish haemophiliacs. One name in that connection should be mentioned, John Cash.<sup>180</sup> He was able to obtain agreement amongst the Scottish blood transfusion directors to favour investment in the plasma fractionation unit in Edinburgh and so reduced the need to use imported material.

As regards the registration of haemophilia, I remember in around 1960 filling in those green cards which Dr Howarth described earlier for issue to the patients and lodging the names with the MRC office in London.

LEE: It's very interesting how Scotland is always so different. I mean the difference remains to the present day, when the Government gives them £2 million so that they can introduce recombinant factor VIII.

I am going to change topic now and I think we need to spend some time hearing about the beginnings and the effects that viral contamination, and the side-effects of treatment, had on haemophilic patients, the people treating them and the whole way really we practise medicine. I think, Peter, you played quite a part in this in the early days. Can you start at the beginning and give us a feel for when the thing first began to hit.

JONES: I think you have to set what has happened in the context, firstly, of a rare disorder affecting a small number of the population of the United Kingdom, hence some of the resistance to the views of the MRC, the Haemophilia Centre directors and the patients' groups early on. You also have to set it against the scenario of how enthusiastic we were once effective treatment became available. Previously we had not been able to treat these little boys who were missing their schooling, had no career to look forward to, were growing up illiterate, were growing up crippled. We had nothing. We had enough factor concentrate to deal with the major surgery and that was really about it. Cryoprecipitate opened our eyes and then the concentrates came. We couldn't use the animal concentrates because they were antigenic, they stopped working after a while, so we turned instead to human concentrates. We knew from the beginning that we were transmitting disease, we knew there was

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<sup>180</sup> Professor John Cash FRCS FRCPEd FRCPath was National Medical Director, Scottish National Blood Transfusion Service headquarters in Edinburgh from 1988 to 1996 and President of the Royal College of Physicians in Edinburgh from 1994 to 1997.

## Haemophilia: Recent history

something then called serum hepatitis, we now know it as hepatitis B, after the Australian antigen was discovered.<sup>181</sup> We knew that hepatitis B was in those concentrates and the companies knew that hepatitis B was in those concentrates. The first outbreaks of hepatitis B in the haemophilia population of the United Kingdom in the early 1970s were because of dumping of concentrates which would not have passed the Food and Drug Administration (FDA)<sup>182</sup> regulations in the United States of America. Even that did not blunt the enthusiasm for treatment, because we moved on, as David Evans has said, to home therapy and from there to prophylaxis and to the prevention of haemophilic arthropathy. We also knew there was another virus in the concentrates which we then called non-A and non-B hepatitis and we now know as hepatitis C,<sup>183</sup> but all the evidence then from around the world then was that this too produced a chronic disorder which might result in ill-health in a few people. It was not thought to result in a devastating disease of the liver which would kill more than a few people. And it was worth trading that off for the improvements in haemophilia care. We didn't know anything about HIV, or AIDS, and this observation is important because in the early 1980s there was a school of thought, particularly amongst people who were campaigning for compensation, that we'd known about AIDS for years.

It is very salutary in talking about the history of haemophilia treatment, and the history of medicine in general, to realize that advances in care are rarely straightforward. There's a cartoon by Matt on the front of the *Daily Telegraph* today and I paraphrase it, 'We have known about spongiform encephalopathy for a long time, but it has taken us two years to know how to pronounce it.' In the early 1980s there was this feeling that we had all known that there was another virus there, and if we look at some of the features at the beginning of the HIV epidemic and what we now know about new variant CJD (nvCJD), it's a little chilling. First of all the timing. In every decade of modern haemophilia therapy a new virus has appeared. We have been through the hepatitis alphabet of A, B, C, delta, E, and we are down to G. We have found parvovirus.<sup>184</sup> Every decade brings a new virus: so HIV in the early 1980s,<sup>185</sup> then hepatitis C

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<sup>181</sup> Baruch Samuel Blumberg won the Nobel Prize in 1976, jointly with D Carleton Gajdusek, for his discovery of the Australian antigen associated with hepatitis B virus. See Blumberg B S. (1984) The Australian antigen story. In Millman I, Eisenstein T, Blumberg B S. (eds) *Hepatitis B: The virus, the disease, and the vaccine*. New York: Plenum Press, 5–31.

<sup>182</sup> The Food and Drug Administration (FDA) of the USA (founded in 1938) is the premier drug regulatory organization in the world, inspecting and licensing the manufacture of foods, cosmetics, pesticides as well as human and veterinary medicines.

<sup>183</sup> See note 92 above.

<sup>184</sup> *op. cit.* note 88 above.

<sup>185</sup> *op. cit.* note 87 above.

recognition in the early 1990s,<sup>186</sup> and now a question mark. Initially, HIV and now nvCJD had well-defined patient groups; with CJD we have the growth hormone group.<sup>187</sup> Animal connections are obvious with nvCJD, the green monkey with HIV. With CJD we don't know where the infection is, there isn't a test; the same for HIV was true. Query – is it transmissible by blood?

With HIV, we realized that we had got a problem after the description of the first cases in 1981. The Haemophilia Centre directors thought very long and hard, and thought that one in a thousand people who had been transfused with contaminated products would develop AIDS. One in a thousand. Again it was something to be concerned about, but perhaps to put on one side in favour of continuing treatment. We didn't know any means of removal. Heat treatment had been tested to try to get rid of hepatitis viruses, but in fact if it had been tested heavily in the 1970s it probably would have been rejected and not thought of for HIV, because it did not stop transmission of hepatitis. With CJD, as was the case initially with HIV, there's no individual donor testing. There's no surrogate testing. There's a very long incubation period which is what caught us out with 'the one in a thousand' at the beginning of HIV. CJD is a deadly disease, there is no known treatment. Now with HIV we've moved on and we have got long-term survivors. Both CJD and HIV have produced terrific dilemmas for the authorities. You have only got to think of beef on the bone, and the scepticism of the public. It's a catch-22 situation,<sup>188</sup> there is enormous publicity, much of it ill-informed. The media like to think in terms of black and white, there is no grey area in the middle. When doctors say they don't know, or scientists say they don't know, it adds to the uncertainty. So there is a tendency for the Government, and we have already heard the MRC perspective about transfusion,<sup>189</sup> to follow a course of action without telling those at the leading edge. That was certainly true at the beginning of HIV and may now be true in the case of CJD in the case of the farmers. At the beginning of the HIV epidemic I thought that it must have been almost like being in World War I when the generals were doing one thing and the men were all doing something else. I felt very much like the brigadier in Dr Who because I felt that I had to be pragmatic and act, but there was nobody to turn to; there was no leadership whatsoever from central Government or the Department of Health. In fact, if

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<sup>186</sup> See note 92 above.

<sup>187</sup> Knight R, Stewart G. (1998) The new variant form of Creutzfeldt–Jakob disease. *FEMS Immunology and Medical Microbiology* 21: 97–100. See also Lee C A. (1996) Transfusion-transmitted disease. *Baillière's Clinical Haematology* 9: 369–394.

<sup>188</sup> Catch-22 – A no-win situation. 'Orr would be crazy to fly more missions and sane if he didn't, but if he was sane he had to fly them. If he flew them he was crazy and didn't have to; but if he didn't want to he was sane and had to.' Heller J. (1961) *Catch-22*, Ch. 5. Leicester: Charnwood.

<sup>189</sup> See discussion on page 59.

## Haemophilia: Recent history

anything, in the initial years there was antagonism. There was an enormous amount of money spent fanning around, when all that was really needed was to put every Haemophilia Centre director and the small number of other people working with the early groups affected by HIV, particularly in London and Edinburgh, onto a jumbo jet and take them to the United States to teach them how to look after people with AIDS and prevent transmission.<sup>190</sup>

Then followed, of course, the discovery that the majority of our severe haemophilic patients were affected, and I wish the story that you gave us about Scotland was true, but it isn't; there were many more patients in Scotland infected and infected with Scottish product.<sup>191</sup> Then there followed a campaign for 'recompense', we called it, because 'compensation' suggested no-fault compensation and Government blocked that, of course, for people with haemophilia and their families and the survivors.<sup>192</sup> And that led to the Macfarlane Trust with the first £10 million which came from Mrs Thatcher. One afternoon at three o'clock she suddenly said, 'We'll do it, there's the money'. Why she did it, we have never discovered.

Lee: Didn't that happen when John Major came in?

Jones: No. The first £10 million for the Macfarlane Trust came from Margaret Thatcher. The later payments, two extra payments to people with haemophilia, were from John Major's Government and that came after prolonged litigation which was very, very uncomfortable. In medical practice when you are being litigated against, normally the patient isn't your own patient. You can push the patient, if that is the right way of putting it, onto a colleague. But in this case, you couldn't. So we had Haemophilia Centre directors looking after patients and families, and at the same time being

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<sup>190</sup> Dr Peter Jones wrote: 'It should be remembered that the haemophilic population was hit by HIV first, about two years before the epidemic became apparent in the general population, because of the direct inoculation of the virus in treatment. So the directors were at the leading edge of the epidemic in this country.' Letter to Dr Daphne Christie, 5 July 1999.

<sup>191</sup> See Simmonds P, Beatson D, Cuthbert R J, Watson H, Reynolds B, Peutherer J F, Parry J V, Ludlam C A, Steel C M. (1991) Determinants of HIV disease progression: six-year longitudinal study in the Edinburgh haemophilia cohort. *Lancet* **338**: 1159-1163.

