Received: 26 January 2022 | Revised: 4 April 2022 | Accepted: 1 May 2022

DOI: 10.1111/hae.14587

Haemophilia WFH WILEY

REVIEW ARTICLE

The legacy of haemophilia: Memories and reflections from three survivors

Albert Farrugia[1] | Cees Smit[2] | Andrea Buzzi[3]

[1]Faculty of Medicine and Medical Sciences, University of Western Australia, Perth, Australia

[2]Department of Epidemiology, Leiden University Medical Center (LUMC), Hoofddorp, The Netherlands

[3]Fondazione Paracelso, Milan, Italy

Correspondence
Albert Farrugia, School of Surgery, Faculty of Medicine and Medical Sciences, The University of Western Australia, 35 Stirling Highway, Crawley WA 6009, Perth, Australia.
Email: Albert.farrugia@uwa.edu.au

Abstract

Following the publication of a book of personal memories by one of us (CS[1,2]), we have attempted to synthesis our joint memories of three ageing men, born in the era preceding universal access to treatment, in an attempt to describe our experience, our challenges and our reflections on the development of therapies, which have ensured that our experience of growing up with haemophilia in the 1950s and 1960s has not been mirrored by the current generation of patients. We describe our upbringing in different parts of Europe in health care systems which, while of varying standards, were all unable to offer the kind of care which developed after the development of specific therapies. We assess the effect of the contamination of these therapies by blood-borne pathogens on our own development, and the development of our communities around us. In addition, we reflect on the lessons learnt, sometimes painfully, by our generation of people with haemophilia and how some of these enabled us to overcome substantial hurdles, survive and build productive lives. Finally, we survey the development of therapies in the past 20 years, and offer some reflections on how our experience can be integrated in a realistic expectation of what the future holds for our community, in our own affluent societies and in countries less advantaged economically. We hope that our thoughts may contribute to continued progress in the field of haemophilia care.

KEYWORDS
biotechnology, blood products, epidemiology, haemophilia, viral infections

1 | HAEMOPHILIA OVER THE COURSE OF OUR LIVES

1.1 | The 1950s: A pivotal decade

Between 1950 and 1960—the decade in which the three authors were born—several important developments in the understanding and management of haemophilia took place, which seeded the advances of the succeeding decades. Improved laboratory tests allowed the differentiation of haemophilia and Christmas Disease, and the delineation of haemophilia A and B was thus established.[3] In addition, the development of specific assays allowed the bleeding phenotype to be related to the level of coagulation factor, resulting in the classification of patients as severe, moderate and mild which is still in use.[4]. The plethora of coagulation factors was organised in a series of Roman numerals by international convention,[5] and, together with intensive research on the mechanism of coagulation, led to the "waterfall/cascade" theory in the succeeding decades.[6,7] Concurrently, the first tentative approaches to effective treatments were undertaken; the first concentrates of Factor VIII (FVIII) [usually called "antihaemophilic globulin (AHG)" at the

time] were developed, in the form of modified preparations of Fraction I from the Cohn fractionation process.[8] These preparations, together with the continued use of plasma, allowed the first attempts at urgent surgical and dental procedures and the treatment of some acute bleeding emergencies. Above all, the recognition that the management of haemophilia demanded a multi-disciplinary, coordinated approach, led to the formation of the first consolidated medical departments, soon to be designated as "Haemophilia Centres". The benefits to patients of committed clinicians and scientists, as exemplified by the collaboration between Inga Marie Nilsson and Birger and Marie Blombäck in Sweden, was evident through the performance of surgery and the first attempts at prophylaxis, as early as the late 1950.[9,10] Concurrently, the first associations of patients formed.[11] These advances all contributed to an enhanced life-expectancy for patients.[12] The reader is referred to the excellent reviews contributed by early opinion leaders in haemophilia, including Professors Rosemary Biggs,[13–15] Kenneth Brinkhous[16] and Isley Ingram.[11]

Despite these developments, the outlook for those of us born in the 1950s remained sombre. The first concentrates, made from animal (with all the limitations due to sensitisation)[17,18] and human plasma, were in desperately short supply. The use of plasma continued, with reasonable results in treating minor episodes in moderate/mild patients in particular, but inadequate for treating major bleeds and of little use in severe patients. For most patients in the major economies, this was the only treatment available. Intriguingly, the therapy which was to revolutionise the treatment of haemophilia A, in the form of cryoprecipitate, was actually discovered and used in the 1950s,[19,20], but this crucial finding was not published in the Anglo-American literature and did not influence care for many years. Hence, even if death from haemorrhage could be avoided, the commonest sequelae of intra-articular bleeding, in the form of haemophilic arthropathy, were practically universal in the population of severe and moderate patients. As specialised care evolved, some level of orthopaedic intervention was attempted, and the patient and careful manipulation of these procedures makes instructive reading today.[21] The limited availability of replacement therapy was sufficient to result in the first reports of inhibitor development.[22]

Albert Farrugia writes

I was born in Malta in 1957, and lived with my family in Swansea, Wales between 1960 and 1962. When I was less than a year old, in Malta, I started to develop bruises on my arms, and a tear in the frenulum in Swansea in September 1960 led to quasi-exsanguination. I was transferred to the Churchill Hospital in Oxford, then the Mecca in the research and treatment of bleeding disorders. I remember these events, shadowed by a dark cloud of anxiety, very well.

Diagnosis of haemophilia B was at the Oxford Haemophilia Centre led by Dr Rosemary Biggs, who described me in my medical history as a "very active child". By the time the family returned to Malta, a second boy, born in 1960, had been diagnosed. The 1960s were a decade of frequent pain for myself as joint bleeds rapidly converted my left ankle, right knee and right elbow into target joints. In the late 1950s/early 1960s therapeutic products for haemophilia B, extracted from fractions of ethanol plasma fractionation, had been developed by Soulier's group in France[26] and later on, by the Oxford workers,[27] but were limited to the countries of origin. During my childhood, occasional plasma transfusion, not necessarily aligned to bleeding episodes, was the only treatment in Malta. Otherwise, early compression bandaging of the afflicted joint and rest, followed by physiotherapy, were the mainstay of managing my and my brother's joint bleeds. My brother had a considerably less severe phenotype but suffered a fatal cerebral haemorrhage at the age of 8 years. After this tragic event, I was, more than ever, not allowed to be a "very active child".

1.2 | The seeds of the 1950s bear fruit: Haemophilia over the 1960s

It must be reiterated that the patchy therapeutic advances recorded above were not universal. The limited amounts of the Factor VIII concentrates available for haemophilia A—for haemophilia B only plasma was available—were not found in most countries. By the start of the 1960s, one of us (CS–below) was already entering the second decade of life, with lifelong effects imposed by his haemophilia. But developments over the first years of the 1960s were to have profound consequences. The systematic classification of the coagulation factors in the 1950s contributed to the development of a theory describing their interaction—the coagulation cascade—published quasi-concurrently by British[6] and American[7] investigators in 1964. This concept, with modifications, still forms the basis of blood coagulation today. Therapeutic progression took a huge step forward when the American biochemist Judith Pool developed her initial observations on the solubility of FVIII in blood bank plasma[23] into a method for the production of concentrated cold-insoluble FVIII (cryoprecipitate) using plastic bag systems.[24] Furthermore, the cryoprecipitate collected and pooled from many donors could be further purified industrially into a high-potency freeze-dried FVIII concentrate,[25] allowing high doses of FVIII to be administered, with all the resulting medical benefits.

1.3 | And a thousand flowers (seemed to) bloom: The therapeutic explosion of the 1970s

By the beginning of the 1970s, haemophilia patient societies had been established in many countries, and the World Federation of Haemophilia (WFH), based in Canada under the leadership of Frank Schnabel since 1963,[11] was holding bi-annual conferences reporting the latest development. In 1969, the WFH established official relations

Cees Smit writes

My life started during a stormy night, while the neighbours rescued the thatched roof of our farmhouse. I was being born under the same roof on New Year's night in 1951 in a small village in West-Friesland, in the north-west of the Netherlands. My parents were running a bakery there and my sister was born seven years before. It was not long after my birth that my mother saw some bruises on my back. Our general practitioner was sympathetic, but patronizingly suggested that my mother should handle me with more care. My mother was somewhat upset by this attitude. As the bruises continued appearing and I also displayed pain with crawling, a referral followed to a paediatrician in a city some 25 kilometres away from our home. Luckily enough, this paediatrician had been trained in Amsterdam by Professor Cornelia de Lange, the first female professor in a medical faculty in the Netherlands, who had seen a lot of haemophiliacs. Hence, I was immediately diagnosed with a severe form of haemophilia before my first birthday.