<sup>192</sup> The term 'recompense' was used because the Government would not support no-fault compensation. Dr Peter Jones wrote: 'The initial campaign in 1987 was orchestrated principally by David Watters [see page 57] and his colleagues in the Haemophilia Society and Dr Jones in Newcastle. Intense lobbying of Parliament was undertaken and included the distribution of a booklet, *This is URGENT. Haemophilia and AIDS*, which detailed the hardship being experienced by people with haemophilia and their families, to members of both Houses and to the media.' Letter to Dr Daphne Christie, 5 July 1999. See Jones P. (1987) Hidden victims of AIDS. *The Times* (9 October 1987). *idem* Haemophilia, AIDS, and no fault compensation. *British Medical Journal* **295**: 944-945.

litigated against for HIV infection and subsequently AIDS, and that took personally two years out of my clinical life. I had to shut my door and just go through all the records for litigation. Some of my personal record of the time has already been published.<sup>193</sup> That still continues with hepatitis C of course. God willing, we are not going to see CJD as a transmittable disease to the haemophilia population. Hopefully it will not be long before we know the risk factors, because the risk committee and SEAC, the Spongiform Encephalopathy Advisory Group, reports to ministers in March, so we may have a better idea then.<sup>194</sup> As Alan [Tanner] said, the Haemophilia Society has grown into a very well-presented professional lobbying body, but in some cases, and in the case of the World Federation as well, it has left in its wake difficulties, some bitterness, some doctors who don't want to know anything about haemophilia ever again, and this continues even today with HIV. Thirty of our colleagues in France have been charged officially with poisoning and stand trial to spend the rest of their lives in prison.<sup>195</sup> These are colleagues just like people sitting in this room, who I know perfectly well behaved just as we did at that time.

Lee: One is a Professor of Transfusion Medicine in this country.

Jones: I see Jean-Pierre Allain<sup>196</sup> was invited to the meeting and couldn't come. He has already been in prison for his role in the French HIV epidemic and, in Japan, colleagues have also been put in prison for their involvement with HIV and still problems exist. So young physicians, young haematologists, are reluctant to treat people with haemophilia because they are frightened that they will be embroiled in litigation and difficulties in their professional lives. So the sadness of HIV from the professional point of view is still with us, and I

<sup>193</sup> Berridge V. (1996) op. cit. note 90 above, for example pages 38–40, 62.

<sup>194</sup> Dr David Tyrrell wrote: '...There was the opinion from SEAC [Spongiform Encephalopathy Advisory Committee, also known after its Chairman as the Tyrrell Committee, see note 203 below] that there was a theoretical risk of new variant CJD from blood. They made recommendations on sourcing and processing of blood products'. Letter to Dr Daphne Christie, 13 March 1999. See a summary of the meeting held on 9 March 1998, in *MAFF News* 119/98, 25 March 1998.

<sup>195</sup> Butler D. (1994) Mitterrand asked to pardon doctors in HIV blood scandal. *Nature* 367: 206. Anonymous. Contaminated blood continues to boil. *ibid.* 301.

<sup>196</sup> Professor Jean-Pierre Allain, Professor of Transfusion Medicine in Cambridge, and Director of the East Anglian Blood Transfusion Service, was sentenced by the French Courts to a term of imprisonment when he was working in Paris in 1984–1985. His alleged crime was to have done too little to prevent the transmission of HIV to haemophiliacs. See Carrell R W, Peters K, Cash J, Mollison P L (and 33 others). (1993) Imprisonment of J-P Allain. *Lancet* 343: 244. Lachmann P J, Bellingham A J, Banatvala J, Carrell R, Hoffbrand V, Wagstaff W. (1993) Statement of the Royal College of Pathologists on the matter of Professor Jean-Pierre Allain: 19 November 1993. *The Bulletin of the Royal College of Pathologists*: 84: 3–4.

## Haemophilia: Recent history

don't really need to say what sadness there has been in the patient population, because it has been dreadful. We have seen three generations now of patients affected and in the face of all this our Government, both the Conservatives and the Labour Party, have refused to endorse the unanimous opinion of the Haemophilia Centre directors that recombinant factor VIII and now factor IX is probably safer than the plasma products and therefore must be the treatment of choice for people with severe haemophilia.

Lee: Thank you, Peter. Before we move onto recombinant [factor VIII and factor IX] for the last part of this there are two things I would just like to encourage along the way. This is a horrific story but alongside that horrific story is a good story, in that the life expectancy for somebody with haemophilia in the late 1930s was 20 years. And this came up very strongly in the conversation we had with Dr Biggs. We were talking about the school at Treloar<sup>197</sup> and I said I had a number of adult patients who were at Alton, and sadly they were ones who had died of AIDS, who'd known each other when they were all boys together at Alton. She responded by saying, 'Of course, the next thing that started to crop up was they started to get jaundice'. Dr Biggs published on jaundice in 1974<sup>198</sup> and, I think, was probably the first person who actually put into print this complication. And she said, 'And what we felt at the time was that they were better alive and having jaundice, than dead with haemophilia'.<sup>199</sup> I think that it is important that although this terrible thing has happened, alongside it has developed good treatment and we'll hear a bit more about that in a minute from Ted [Tuddenham].

Charlie [Rizza], before we leave HIV, I hesitate to say this, but from the haemophilic patients who'd been infected, a lot of science has come which has actually helped our understanding of the natural history and the biology of HIV. Would you like to talk a little bit about those data and how they've been published, and collated, and helped our understanding.

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<sup>197</sup> The Lord Mayor Treloar Hospital and College at Alton accepted pupils with crippling diseases and nearly a third of the boys at the college were haemophiliacs. See Gaumont British Instructional (1945) *A Job Well Done (Lord Treloar Hospital and College in Alton, Hants)*. Videocassette copy, 1989, Handlist number 183, Wellcome Trust Video Library. See also Britten M I, Spooner R J D, Dormandy K M, Biggs R. (1966), op. cit. note 170 above.

<sup>198</sup> Biggs R. (1974) Jaundice and antibodies directed against factors VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom. *British Journal of Haematology* 26: 313–329.

<sup>199</sup> op. cit. note 2 above, 772.

Rizza: This stems largely from the organization of care, the registration of information, the gathering of data. We were in a very strong position in this country, compared with other countries, in that we had a very good database to start with. Very easily we picked up information on the prevalence and consequences of HIV, and along with the people working with Sir Richard Doll<sup>200</sup> worked on the long-term effects, and the effects of age for instance at the time of infection. But we also managed to scupper the story which was being put about by some very serious people in the United States, that HIV had nothing to do with AIDS and it was a ‘bystander effect’<sup>201</sup> and it was this thing called ‘lifestyle’ which caused AIDS. No-one could explain to me what the lifestyle was of the wife of a haemophiliac who had got AIDS or the lifestyle of a newborn babe who had got it from his mother, the wife of a haemophiliac. So the data we collected was valuable in that respect and probably put an end to that story.<sup>202</sup> It hasn’t surfaced again. It tends to come up when Professor Duesberg is asked to speak. It’s my own personal view that medicine seems to stumble from one disaster to the next. All the way through it has been like that. You develop what you think is good therapy and you find that a significant number of patients suffer as a consequence, but at the end of it there’s been a little bit of advance. It is a shame that people have to suffer to get there and this is my own personal feeling, others may not think that. All new therapies are potentially dangerous, I think, and have to be used with great care.

Lee: One of the really good things that came out of HIV was a real push to get a safe product and I suppose in the beginning it was sterilization, but then there was the push to move to recombinant.

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<sup>200</sup> Professor Sir Richard Doll Kt CH OBE FRCP FRS (b. 1912) was Regius Professor of Medicine at the University of Oxford from 1969 to 1979, now Professor Emeritus. He was Chairman of the Adverse Reaction Sub-Committee, Committee on Safety of Medicines, from 1970 to 1977 and has been Honorary Consultant, Imperial Cancer Research Fund Cancer Studies Unit, Radcliffe Infirmary, Oxford, since 1983. See Darby S C, Rizza C R, Doll R, Spooner R J, Stratton I M, Thakrar B. (1989) Incidence of AIDS and excess mortality associated with HIV in haemophiliacs in the United Kingdom: report on behalf of the directors of haemophilia centres in the United Kingdom. *British Medical Journal* **298**: 1064–1068. Darby S C, Doll R, Thakrar B, Rizza C R, Cox D R. (1990) Time from infection with HIV to onset of AIDS in patients with haemophilia in the UK. *Statistics in Medicine* **9**: 681–689.

<sup>201</sup> Professor Peter Duesberg, a Californian molecular biologist, claimed no connection between HIV and AIDS. See for example Duesberg P. (1988) HIV is not the cause of AIDS. *Science* **241**: 514, 417. *idem* (1994) Infectious AIDS – stretching the germ theory beyond its limits. *International Archives of Allergy and Immunology* **103**: 118–127. See also Berridge V. (1996) ‘Orthodoxy and fringe’: the anti-AIDS alliance, *op. cit.* note 90 above, 231–251.

<sup>202</sup> See Darby S C, Ewart D W, Giangrande P L F, Dolin P J, Spooner J D, Rizza C R. (1995) Mortality before and after HIV infection in the complete UK population of haemophiliacs. *Nature* **377**: 79–82.

## Haemophilia: Recent history

RIZZA: Don't let us assume that recombinant is perfectly safe. That is the next step. You mustn't assume that. That will take 20 years of work, or ten years to see the fallout. I hope it is perfectly safe, but you can't assume that.