As there was no effective treatment during the first sixteen years of my life, I hardly survived some critical bleeding episodes in my youth. A new paediatrician told my parents that he had used diethylstilbestrol (the DES hormone) to treat his other young patients with haemophilia. DES was used at that time as a medication for a variety of female reproductive problems and to stop growth in adolescent girls who were growing very tall. The use of DES in haemophilia had been presented by a French paediatrician, Raymond A. Turpin, at a medical conference in Paris in the late 1940s.[28] The use of DES had a devastating impact on my growth. I gradually stopped growing and its effect is still visible as my length is only 1.45 metres.

In the summer of 1967, I was transferred with a knee bleed to the recently founded Haemophilia Clinic in The Netherlands, where Professor Simon van Creveld himself immediately stopped my DES treatment. It was in that clinic, on the afternoon of July 9, 1967, that I had my first transfusion with cryoprecipitate. Soon after the first infusion was administered, I could hardly breathe; I thought I was dying. I was lying in a single room with the door closed. I tried to scream but that was almost impossible because of my swollen throat. Luckily enough a nurse entered the room and saw the seriousness of the situation. I guess she reduced the infusion rate immediately, which gave some relief. From my patient record, I can trace that I received some antihistaminic treatment as well. So, I almost died from my first Factor VIII infusion, due to an aphylactic reaction to the cryoprecipitate.

Andrea Buzzi writes

I was born in a small seaside town in the middle of Italy in 1960. When I was about one year old my parents, worried that I was developing large and unusual bruises, took me to the hospital where I was diagnosed with severe haemophilia A. Neither side of my family had a history of haemophilia, and hence the diagnosis came as a bolt out of the blue. Obviously, I have no recollection of these early months, and I can only convey these events through subsequent familial narration. It seems that my first bleedings, as a toddle, were frequent bumps in the forehead which, in the absence of any therapy, were drained using a syringe and a needle. I can only imagine the despair of my parents during this unpleasant time, as I cried and twisted my body in an attempt to escape from the pain.

My first memories date back to a few years later. As a toddler and then a young boy, my target joints were the ankles. Once a month my left or right ankle swelled, giving me pain which resulted in sleepless nights on end. Soon I learned to feel very early, before any sign showed, when a bleed was starting, and I would struggle to resist the pain for as long as I could, because I didn't want to go to the hospital, where I was treated, mostly to no or little avail, with whole blood transfusions and, at a later time, with fresh frozen plasma.

Needless to say, I was not at all happy with long hospitalizations, but I was admitted in a paediatric ward with many other boys about my age. As a result of this, my young mind concluded that boys often need to be hospitalized.

with the World Health Organisation (WHO).[29] The rapidly increasing access to factor concentrates for haemophilia A continued to improve patient life expectancy[30] (Figure 1).

The increase in availability of haemophilia A concentrates ensued from the rapid mobilisation of blood and plasma collection agencies for the purpose of collecting, preserving and purifying FVIII. Blood donation in plastic bags was converted from the transfusion of mainly whole blood to the transfusion of plasma depleted cellular concentrates, to allow plasma to be harvested from the donated blood and despatched to fractionation agencies. The preparation of cryoprecipitate as the preliminary fraction for FVIII manufacture allowed FVIII purification while not hindering the further fractionation of the residual plasma to other fractions such as albumin. This was underpinned by an improved understanding of the stability of FVIII in plasma and during manufacture.[31,32] The manufacture of concentrates of Factor IX (FIX) also progressed rapidly, with the development of ion-exchange processes also able to extract FIX from the plasma after cryoprecipitate removal, again without hindering further fractionation.[33–35] The

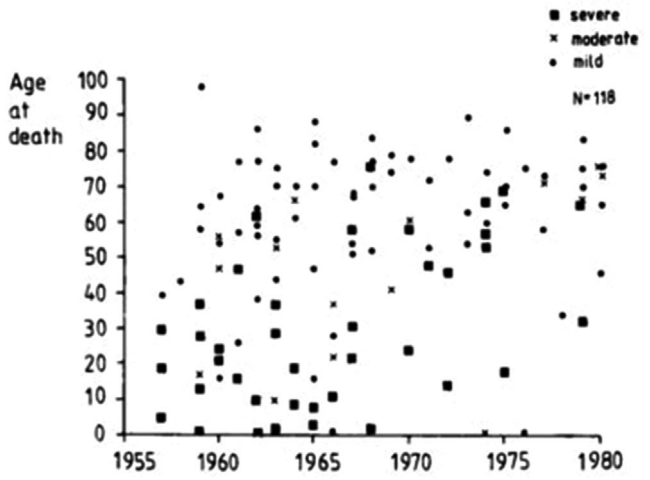

FIGURE 1 Age at death and severity of haemophilia in Sweden 1957–80. From Larsson SA et al, Acta Med Scand. 1983;214(3): 199-206.

TABLE 1 Annual consumption of factor VIII in UK (including N.I.) in Million IU over the 1970s

Year	FVIII issued from NHS 10^6 units	FVIII issued from commercial product 10^6 units	Total FVIII issued 10^6 units
1969	1.025	0	1.025
1970	.884	0	.884
1971	3.071	0	3.071
1972	1.939	.095	2.89
1973	2.481	.875	3.36
1974	2.732	2.681	5.41
1975	3.085	5.152	8.24
1976	6.915	11.069	18
1977	12.949	15.017	27.97
1978	14.6	19.273	33.9
1979	15.092	26.178	41.27
1980	14.364	34.739	49.11

The amount of FVIII (10^6 units) supplied from National Health Service (domestic fractionation of plasma collected in the UK) and Commercially sourced plasma products is shown. From UK Dept of health. Self-Sufficiency in Blood Products in England and Wales: https://haemophilia.org.uk/wp-content/uploads/2017/05/Self-sufficiency-in-blood-products-in-England-and-Wales-A-chronology-from-1973-to-1991.pdf.

increase in availability of FVIII in the UK[36] (Table 1) is just one example of the explosion in access to concentrate over the decade. The continued use of cryoprecipitate up to the end of the decade is noteworthy.[37] Towards the end of the 1970s estimates of the amount of FVIII needed to treat haemophilia A started to be published, with 1 to 2 International Units (IU) per head of total population–IU/capita mooted as optimal.[38] The plasma economy, based on the ever-increasing need for FVIII, and in its turn the blood economy, had become inexorably linked to haemophilia A by 1980. This was not the case for haemophilia B, where the needs for FIX were met amply by a fraction of the plasma collected.

Albert Farrugia writes

By 1970, my first target joint (left ankle) had stopped bleeding overtly. Like many patients, the target joints were inexplicably selective; I never had a bleed in the right ankle, left knee or left elbow. The right knee continued its deterioration, with regular minor bleeds, managed by rest and bandaging, punctuated by major episodes imposing prolonged immobilisation and muscle weakness. I am aware that over this period of childhood, my parents became involved in the nascent efforts to organise care in Malta. In this, the small community was fortunate, as were many such communities globally, in engaging the interest of a prominent Maltese physician–John Rizzo Naudi, later Minister of Health and Chancellor of the University of Malta.[39] His endeavours for the community were tireless. He ensured the first availability of FVIII and FIX concentrates and worked to introduce laboratory and physiotherapy services. As I grew older and approached puberty, I was struck by the experience of a marked and rapid decrease in my joint bleeds over 1974. This apparent change in the bleeding phenotype was not confirmed through FIX assay, which was not performed. At this time, and up to 1982, my sole FIX measurement had been the original diagnostic assay done in Oxford in 1960, which classified me as a severe patient with 0-1% FIX. This level was reflected in my bleeding phenotype until 1974, when, as noted, a change developed. The probable reason for this will be discussed below.