Dr David Tyrrell:<sup>203</sup> I would like to mention one other group who were involved, a group with whom I sat, namely the Biological Products Subcommittee of the Committee on Safety of Medicines<sup>204</sup> and its predecessors. I always felt we were sitting in a rather hot seat in respect of the successive applications which various manufacturers made for products derived from blood. I think it is important to realize that from the very beginning people knew that they were dealing with a gamble. Blood transfusion began as we have heard in the 1930s and 1940s and that revealed the presence of hepatitis viruses in blood. We knew also that although you could do some biochemistry, there was no way of ensuring that they wouldn't be there in the product. Therefore there is an aphorism used by people in this area, saying that the one way of making a non-infectious product is to start with something that is non-infectious. So, if you want to make a product that you are sure is non-infectious the only place you know that you can find your product is in blood, that means you don't make the product! As we were aware of this, it was part of the documentation that every ampoule should have a warning that there was a risk of infection. It was up to us to evaluate how the product had been made (which would include its source, its processing and so on), and the physician who used it to decide whether there was more benefit to the patient to have this product or not to have it and receive some other form of management. The succession of catastrophes as you described them parallel the series of advances in virology. Once, as you said, we were worried about hepatitis B, but after some very hard and very good work a way of testing for hepatitis B was discovered,<sup>205</sup> so it was removed from the initial starting material. The same thing happened over hepatitis A, then it happened over hepatitis non-A, non-B, now called hepatitis C. I am recalling this because people have said that the manufacturers didn't care. I have heard this said in emotional broadcasts, 'They didn't bother about the fact that they might kill my child or whoever'. I think it is important to

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<sup>203</sup> Dr David Tyrrell CBE FRCP FRCPath FRS (b. 1925) was a member of the scientific staff of the MRC Common Cold Unit at Salisbury from 1957 and its Director from 1982 until his retirement in 1990. He was Chairman of the Spongiform Encephalopathy Advisory Committee (SEAC), from February 1989 until 1995.

<sup>204</sup> The Committee on Safety of Medicines (CSM) was created by the Medicines Act 1968 with similar functions to the preceding Committee on Safety of Drugs, which operated from January 1964 to September 1971, when the new Committee started. Along with the Committee on Veterinary Products, it advises the Licensing Authority. See Tansey E M, Reynolds L A. (eds) (1997) *The Committee on Safety of Drugs*. In *Wellcome Witnesses to Twentieth Century Medicine*. vol. 1. London: The Wellcome Trust, 103–135.

<sup>205</sup> *op. cit.* note 181 above.



sometimes try and see it as a necessary corollary of the way science actually works. As somebody said we actually do not go forward like a *Horizon* programme suggests, with a hypothesis that is followed by a neat series of experiments all of which build up to a tidy conclusion. We stumble forward, and this is part of the stumbling; in the stumbling process we can do good on the way and it's a matter of the art of medicine (which hasn't gone away I am sure) to try and do the good and minimize the harm. But the aphorism which I mentioned before still applies and supports what you have just said about recombinant products. We know we can make recombinants in a bottle or a tube which doesn't contain an infectious virus and if you want a non-infectious product in the end, that must be a better place to start than one which is bound to contain at some stage some infectivity.

Dr Angela Dike:<sup>206</sup> I worked at the Oxford Blood Transfusion Centre for the last 19 years and what I wanted to say complements the previous speaker. I would like to fill in a gap between the discovery of viruses in blood, and the leap to the demand for recombinant plasma products. During this interval the National Blood Transfusion Service made rapid progress towards improving the safety of blood transfusion, by introducing a succession of increasingly sensitive laboratory tests for the presence of hepatitis viruses and HIV in individual blood donations, and by progressing towards very searching questioning of would-be blood donors so as to exclude any with obvious infection risks, so that blood transfusion now is considerably safer than it was in the 1970s.<sup>207</sup>

Jones: I think that the last two speakers are obviously absolutely right and perhaps it's what Christine said before: that haemophilia and what has happened to people with haemophilia as a result of a viral infection has been a spur to a lot of science. It was probably individual donor testing that made blood safer rather than any of the early anti-HIV tests and the treatment of the blood products themselves. I take what you [Tyrrell] are saying about the Committee on Safety of Medicines,<sup>208</sup> but still blood products in this country that are

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<sup>206</sup> Dr Angela Dike FRCPATH (b. 1936) joined the Oxford Haemophilia Centre in 1966 as a medical registrar, when Rosemary Biggs and Gwyn Macfarlane were still working there, and where she met Ross (see note 177 above), her husband. She became an Associate Specialist at the Oxford Blood Transfusion Centre from 1977 to 1996 and is now retired.

<sup>207</sup> Dr Angela Dike wrote: 'The risk of transmitting hepatitis B, hepatitis C or HIV in an individual blood donation is now of the order 1 in 500 000. If plasma products were now made from small pools they would, of course, be much safer than the products being made nowadays from pools of 5000 or more individual blood donations.' Letter to Dr Daphne Christie, 4 July 1998.

<sup>208</sup> *op. cit.* note 204 above.

## Haemophilia: Recent history

imported are not labelled with their country of origin. When I buy fishfingers from Sainsbury's, I know where they have come from, and I know where my honey comes from, but I don't know where blood products come from. I also know that as well as hepatitis B, manufacturers knowingly imported blood products which were known to be HIV positive. I also know that within the European Community, and I have documentary evidence, there has been re-labelling of blood products, unknown to the Committee on Safety of Medicines. These things go on whenever you've got a product which is being sold for profit and they are bound to happen, we have to say that they happen, and it's our duty to try to stop them happening. We are involved with this very much in the World Federation of Hemophilia in the developing world with the companies at this moment, because we rely on the companies for the treatment of haemophilia. We have to work with them and the best way of working with them is to be open and honest and work towards a safe product. So I take everything you say from the Committee on Safety of Medicines, but the background of it is again what I refer to as secrecy. It's the difficulty of being at the sharp end and facing a family and somebody with haemophilia with the knowledge that things have gone wrong in the past, and not being completely up to date with the Committee on Safety of Medicines, perhaps for very legitimate reasons, for commercial secrecy reasons at the same time.

Lee: We can't leave this room tonight without discussing the history of recombinant and I am looking at Professor Tuddenham who, as many people will know, was involved in the purification of factor VIII that made this possible. Ted could you just give us a little bit of the insight. Why did you start purifying factor VIII?

Tuddenham: I began my career in pathology in 1969 in Liverpool where I was an SHO [senior house officer] on a pathology rotation. One of the duties was to treat the haemophiliacs under David Weatherall's<sup>209</sup> care. This involved going down to what was called the tropical ward then, which was part of that wonderful Victorian building that's now all boarded up in central Liverpool, and filling out bag, after bag, after bag of cryoprecipitate, drawing it up in syringes and injecting it very slowly and I found this a terribly primitive,

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<sup>209</sup> Professor Sir David Weatherall Kt FRCP FRCPath FRS is Regius Professor of Medicine at the University of Oxford, since 1992, Honorary Director of the MRC Molecular Haematology Unit, since 1980 and a Wellcome Trust Governor since 1990. He was Nuffield Professor of Clinical Medicine at the University of Oxford from 1974 to 1992 and Fellow of Magdalen College, Oxford, from 1974 to 1992, Emeritus Professor since 1992. He has been President of the British Society for Haematology since 1980 and the International Society of Haematology, since 1992.

intriguing process. I started talking to haemophiliacs. We had one patient who didn't respond at all and I went along to the lab and tried to sort it out with Alan Smith, the technician, and we came to the conclusion that there had to be an inhibitor, so it sort of sparked off my interest in haemophilia. Then I got a job in Cardiff with Arthur Bloom<sup>210</sup> and that really was what got me launched on the serious study of blood coagulation. That was 1971. At that time there were a lot of confusing ideas around as to the nature of haemophilia and von Willebrand's disease, recognized as a separate and distinct genetic entity, and there were rival theories which were really quite hotly contested in the literature.<sup>211</sup> One idea was that there was just one molecule of factor VIII which was also deficient in von Willebrand's disease, and a biochemist called McKee in the States refused to be convinced that you could in any way separate the von Willebrand property, the platelet adhesion-promoting property, from the coagulation-promoting property. At one point if you said that they were in any way separable you couldn't actually get the thing published in either the *Journal of Biological Chemistry* or the *Journal of Clinical Investigation* which I presumed was because he was a reviewer. A great advance, as has already been mentioned, was made in 1971 by Zimmerman, Ratnoff (the other proposer of a cascade hypothesis) and Powell who had raised an antibody that detected a line in the plasma of severe haemophiliacs, but no line<sup>212</sup> in the plasma of a severe von Willebrand's disease patient, which they called factor VIII-related antigen.<sup>213</sup> There were various names floating around for this, including antihemophilic factor antigen, while the coagulation-promoting activity was also called various things.

When I arrived in Cardiff, Arthur Bloom had just started putting together all these differing and confusing biochemical, immunological and genetic results. He called us into his office one morning in 1972 to give us the benefit of his way of explaining all of this. He said there had to be a high molecular weight protein that's deficient in the von Willebrand's disease and a low

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<sup>210</sup> Professor Arthur L Bloom (1930–1992) was one of the first to establish factor VIII and von Willebrand's factor as separate molecular entities. He was awarded a Personal Chair in Haematology in Cardiff in 1976 and was a past President of the British Society of Haematology and of the British and International Societies of Haemostasis and Thrombosis. He was Chairman of the United Kingdom Haemophilia Centre Directors Organization from 1979 to 1985.

<sup>211</sup> For example McKee maintained that the two activities – antihemophilic and platelet adhesive – are properties of one molecule. McKee P A. (1981) Observations on structure function relationships of human antihemophilic/von Willebrand factor protein. *Annals of the New York Academy of Sciences* 370: 210–226.

<sup>212</sup> See note 12 above.