The second half of 1976 shook me out of the complacency which had developed over the previous two years. In September 1976, following a week of increasing lower abdominal pain (from no obvious cause), I was rushed to hospital where, for a tense hour or so, a tentative diagnosis of appendicitis was considered. This could have had dire consequences if an exceptional diagnostician had not correctly diagnosed a haematoma and FIX concentrate was administered over a few days. The episode resolved, and I went home……

1.4 | And then it all came crashing down: The tragedy of the 1980s

The knowledge that blood products can transmit hepatitis precedes the era of the treatment of haemophilia, and was the reason for the inclusion of heat treatment of albumin solutions when these were developed.[40] With the advent of replacement therapy in the form of plasma transfusion, hepatitis was reported in patients with haemophilia.[41] A clearer understanding of the viral aetiology of

Cees Smit writes

The regular infusions with cryo changed my life. I was put on prophylaxis quite soon and this enabled me to lead an almost normal life. Frequent absence from school diminished and I was ready to start a study in business economics at the Free University in Amsterdam. That was in 1971, the same year as the Netherlands Haemophilia Society was founded. As a volunteer for the Society, I started to write articles for their haemophilia magazine.

My first years at the university did not go very well. Whereas during my high school years, my parents, teachers, and hospital carers were very supportive, my first haematologist at the university hospital was not at all enthusiastic about my idea to commence academic study. Moreover, he told me that he was reluctant to treat haemophiliacs and that it was too expensive. My feeling was that the situation would improve over time but this proved to be unrealistic. Hence, after two years I switched to the other university clinic in Amsterdam, the haematology department then led by the young and enthusiastic Jan Wouter ten Cate. He taught me to self-infuse and my motivation to go on with my life returned. My experiences drove me to work closer as a volunteer for the haemophilia community. It was also through the support of Jan Wouter ten Cate, that I travelled in February, 1976 to the Italian Dolomites to join a large group from the Italian Haemophilia community. The group undertook a "white week" of swimming and cross-country skiing through the initiative of the Milanese haematologists Pier Mannuccio Mannucci and Zaverio Ruggeri. For me, it was the first time that I could participate in this kind of sporting event, which was seen by many as being too risky for haemophiliacs. And there I also met Andrea Buzzi, one of the co-authors of this article.

blood-borne hepatitis followed the discovery of the hepatitis B virus and its associated antigen,[42] permitting the development of a blood screening test and an improvement in the safety of blood transfusions.[43] However, hepatitis B infection continued to occur in haemophiliacs treated with concentrate, despite the screening of the plasma using tests for antigen.[44] A consideration of the limited sensitivity of viral screening tests and the consequences of the large plasma pools used in fractionation[45] leads to an understanding of why these tests, applied in the absence of additional measures, have a limited effect on the safety of plasma products from blood-borne viruses.

In addition to continued infection with hepatitis B,[44,46] it became apparent that, like the majority of transfusion transmitted hepatitis following the introduction of hepatitis B screening, haemophiliacs are being infected with a different form of hepatitis, designated as "Non A, Non B hepatitis" (NANB).[47,48] Some initial studies suggested that this infection did not lead to progressive progressive liver disease in

Andrea Buzzi writes

I keep innumerable, undated mental snapshots of a vacuum plastic bag filled with dark red liquid, which in colour and through its irregular shape resembled slices of liver before my mother cooked them for me ("This is the best medicine"), and months or maybe years later glass bowls filled with a thick liquid and yellow, like the zabaglione (an Italian dessert made from eggs and sugar) which my grandmother made for me by beating the eggs in a bowl with a spoon; she too had her miraculous food recipe and was convinced that it would do me good, in contrast to the filth which they considered I was given at the hospital which, as far as anyone could see, gave me no benefit at all.

The bag or bowl hung on top of a grey metal rod, and was connected to my arm through a transfusion set, as I had heard the gizmo being called (the doctor: "Miss (the nurse) bring me a set"), consisting of a huge metal needle, an enlarged version of the one stuck in my vein, which the doctor pushed hard into the rubber stopper at the bottom of the bowl; under this giant needle, a drip chamber, a small tube through which the flow was regulated and finally the fitting to which the needle was attached. The bag or bowl emptied drop by drop in the chamber over a period of a few minutes, a few hours or a whole night, depending on the particular doctor's inclination.