<sup>213</sup> Zimmerman T S, Ratnoff O D, Powell A E. (1971) Immunologic differentiation of classic hemophilia (factor VIII deficiency) and von Willebrand's disease. *Journal of Clinical Investigation* 50: 244–254. Kernoff P B, Rizza C R. (1973) Factor-VIII-related antigen in female haemophilia. *Lancet* ii: 734.

## Haemophilia: Recent history

molecular weight protein deficient in haemophilia A that's coded on the X chromosome. They are associated together in plasma and you can separate them, as had been shown earlier by Owen and Wagner.<sup>214</sup> A high molecular weight protein would be involved in platelet adhesion, but also in supporting factor VIII in the circulation. This was to explain why, if you infused plasma or factor VIII concentrate into a patient with von Willebrand's disease there appeared in the circulation more factor VIII activity than you had infused in the first place.

The other thing he did that got me absolutely hooked on biochemical coagulation, was he paid for me to go to a meeting of the International Society of Thrombosis and Haemostasis in Vienna in 1973. At that meeting Stephan Magnusson announced the complete primary amino-acid sequence of bovine prothrombin.<sup>215</sup> I thought, 'Right, I want to get the complete amino-acid sequence of factor VIII'. It took another 12 years, but that is what originally inspired me. I also had the privilege of having a waltz in Vienna with Katharine Dormandy, who became significant later in my life. I also bumped into Rosemary Biggs in the street when I'd got lost and asked her the way to the conference centre and she gave me directions. As far as I can remember that was the first and last time that I had any kind of interaction, social or scientific, with the research group in Oxford.

In 1976 I had the opportunity to go to the States after I had completed my training, got the various bits of paper, and Arthur Bloom got me a job with Leon Hoyer who was the other most prominent researcher on factor VIII at that time.<sup>216</sup> He had started on separating factor VIII from von Willebrand's factor and I spent two very happy years there. We had an antibody to the von Willebrand's factor, which enabled us to grab the whole complex out of plasma, and then we could elute factor VIII with, as it happened, 0.24 M calcium chloride, which was free of von Willebrand's factor, and we were able to start doing some biochemical studies on that. We published that data,<sup>217</sup> then

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<sup>214</sup> See for example Hurt J P, Wagner R H, Brinkhous K M. (1966) Human antihemophilic factor (AHF) purification: a comparison of two procedures. *Thrombosis et Diathesis Haemorrhagica* 15: 327–337. Wagner R H. (1968) Recommendations of the subcommittee on human factor VIII (AHF) and factor IX (PTC) preparations. *ibid.* 35: 235–237.

<sup>215</sup> Magnusson S, Sottrup-Jensen L, Claeyss H, Zajel M, Patersen T E. (1975) Complete primary structure of prothrombin. Partial primary structures of plasminogen and hirudin. *Thrombosis et Diathesis Haemorrhagica* 34: 562–563.

<sup>216</sup> See for example Hoyer L W, DeLos Santos F R P and Hoyer J R. (1973) Antihemophilic factor antigen – localization in endothelial cells by immunofluorescent microscopy. *Journal of Clinical Investigation* 52: 2737–2744. Hoyer L W. (1975) Factor VIII subunits. *Annals of the New York Academy of Sciences* 240: 84–94.

<sup>217</sup> Tuddenham E G, Trabold N C, Collins J A, Hoyer L W. (1979) The properties of factor VIII coagulant activity proposed by immunoabsorbant chromatography. *Journal of Laboratory and Clinical Medicine* 93: 40–53.

I came back to the Royal Free and set up a small lab to start trying to do this on a larger scale. We did have support from the MRC towards developing monoclonal antibodies and these were absolutely key. Over the next three years, especially with the help of Alison Goodall, we got monoclonal antibodies to factor IX which were the first monoclonals to a clotting factor, to factor VII and to factor VIII, and I remember talking to the head of the transfusion service at Elstree during that period, suggesting to him that the future of high purity for blood coagulation factors would be monoclonal purification. For various reasons, which we haven't got time to go into, they didn't get taken up by the transfusion service here. It is now, of course, used by all commercial laboratory concerns for high-purity fractionation.

In our efforts to purify factor VIII we worked with Speywood;<sup>218</sup> David Heath ran Speywood in Wrexham and he'd been developing a method of making pig factor VIII which would be free of the platelet-clumping activity which Charles Rizza referred to earlier, and I was very interested in his story of patients seeing stars. When you purify pig factor VIII you also get pig von Willebrand's factor and that directly aggregates human platelets, so to get a good product, you need to get rid of that. Something that Alan Johnson,<sup>219</sup> who was also mentioned earlier, had developed was a process for purifying factor VIII, human factor VIII he was working with, which would get rid of the von Willebrand's factor and give you mainly factor VIII.<sup>220</sup> The problem with dissolving the early concentrates was that they were actually a heavy cake of fibrinogen and fibronectin with an extremely light contamination of factor VIII, more or less just sort of a little bit of a dirty scum on the main cake of stuff. So getting rid of all that was very important. We formed a collaboration with Speywood to have a major go at purifying factor VIII, which we achieved by 1982, and went to a congress in San Diego where we announced that.<sup>221</sup> We got talking to Genentech Inc. and as they say the rest is history; we purified about 20 milligrams of factor VIII from about 2000 litres of human blood, and that was sequenced and enabled the cloning and expression of recombinant factor VIII. Over this period I have always felt that what we should be aiming

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<sup>218</sup> Speywood Laboratories (Wrexham, UK) prepared a highly purified antigen using Maws porcine factor VIII material. See note 53 above.

<sup>219</sup> See note 35 above.

<sup>220</sup> Tuddenham E G, Lane R S, Rotblat F, Johnson A J, Snape T J, Middleton S, Kernoff P B. (1982) Response to infusions of polyelectrolyte fractionated human factor VIII concentrate in human haemophilia A and von Willebrand's disease. *British Journal of Haematology* 52: 259–267.

<sup>221</sup> These conference proceedings were not published. Results were published later in 1985, see Rotblat F, O'Brien D P, O'Brien F J, Goodall A H, Tuddenham E G D. (1985) Purification of human factor VIII:c and its characterisation by Western blotting using monoclonal antibodies. *Biochemistry* 24: 4294–4300.

## Haemophilia: Recent history

at is the highest level of biochemical purification, first to produce high-level purity concentrates that are free not just of viruses but of the other unwanted side-effects of infusing very impure concentrates. Secondly, to lead into the era of molecular biology, because the purpose of sequencing factor VIII was to enable its cloning by the classical biochemical route and to enable synthesis.

I heard Charles Rizza mention that it has yet to be proved that the recombinant material is completely safe and, of course, I would agree with that. Everything that we give to a patient has to be subjected to the most intense scrutiny and I think I would say, and others might agree, that the trials of the recombinant material have been more intensively scrutinized and more extensively followed than the introduction of any other blood products have been in the past. Of course, we have had the benefit of hindsight, learning from the problems of introducing other concentrates that weren't sufficiently closely followed at the time. Up to this point, I am not aware of any serious or indeed any complication of using recombinant material for treating haemophiliacs, other than the development of inhibitor antibodies,<sup>222</sup> another large issue we don't have time to go into, but up to this point they appear to have a perfect safety record. The only down side that I can see is that we are still using plasma-derived albumin as the protein for the carrier for these concentrates, the recombinant concentrates, but shortly that will surely be replaced with recombinant albumin.

Lee: It's interesting that the first patient in the UK who had recombinant, I think, was in 1988. We at the Royal Free continued treating a second patient until 1994 when it was licensed. Promptly when it became licensed that patient had to be treated with plasma-derived concentrate, because it was too expensive to continue giving him the recombinant. It's with that really in mind that I thought we should end with a note of where we are at now. Peter Jones alluded to the fact that the UK Haemophilia Centre directors have guidelines<sup>223</sup> which recommend that patients should be treated with recombinant factor VIII which is licensed now, and recombinant factor IX when it becomes licensed and we are reasonable people and we realize that there isn't a bottomless pit, so we've suggested that children should be the priority. In this country, I think there are about 600 children with severe haemophilia A and half of them are being

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<sup>222</sup> Nilsson I M, Berntorp E, Zettervall O. (1988) Induction of immune tolerance in patients with hemophilia and antibodies to factor VIII by combined treatment with intravenous IgG, cyclophosphamide and factor VIII. *New England Journal of Medicine* 318: 947–950. Hoyer L W. (1995) Factor VIII inhibitors. *Current Opinion in Hematology* 2: 365–371.

<sup>223</sup> United Kingdom Haemophilia Centre Directors Organization Executive Committee. (1997) Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders. *Haemophilia* 3: 63–77.

treated with recombinant as of now, and the other half aren't for reasons of economics. I thought it would be helpful to really tie up the issues of cost and I want to refer again to Dr Biggs's interview.<sup>224</sup> She talked about the factor VIII, this was in the 1970s, being on the pharmacy budget and she said, 'Yes it was, we used more than half the area's money for medicine, just on haemophilic patients'. At the Royal Free we spend £10 million a year on haemophilia and I think the total hospital budget is £124 million pounds, so it's a tenth of the hospital's budget.

Before I hand over to Clifford [Welch] to talk about this issue, I think we have to remind Ted that some of his research, since we are in the business of reminding who's helped in this business, was actually funded by The Katharine Dormandy Trust.<sup>225</sup>

In the summer, Clifford, who doesn't mind me sharing with you that he has mild haemophilia, had a terrible bout of cholecystitis. He was pretty close to going, and he had his gall bladder removed using continuous infusion of recombinant factor VIII, so I think he understands where we have been and where we have arrived at, and he certainly understands the problems of the economics of delivering this care in 1998.

Welch: I'll be very, very brief because time is getting on, but to me the last 65, 70 years, have been quite extraordinary. I trained as a scientist and therefore, although I have no special knowledge of medicine, I do have some knowledge of research. To see what an extraordinary transformation has occurred from the time when I remember going, as I mentioned earlier, to Bart's with one of my brothers and my mother, to today. This boy was practically at death's door, and I vividly recall the expression on the faces of the house surgeon and physicians who were trying to deal with a situation totally outside their experience. They didn't know what to do. Today we have these extraordinary developments. Despite the scourge of HIV and hepatitis C, the fact is that we can now expect to live normal lives as haemophiliacs, to grow up, to have children, and to see our children grow up as normal children too and 30, 40, 50 years ago that was certainly not the case.

As a result of all that Katharine Dormandy achieved, she, like Gwyn Macfarlane, had a profound influence upon my life and enthused me enormously, by virtue of the unwavering dedication she gave to her patients. I

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<sup>224</sup> *op. cit.* note 2 above.

<sup>225</sup> Dr Katharine Dormandy, Director of the Centre for Haemophilia and Haemostasis, set up the Trust Fund in 1971; see biographical note 111 above.

## Haemophilia: Recent history

felt that one had got to try to put something back. And one of the things that we have been trying to do with Katharine Dormandy's Trust down the years is to make sure that her objective of searching for a cure for haemophilia and relieving the distress caused by this inherited disease should be prosecuted with all the vigour that we can.

It was in 1996 at the Royal Free that we first realized that the other side of the coin of this great success in treating haemophilia was the fact that it was costing so much money. Peter Jones mentioned before tea that haemophilia is 'a bloody nuisance to everybody'. And indeed it is, and it has become an increasing nuisance in the sense that whilst recombinant factor VIII should obviously be the treatment of choice, particularly for children, so that they grow up without running the risk, or too great a risk, of other side-effects. So is this refined treatment that much more expensive? The fact remains that we were finding at the Royal Free in 1996 that we had patients side by side, one boy being treated with recombinant material and the boy next door not, simply because some of the purchasing authorities buying the services in the hospital were prepared to pay the extra cost and some were not. And when one looks at the enormous cost and the ever-increasing demand for money within the National Health Service, one realizes what a dreadful dilemma this is.

What we did at the Royal Free in 1996 was to set up a task force, initiated by Martin Else, the Chief Executive of the hospital, which for the first time brought together all of the different disciplines to address the problem. In the past the Haemophilia Centre, important though it is, is when seen against the totality of the work going on in the hospital, a very small unit in a great enterprise. It was the first time that we brought together the legal people, the purchasing officers, all the different experts who were responsible in their individual way for moving things forward and we said to them, 'How are we going to persuade the funding bodies to give us the money, what techniques can we use, ranging from blackmail to appeal, to bursting into tears if you like, and secondly what proposals could we put forward to deal with this problem which was clearly going to get worse year by year and which was going to get ever more expensive'. The first part of the problem was successively resolved in the sense that in 1997 all of the young children at the Royal Free were on recombinant treatment. What's going to happen in 1998 and 1999, heaven knows! Possibly we shall still be having these arguments with the individual purchasing trusts as long as the concept that 'money follows patients' exists. But the more important outcome was that we were able to develop a detailed report to propose a national specialist commissioning advisory group to take this problem over as a national problem rather than it being regarded as a local problem for individual health authorities. And that report derived precisely



from the fact that Katharine Dormandy's Trust gave us the opportunity, and the authority to get on with the job. I hope that the effect will be to lift this particular cost problem out of the domain of the individual purchasing trusts on to a more national basis. Whether that is a hope that has foundation remains to be seen, but I do very, very much pay tribute this afternoon to all of the people who have given so much to haemophiliacs, from Rosemary Biggs, Ethel Bidwell, Gwyn Macfarlane, Charles Rizza, Ted Tuddenham, Katharine Dormandy, Peter Kernoff, to all the other specialists in this area.

Lee: Has anybody got some final comments that they are burning to contribute? I would like then to thank everybody. I speak for myself and say I don't think I have spent such an interesting afternoon for many a long day. I think it has been absolutely fascinating, and I think we should all be very grateful to the people who have travelled for very long distances.

Tansey: On behalf of the Wellcome Trust, I would like to thank you all for participating in this afternoon's seminar. Speaking as a historian who came here knowing very little about haemophilia, it has been a great privilege listening to the accounts and I am convinced that the edited transcript of this meeting will be a valuable resource for future historians who will want to know about haemophilia at the end of the twentieth century. May I add my particular thanks to our Chairman, Christine Lee. We actually set this in motion only four months ago and had to put this meeting into our programme at very short notice. The driving force behind this meeting has come from Christine and I hope you will join me in thanking her.

APPENDIX

CLASSICAL THEORY OF BLOOD CLOTTING<sup>1</sup>

A three-stage process involving conversion of fibrinogen into fibrin following thrombin formation.

1. Platelet breakdown → Thromboplastin  
Tissue damage → Thromboplastin
2. Prothrombin + Thromboplastin + Ca<sup>2+</sup> → Thrombin
3. Fibrinogen + Thrombin → Fibrin

A PRESENT DAY THEORY<sup>2</sup>

**Intrinsic pathway**

Kallikrein + foreign surface (collagen, platelets)

XII → Activated XII

XI → Activated XI

IX → Activated IX + VIII + platelet phospholipid + Ca<sup>2+</sup>

X → Activated X

Activated X + V + platelet phospholipid + Ca<sup>2+</sup>

II (prothrombin) → Activated II (prothrombin)

I (Fibrinogen) → Fibrin

**Extrinsic pathway**

VII + III (Tissue thromboplastin)

**Common pathway**

XIII

Activated XIII

Fibrin → Fibrin clot

BLOOD COAGULATION FACTORS

Factor	Synonyms
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin
IV	Calcium
V	Labile factor, proaccelerin
VII	Stable factor, proconvertin
VIII	Antihaemophilic globulin, antihaemophilic factor A
IX	Christmas factor, antihaemophilic factor B
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin-stabilizing factor

<sup>1</sup>Adapted from Morawitz P. (1905) The chemistry of blood coagulation. *Ergebnisse der Physiologie* 4: 307-422.

<sup>2</sup>See for example O'Neil R. (1988) The blood. In Emslie-Smith D, Paterson C R, Scratcherd T, Read N W. (eds) *Textbook of Physiology*. Edinburgh: Churchill Livingstone, 35-36.

## GLOSSARY

- Acquired immune deficiency syndrome (AIDS)** – A condition linked to the retrovirus, **human immunodeficiency virus** (HIV-1).
- Anaphylactic reaction** – An acute allergic response following injection of, or exposure to, a foreign protein or other substance, caused by the release of histamine or another vasoreactive substance.
- Antihaemophilic globulin (AHG)** – See **factor VIII**.
- Arthropathy** – The abnormality seen in joints of **haemophiliacs** after repeated episodes of spontaneous bleeding (e.g. secondary gross degeneration of the articular cartilage and bone).
- Bethesda unit** – A unit used in the measurement of **inhibitors** arising in haemophiliacs (see note 83).
- Bleeding time** – The time during which a small puncture or incised wound in the skin (made under controlled conditions) continues to bleed, normally less than ten minutes.
- Calcium-clotting time** – The time for coagulation to occur when calcium chloride is added slowly to a mixture of saline and citrated plasma. With normal plasma the clotting time ranges from 90 to 250 seconds.
- Christmas disease** – See **haemophilia B**.
- Christmas factor** – See **factor IX**.
- Clotting time** – A test of the clotting mechanism and the amount of thromboplastin formed.
- Creutzfeldt–Jakob disease (CJD)** – A disease in which spongiform encephalopathy virus is implicated.
- Cross-correction** – The haemophilic patient's plasma corrects, and is corrected by, the plasma of a known haemophiliac (see note 16).
- Cryoprecipitate** – The plasma fraction that is obtained by freezing ( $-20^{\circ}\text{C}$ ) and then thawing ( $4^{\circ}\text{C}$ ) normal human plasma. When frozen plasma is thawed slowly, the last proteins to dissolve include **fibrinogen** and **factor VIII**, and these make up the cryoprecipitate (see note 24).
- DDAVP** – 1-deamino-8-D-arginine vasopressin (**desmopressin**). A synthetic analogue of the antidiuretic hormone L-arginine vasopressin, raises **factor VIII** levels when infused into healthy volunteers.
- Desmopressin** – See **DDAVP**.
- Extrinsic (coagulation cascade) pathway** – The pathway where tissue factors are required from outside the plasma in the process of coagulation (see Appendix).
- Factor VII** – A plasma coagulation factor intermediate in the clotting cascade (see Appendix). It normally circulates in an inactive form.
- Factor VIIa – Activated factor VII.**  
Contact with tissue extracts (released by tissue damage) converts factor VII to an active form, factor VIIa. (The pathway is different from that involving **factor VIII**, so factor VIIa can lead to clot formation in the absence of **factor VIII**.)
- Factor VIII (antihaemophilic globulin (AHG))** – A plasma coagulation factor whose inherited deficiency is responsible for classic **haemophilia** (lack of **factor VIII:c**) or **von Willebrand's disease**.
- Factor VIII:c** – The coagulant moiety of the **factor VIII** complex, primarily deficient in classic **haemophilia**.
- Factor IX (Christmas factor)** – A plasma coagulation factor that may be deficient on an inherited basis (**haemophilia B**).
- Fibrinogen** – The precursor of **fibrin** in clot formation.

**Haemarthroses** – Joint bleeds.

**Haematuria** – Excretion of urine containing blood.

**Haemophilia** – A hereditary bleeding disorder which affects the clotting of blood (see **haemophilias A and B**).

**Haemophilia A\*** – **Factor VIII** deficiency.

**Haemophilia B\*** – **Factor IX** deficiency (**Christmas disease**).

**Haemostasis** – The arrest of haemorrhage.

**Hepatitis** – Inflammation of the liver.

**Human immunodeficiency virus (HIV-1)**  
– The retrovirus linked to **AIDS**, formerly **AIDS-related virus**.

**Inhibitor patients** – Individuals who raise antibodies to **factor VIII**.

**Intrinsic (coagulation cascade) pathway** – Intrinsic to plasma since all factors can be generated from plasma (see Appendix).

**Kallikrein** – The enzyme that releases bradykinin from the plasma protein kininogen.

**Platelet** – Platelets are present in large numbers in blood and play an important role in **blood clotting**. Properties of adhesion and aggregation allow **haemostasis** when vascular endothelium is damaged, and also permit clotting (see Appendix).

**Port-a-Cath** – A device used when treatment into a vein is needed regularly. One end of the catheter lies in the right atrium of the heart. The other end, which provides access for injection of treatment, is either implanted under the skin of the chest wall or is taped to it.

**Prothrombin** – A plasma protein yielding **thrombin** following activation by prothrombinase.

**Radiosynovectomy** – A non-operative technique of injecting a radioactive isotope into the joint (see **synoviorthrosis**).

**Synovectomy** – The excision of the synovial membrane that lines a joint or tendon sheath, used to treat chronic haemophilic **arthropathy**. It reduces but does not abolish further bleeds as it is rarely complete.

**Synoviorthrosis** – The technique of using isotopes (e.g. radiocolloids) to produce fibrosis of the synovial membrane and hence reduce bleeding and subsequent damage.

**Thrombasthenia** – An autosomally inherited haemorrhagic disease with unique abnormalities of **platelet** function.

**Thrombin** – A proteolytic enzyme which induces clotting by the conversion of **fibrinogen** to **fibrin**.

**Thrombocytopenia** – A deficiency of **platelets** often associated with haemorrhage.

**Thromboplastin generation test** – A test for the efficiency with which thromboplastic activity appears in a mixture of coagulating blood components.

**von Willebrand's disease\*** – An inherited bleeding disease resulting from a deficiency or abnormality of the von Willebrand factor part of the plasma **coagulation factor VIII** complex. Clinical features include prolonged **bleeding time** and reduced **platelet** adhesiveness.

\*Haemophilias A and B are inherited in a sex-linked manner, while von Willebrand's disease is inherited as an autosomal dominant condition.

## INDEX: SUBJECT

- acid-citrate-dextrose (ACD), 29  
 accelerated degradation tests, 20, 21  
 acquired immunodeficiency syndrome,  
*see* AIDS  
 adrenaline, 10–11  
 AHG, *see* antihæmophilic globulin  
 AIDS, 64, 67, 80, *see also* human  
 immunodeficiency virus  
   as ‘bystander effect’, 68  
   first cases in hæmophiliacs, 26  
   litigation, 63, 65–66  
 albumin, 30, 75  
 allergic reactions, 33, 80  
 amputation, 18–19  
 anaphylactic reactions, 14, 16, 80  
 animal factor VIII concentrates, 13–15, 33,  
*see also* bovine antihæmophilic  
 globulin  
 antenatal diagnosis, 26, 27  
 anticoagulants, 29  
 antidiuretic hormone, 11  
 antifibrinolytic drugs, 7  
 antihæmophilic globulin (AHG), 43, 44,  
 80, *see also* factor VIII  
   animal, preparation, 48–51  
   bovine, *see* bovine  
   antihæmophilic globulin  
   discovery, 4–5  
   human, *see* factor VIII  
   porcine, 7, 14, 74  
 arthritis, hæmophilic, 36  
 arthropathy, hæmophilic, 80, 81  
 Australian antigen, 62
- Barcelona, Public Health  
 Department, 23  
 Baxter (UK), 25  
 Bethesda unit, 25, 80  
 bleeding  
   abnormal, 4  
   acute episodes, 6, 33, 35, 40  
   post-traumatic, 5  
   time, 6, 80, 81  
   tissue destruction, 17
- blood, *see also* plasma  
   bags, 25  
   coagulation, *see* coagulation, blood  
   donors, 24–25, 55–56, 70  
   products, safety, 69–71  
 Blood Products Laboratory, Elstree,  
 19, 29, 30, 38, 59, 60  
   blood factor purification, 73–74  
   plasma fractionation methods, 19  
 blood transfusion  
   early, 6–7, 33, 40  
   equipment, 28–29, 32–33  
   safety, 69–71  
   services, origins, 23  
 Blood Transfusion Service, National, 23  
   availability of blood products,  
   24, 25, 33, 35–36, 38, 60  
   safety of blood transfusion, 27, 70  
 Booth Hall Children’s Hospital,  
 Manchester, 22, 23  
 bovine antihæmophilic globulin  
 (factor VIII), 7, 12  
   clinical use, 14–16, 17  
   preparation, 13–14, 61  
   standards, 20–21  
 brain, thromboplastic activity, 43–44  
 Bristol Transfusion Centre, 30  
 British Haemophilia Society, 7  
*British Medical Journal*, 45–47  
 British Working Standard, 21
- calcium, 44  
 calcium-clotting time, 80  
 carriers, hæmophilia, 4  
 catch-22, 64  
 catheters, *see* venous; Port-a-Caths  
 centrifuges, 13  
 cerebral hæmorrhage, 24  
 Chapel Hill, North Carolina,  
 United States, 8  
 children, 22  
   blood transfusions, 33, 35  
   HIV-positive, 27–28

## Index: Subject

- home treatment, 37
- hospitals, 27, 37
- recombinant factor VIII therapy, 74, 77
- self-treatment, 39
- Christmas disease (factor IX deficiency), 11–12, 46–47, 80, 81
  - discovery, 6, 8, 9–10, 44–45, 46
  - early treatment, 12
  - factor IX concentrate therapy, 18–19
  - origin of name, 46, 47
- Christmas factor, *see* factor IX
- chromosomes, autosomal, 80
- Churchill Hospital, Oxford, 12, 32, 61
- citrate-phosphate-dextrose with adenine (CPD-Ad), 29
- CJD, *see* Creutzfeldt–Jakob disease
- cloning, factor IX and VIII genes, 26, 74
- clotting
  - blood, *see* coagulation, blood
  - time, 5, 10, 80
- coagulation, blood, 43–44, 79
  - cascade hypothesis, 45
  - classical theory, 79
  - extrinsic pathway, 43, 79, 80
  - factors, 5, 79
  - intrinsic pathway, 43, 79, 81
- Cohn's fibrinogen fraction, 12
- colour blindness, 7
- Committee on Safety of Medicines, 69, 70–71
- concentrates, *see also* factor IX, concentrate; factor VIII, concentrate
  - availability, 25, 29–30, 33, 35, 36, 38
  - continuous infusions, 28–29
  - freeze-dried, 7, 20, 25, 34
  - heat treatment, 64
  - HIV contamination, 25, 30
  - home treatment, 34, 36
  - imported from USA, 25, 30, 36, 55–56, 63
  - manufacture, 53, 54
  - storage at home, 34, 35
  - viral contamination, 26, 28, 62–71
- coronary thrombosis, 42
- coumarin plasma/serum, 43, 44
- Creutzfeldt–Jakob disease (CJD), 28, 40, 66, 80
  - new variant (nvCJD), 63–64, 66
- Crookes Healthcare Ltd, 17
- cross-correction (mixing) experiments, 6, 8, 9–10, 44–45, 80
- cryoprecipitate, 62, 71, 80
- availability, 24, 25, 36
- discovery, 7, 35
- HIV contamination, 25
- home treatment, 33–34, 35, 36, 37, 39
- cystic fibrosis, 37
- cysts, haemophilic, 16–17, 32
- DDAVP (1-deamino-8-D-arginine vasopressin, desmopressin), 7, 10–11, 80
- dental extraction, 7, 14, 42
- Department of Health (and Social Security) (DHSS), 54, 64
  - availability of blood products and, 30, 59
  - Haemophilia Register, 60
  - HC-76/4, publication, 26
  - Health Services Guidelines (93/30), 28
  - MRC and, 59, 60
- desmopressin (DDAVP), 7, 10–11, 80
- developing countries, 57, 71
- diagnosis
  - antenatal, 26, 27
  - of haemophilia, 8–9, 10, 26–27
- drug users, 59
- economic aspects, haemophilia therapy, 35, 75–77
- Edgware Transfusion Centre, 21
- Edinburgh, 11, 59, 60, 62
- egg white, Timperley's, 41, 52, 53
- Elephant and Castle, Department of Health and Social Security, 59, 60
- Elstree, *see* Blood Products Laboratory, Elstree
- epistaxis (nose bleed), 43
- epsilon-aminocaproic acid, 7
- equipment, laboratory,
  - availability, 13, 47, 61
  - made of Meccano, 40, 41, 47
  - transfusion/infusion, 28–29, 32–33
- European countries, 36
- exercise, factor VIII levels after, 11
- extrinsic pathway, *see* coagulation, blood
- factor V (labile factor), 42, 44, 45, 79
- factor VII, 42–43, 44, 79, 80
  - activated (factor VIIa), 26, 80
  - recombinant, 28

- factor VIII, 79, 80, *see also*  
 antihaemophilic globulin  
 assays, 5, 20–22, 26, 45  
 concentrate, 7, 12–17, *see also* bovine  
 antihaemophilic globulin; porcine  
 antihaemophilic globulin  
 availability, 25, 29–30, 33, 38, 60  
 continuous infusion, 28–29  
 early clinical use, 14–16, 17, 24  
 freeze-dried, 7, 20, 25  
 human, 15, 16  
 initial preparation, 12–14, 44, 48–51, 61  
 manufacture, 15, 17, 53  
 solubility, 17  
 cryoprecipitate, *see* cryoprecipitate  
 DDAVP therapy and, 11  
 deficiency (haemophilia A), 75, 81  
 discovery, 4–5, 12  
 effects of adrenaline, 10–11  
 effects of exercise, 11  
 function, 45, 79  
 gene cloning, 26–27, 74  
 immunological detection, 5  
 inhibitors (antibodies), *see* inhibitors,  
 patients with  
 long-term stability, 21  
 purification, 71–74  
 recombinant, 28, 67, 74  
 availability, 62, 75  
 economic aspects, 75–77  
 guidelines on use, 74  
 safety, 68, 70  
 sequencing, 73, 74  
 standards, 5, 20–21  
 in von Willebrand's disease, 6, 81  
 von Willebrand's factor and, 72–73, 74
- factor VIII-related antigen, 72
- factor IX (Christmas factor), 79, 80  
 assays, 19, 20–21, 45  
 concentrate  
 first clinical use, 18–19  
 preparation, 19, 61  
 deficiency, *see* Christmas disease  
 gene cloning, 26  
 purification, 73  
 recombinant, 67, 75
- females  
 haemophilic, 4, 17  
 transmission of haemophilia, 4
- fetal blood sampling, 26
- fibrinogen, 44, 79, 80  
 factor VIII separation, 12, 61, 74  
 fraction, Cohn's, 12
- Food and Drug Administration (FDA), 63
- fractionation, plasma, *see* plasma,  
 fractionation
- France, 66
- freeze-dried concentrate, 7, 25, 34
- freezers, 34, 35
- gangrene, 13, 18, 19
- Genentech Inc., 74
- genetic counselling, 56
- Glasgow Royal Infirmary, 43
- Government, 57, 62  
 HIV infection and, 64–65  
 safety of blood products and,  
 30, 55–56, 67
- Great Ormond Street Hospital,  
 London, 22, 39
- gun shot wound, patient with, 14, 16
- haemarthroses, 4, 81
- haematologists, 20, 24, 26
- haematuria, 43, 81
- haemophilia, 81  
 A, 75, 81, *see also* factor VIII  
 B, *see* Christmas disease  
 care, 3–4, 22, 26, 38–39, 53  
 carriers, 4  
 diagnosis, 8–9, 10, 26–27  
 distinction of two types,  
 6, 8, 9–10, 44–45  
 epidemiology, 31  
 mild, 5, 7, 10–11, 40  
 origin of name, 4  
 treatment, *see* treatment of haemophilia  
 von Willebrand's disease and, 5–6,  
 72–73
- Haemophilia Centres, 6, 53, *see also*  
 United  
 Kingdom Haemophilia Centre  
 Directors Organization; Katharine  
 Dormandy Haemophilia Centre  
 annual returns, 53–54  
 comprehensive care, 38, 39  
 concentrate supplies, 38  
 Haemophilia Society and, 56  
 three-tier system, 26  
 two-tier system, 28

## Index: Subject

- Haemophilia Society, 23, 26, 47, 54–56, 58  
beginnings, 7, 22, 41, 54–55  
HIV infection and, 56, 65, 66  
lobbying function, 55–56, 65, 66  
Manchester meeting, 27  
premises, 54, 55  
haemorrhoid surgery, 19  
haemostasis, 41, 81  
Hammersmith Hospital, London,  
44, 45–46  
Health Services Guidelines (93/30), *see*  
Department of Health  
heart failure, 24, 35  
heat treatment, 64  
hepatitis, 21, 40, 56, 62–63, 81  
A, 28, 69, 81  
B, 62–63, 69, 70, 81  
C, 28, 63, 66, 69, 70, 81  
non-A, non-B, 63, 69  
prevention of transmission, 64  
hip fracture, 17  
HIV, *see* human immunodeficiency virus  
home treatment, 33–35, 36–38, 39, 63  
availability of supplies for, 35, 36  
concentrate storage, 34, 35  
resistance to, 36  
hospitals, children's, 27, 37  
human factor VIII concentrate, 15, 16  
human immunodeficiency virus (HIV),  
63–68, 81, *see also* AIDS  
contaminated blood products, 25, 30,  
70–71  
infection, 40, 67–68  
Haemophilia Society and, 56, 65, 66  
litigation, 63, 65–66  
recompense for, 65  
in Scotland, 59, 65  
surgery in, 30–31, 32  
-positive children, 27–28  
television advertisements, 27  
testing, 27, 70  
hypoprothromboplastinogenaemia, 47  
hypothalamic–pituitary axis, 11  
infusions, continuous, 28–29  
inhibitors, patients with, 25, 71, 75, 81  
factor VIIa therapy, 26, 28  
orthopaedic surgery, 32  
International Haemophilia Society, 7  
International Society of Thrombosis and  
Haemostasis Meeting, 73  
intrinsic pathway, *see* coagulation, blood  
Japan, 66  
jaundice, 67, *see also* hepatitis  
John Bell and Croyden, London, 40  
joint bleeds (haemarthroses), 4, 81  
kallikrein, 81  
Katharine Dormandy Haemophilia  
Centre, 34, 58  
Katharine Dormandy Trust, 76, 77  
labile factor, *see* factor V  
Lawn Road Hospital, Hampstead, 34, 58  
life expectancy, 31, 67  
Lister Institute, Elstree, 19, *see also* Blood  
Products Laboratory, Elstree  
litigation, for HIV infection, 63, 65–66  
Lord Mayor Treloar Hospital and  
College, Alton, Hampshire 67  
Macfarlane Trust, 3, 28, 65  
Manchester, 22, 23, 24–25, 27, 60  
Manchester Royal Infirmary (MRI), 23,  
24, 25, 37  
Maws & Son Ltd, 15, 17  
Meccano, *see* equipment  
Medical Research Council (MRC), 52, 53,  
58–60, 61, 62, 73  
Blood Coagulation Research Unit,  
Oxford, 12, 58, 61  
Blood Products Laboratory, Elstree, 29,  
59  
Blood Transfusion Research  
Committee, 58–59  
Central Workshops, 61  
Haemophilia Committee, 58  
Haemophilia Register, 59–60, 62  
Park Crescent headquarters, 59, 60  
Ministry of Health, 52, 53, *see also* DHSS  
monoclonal antibodies, 73–74  
MRC, *see* Medical Research Council  
National Blood Authority, 60  
National Blood Transfusion Service, *see*  
Blood Transfusion Service, National  
National Health Service, 52, 77  
National Institute for Medical Research,  
Biological Standards Division, 5, 20–21, 61  
needles, 28–29, 33



- New York Medical Center, 21  
 Newcastle, 35, 39  
 Norwich, patient from, 14, 16  
 nose bleed (epistaxis), 43  
 Nuffield Orthopaedic Hospital, Oxford, 3  
 nurse, haemophilia, 37–38  
 nvCJD, *see* new variant CJD
- orthopaedic surgery, elective, 31–32  
 osteomyelitis, 18  
 Oxford, 3, 9–10, 39, 53  
     blood coagulation studies, 41–42, 43, 44–45, 58, 61  
     Blood Transfusion Centre, 13, 33, 70  
     factor VIII concentrate, 13–15  
     Haemophilic Unit, 30, 31–32  
     referral of patients to, 17, 18–19
- parents  
     HIV-positive children, 27–28  
     home treatment and, 36, 37, 39  
     views of one, 38–40
- parvovirus, 26, 63
- patients, haemophilic, 22, *see also* children;  
     parents  
     independence, 39–40  
     life expectancy, 31, 67  
     plasma donation by, 8  
     recollections of, 40–41
- peptic ulceration, 15, 17
- plasma  
     cross-correction (mixing) experiments, 6, 8, 9–10, 44–45, 80  
     donation by haemophiliacs, 8  
     fractionation, 4–5, 12, 38  
     facilities, 30, 54, 59, 61, 62  
     methods, 19, 44  
     fresh-frozen, 24, 33, 35  
     snap-frozen, 24  
     supplies, 60
- plastics, 13, 15
- platelets, 43, 44, 81, *see also*  
     thrombocytopenia  
     clumping, 16, 72, 74
- porcine antihaemophilic globulin (AHG, factor VIII), 7, 14, 74
- Port-a-Caths, 28–29, 81
- pregnancy, termination, 26
- prothrombin, 43, 79, 81  
     sequencing, 73  
     time, 4, 42, 43
- Quick's one-stage prothrombin time test, 42
- Radcliffe Infirmary, Oxford, 3, 9, 61  
 radiosynovectomy, 29, 31, 81  
 recombinant products, *see also* factor VIII, recombinant  
     safety, 68, 70, 74–75  
 recompense, campaign for, 65  
 Red Cross, 23, 25  
 Register, Haemophilia, 59–60, 62  
 Registry, Haemophilia, 47, 53–54  
 rehabilitation, after orthopaedic surgery, 32
- Royal Free Hospital, London, 17, 22, 36–37, 39, 73, *see also* Lawn Road Hospital, Hampstead; Katharine Dormandy Haemophilia Centre  
     recombinant factor therapy, 75, 77
- Royal London Hospital, 17, 37–38
- Russell's viper venom (Stypven), 6, 39, 40
- St Bartholomew's Hospital (Bart's), London, 40, 41, 76  
 St Mary's Hospital, London, 29  
 St Thomas' Hospital, London, 4, 22  
 schooling, 37  
 Scotland, 59, 60, 62, 65  
 SEAC, *see* Spongiform Encephalopathy Advisory Group  
 sheep, 16  
 slaughterhouse, 13, 47  
 Spanish Civil War, 23  
 Speywood Laboratories, 74  
 spongiform encephalopathy, 63, *see also* Creutzfeldt–Jakob disease  
 Spongiform Encephalopathy Advisory Group (SEAC), 66, 69  
 standards, reference, 20–22, 25, 61  
     factor VIII, 5, 20–21  
 stars, seeing, 16, 74  
 sterilization, 14  
 Stypven, *see* Russell's viper venom
- surgery  
     elective orthopaedic, 31–32  
     HIV-infected patients, 30–31, 32  
     manufacture of factor VIII for, 15–16, 19  
     synovectomy, 29, 31, 81

## Index: Subject

- synoviorthrosis, 31, 81
- synovitis, chronic, 31
- syringes, 33
  
- termination of pregnancy, 26
- thrombasthenia, 44, 81
- thrombin, 4, 43, 44, 79, 81
- thrombocytopenia, 11, 16, 81
- thromboplastin, 44, 79
  - generation test, 6, 8–9, 43–44, 45, 46, 81
  - time, partial, 8
- thrombosis, 41, 42
- Timperley's egg white, 41, 52, 53
- tongue, bleeding, 46
- tooth extraction, 7, 14, 42
- transport, for disabled, 55
- travel, by patients, 39–40, 57
- treatment of haemophilia, *see also* surgery
  - cryoprecipitate, 24–25
  - early, 6–7, 12, 32–33, 39, 40–41, 52–53
  - economic aspects, 35, 75–77
  - factor IX concentrate, 18–19
  - factor VIII concentrate, 14–16, 17, 24
  - historical sequence, 28–29
  - home, *see* home treatment
  - mild disease, 10–11
  - recommended, 67, 75
  - resistance to, 35–36, 76
  - side-effects, 4, 62–71, 74
- Tuta (Australia), 25
  
- United Kingdom Haemophilia Centre Directors Organization (UKHCDO), 52–53, 62
  - beginnings, 28, 47, 52–53
  - guidelines on treatment, 75
  - HIV infection and, 64, 65–66
  - on safety of blood products, 67
- United States of America, 73
  - concentrates from, 25, 30, 36, 55–56, 63
  - diagnostic tests, 8
  
- vasopressin, 11
- venepuncture, 18, 43
- venous catheters, in-dwelling, 28–29
- Victoria, Queen of England, and haemophilia, 4
- viruses, *see also* human immunodeficiency virus
  - contamination of concentrates, 26, 28, 62–71
- volunteerism, 55, 56, 57
- von Willebrand's disease, 5–6, 23, 81
  - haemophilia and, 5–6, 72–73
  - treatment, 7, 11
- von Willebrand's factor, 72–73, 74, 81
  
- Wellcome Foundation, 13
- Wellcome Trust, 78
- WHO, *see* World Health Organization
- Wilkinson Committee, 58
- World Federation of Hemophilia, 40, 47, 56–57
  - beginnings, 7, 57
  - safety of blood products, 66, 71
- World Health Organization (WHO)
  - factor VIII availability, 30
  - international standards, 20, 21

## INDEX: NAME

- Addis, T, 4  
 Alexander, B, 6  
 Allain, Jean-Pierre, 66
- Bangham, Derek, 20–21, 61  
 Bergsagel, Danny, 14  
 Bidwell, Ethel, 7, 11, 12, 13–14, 15, 16,  
 18, 19, 20, 41–42, 47, 48–51, 61, 77  
 Biggs, Rosemary, 3, 6, 7, 8, 9, 10, 14, 16,  
 18, 19, 20, 21, 36, 41–42, 43, 44, 46,  
 47, 54, 58, 59, 67, 70, 73, 75, 77  
 Blombäck, M, 7  
 Bloom, Arthur, 71–72, 73  
 Blumberg, Baruch Samuel, 62  
 Booth, Sir Christopher, 45–46  
 Brinkhous, K N, 8  
 Britten, Peggy, 57, 58  
 Brozovi\_, Milica, 21  
 Bull, Sir Graham, 46  
 Bulloch, W, 4
- Cash, John, 7, 11, 62  
 Christie, Daphne, 6, 19, 20, 21, 29, 31,  
 32, 36, 43, 57, 59, 61, 65, 66, 70  
 Christmas, Stephen, 9, 10, 44, 46–47  
 Cohn, E J, 12  
 Colvin, Brian, 17, 37–38
- Dacie, John, 10, 44, 46  
 Dalrymple-Champneys, Sir Weldon,  
 52, 54  
 Denson, Ken, 20  
 Dike, Angela, 70  
 Dike, Ross, 12, 14, 19, 47,  
 48–51, 61, 70  
 Dodsworth, Helen, 29–30, 59, 60  
 Doll, Sir Richard, 68  
 Dormandy, Katharine, 34–35, 37, 38,  
 39, 57, 58, 73, 76, 77  
 Douglas, Stuart, 6, 9–11, 41–45, 62  
 Duesberg, Peter, 68  
 Duran-Jorda, Frederico (Frederick),  
 23–24  
 Duthie, Robert, 18, 30–32
- Else, Martin, 77
- Evans, David, 22–29, 30, 37, 47, 63
- Fildes, Paul (later Sir) 4
- Goldstein, R, 6  
 Goodall, Alison, 73  
 Graham, J B, 5, 8  
 Grant, Jean, 33
- Haldane, J B S, 7  
 Hardisty, Roger, 22, 39  
 Heath, David, 74  
 Hill, Graham, 55  
 Hopff, F, 4  
 Howarth, Sheila, 58, 60, 62  
 Hoyer, Leon, 73
- Ingram, Ilesley, 4–8, 9, 10, 11, 12, 15, 16,  
 17, 22–23, 39, 47, 58
- Jenkins, George, 37  
 Johnson, Alan, 9, 21, 74  
 Jones, Peter, 15, 17, 22, 27, 35–36,  
 37, 39, 57, 62–67, 70–71, 75, 76
- Kekwick, Ralph, 7, 19, 20, 24  
 Kernoff, Peter, 34, 35, 77
- Lane, S, 6  
 Larrieu, M J, 6  
 Lee, Christine, 3–4, 8, 9, 11, 12, 13,  
 14–15, 16, 18, 20, 22, 31, 32, 33,  
 34, 38, 39, 41, 46–47, 53, 54, 56,  
 57, 58, 60, 62, 65, 66, 67, 68, 71,  
 75–76, 77–78  
 Lewis, J H, 5
- Macfarlane, Gwyn, 3, 5, 6, 7, 9, 10, 12,  
 13, 14, 15, 18, 20, 38, 40, 41–42, 45,  
 46, 47, 52, 58, 59, 61, 70, 76, 77  
 Mackay, M E, 19  
 McKee, P A, 72  
 Magnusson, Stephan, 73

## Index: Name

- Major, Rt Hon John, 65  
Mannucci, P M, 7, 10, 11  
Matthews, James, 7, 16, 32–33, 34  
Merskey, Clarence, 5, 9–10, 44, 45  
Miller, Riva, 36–37  
Minot, G R, 5–6  
Mollison, Patrick (Pat), 30, 58, 59
- O'Brien, John, 10  
Owen, David (later Lord), 55–56  
Owren, P A, 42
- Patek, A J, 5  
Pavlovsky, A, 6, 10  
Pitney, W R (Bob), 10, 44, 46  
Pool, Judith (Judy), 7, 24, 35  
Poole, John, 9, 10, 45  
Powell, A E, 72
- Quick, A J, 4, 42
- Ratnoff, O D, 5, 72  
Reynolds, Lois, 69  
Rizza, Charles (Charlie), 3, 7, 9, 10, 11,  
12, 16, 17, 18–19, 20, 31–32, 34, 37,  
38, 43, 52–54, 59, 60, 67–68, 74, 77
- Schnabel, Frank, 57  
Shannon, A E, 7, 35  
Skegg, Joyce, 21  
Smallpeice, Victoria, 18  
Smith, Alan, 71  
Smith, Frank, 41, 52  
Soulier, J P, 6, 7  
Spooner, Rosemary, 37, 53–54
- Stockford, Victoria, 55  
Stratton, Frederick (Fred), 24, 25
- Tanner, Alan, 38–39, 40, 54–56, 57, 66  
Tansey, E M (Tilli), 3, 4, 10, 69, 78  
Taylor, F H L, 5  
Teitle, Jerry, 46  
Thatcher, Margaret (later Dame), 65  
Timperley, W A, 41  
Tovey, Geoffrey, 30  
Treves, F, 4, 17  
Trueta, Joseph, 18, 23  
Tuddenham, Edward (Ted), 34–35, 37,  
67, 71–75, 77  
Tyrrell, David, 66, 69–70
- Vallet, Leon, 19
- Wagner, R H, 8, 72  
Walsh, P N, 7  
Walton, Peter, 20  
Watson, Irene, 55  
Watson-Williams, Dr, 24  
Watters, David, 56, 65  
Weatherall, Sir David, 71  
Welch, Clifford, 36, 40–41,  
52, 75, 76–77  
Whitby, Sir Lionel, 22  
Wilkinson, John, 23, 52, 58  
Willebrand, E A von, 5–6  
Witts, Leslie, 43  
Wolf, Peter, 7, 24  
Wright, Irving, 5
- Zimmerman, T S, 5, 72