I remember one doctor, small and wiry – even in his manner – a true Priest of Slowness–who seemed to take pains in ensuring a slow infusion, and of course, in my child's mind I hated him. There was another that seemed to me to have a harsh face, young but already almost bald and with a stoop, who didn't even use the flow regulator, the drops descending into the drip chamber in a wonderful and uninterrupted cascade and everything was over quickly.

In a subsequent and (in my memories) very long hospitalization in Rome, for the first time, instead of plasma or whole blood I was administered a concentrate of factor VIII, a new preparation, a colourless liquid, which was the first effective drug to treat the manifestations of haemophilia. For myself, at least in this first instance, it was not effective, perhaps due to an insufficient dosage or perhaps because my immune system had developed an antibody response against the administered FVIII, as is the case with 30 percent of haemophiliacs. This further complication of my haemophilia was confirmed in Milan years later.

It is likely that the red blood, yellow plasma and colourless FVIII one of those bags or bowls, given to me to correct my haemophilia, also contained one of the viruses which proceeded to enter my body, many years before 1983, when I was tested for what rapidly became known as AIDS.

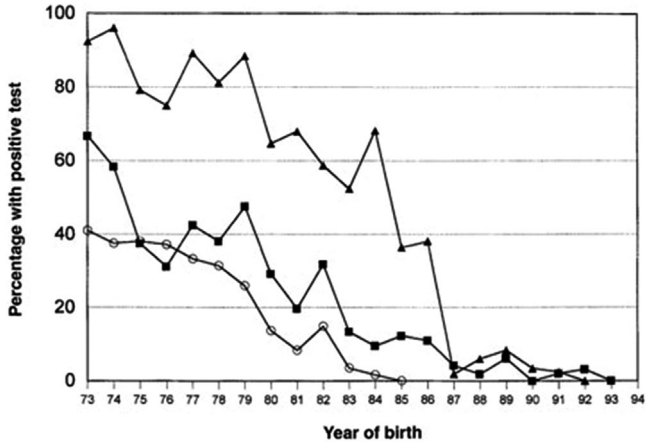

FIGURE 2 Birth cohorts of haemophilic patients in the USA, showing the proportion of patients infected with the three main transfusion transmitted viruses HBV (■), HCV (▲), and HIV-1 (◯). Following 1985, no patients were infected with HIV, for HCV and HBV the dates were 1992 and 1993 respectively. From Soucie JM et al. Transfusion 2001 Mar;41(3):338-43.

haemophiliacs.[49,50] It might be argued that the resolution of most cases of hepatitis B, and the apparently non-progressive nature of NANB hepatitis, induced a feeling of complacency in the patient and treater community, which, reluctant to impact on the benefits of the first decade of wisely available therapy, accepted these hepatitis infections as inevitable and relatively benign side-effects of a therapy which revolutionised, and extended, their lives.

And then ……AIDS happened.

The reader is referred to Evatt's excellent review[51] for a comprehensive and objective description of the AIDS epidemic in haemophiliacs by one of the foremost players. Suffice it to record that that, by the time this infection was halted in the haemophilia community by the introduction of manufacturing steps to kill the virus, as much as half the treated patient community was infected. Many of them died before effective medications became available. The seemingly inexorable progress in the life expectancy of haemophilia was halted.[12] The situation was compounded with the growing recognition that, contrary to the initial hopes, the hepatitis caused by the NANB agent, subsequently discovered as hepatitis C,[52] caused chronic liver disease and significant morbidity.[53,54] This dismal picture was, however, offset by further and dramatic progress in therapeutic options. Spurred on by the calamity of the viral epidemics, the plasma industry rapidly developed processes to inactivate viruses over the process of manufacture.[55] These proved to be very effective in eliminating the risk from the established viruses responsible for the epidemics in haemophilia[56] (Figure 2), and also protected patients from the continued emergence of infectious agents in the blood supply.[57] By the end of the 1980s, virtually total safety for plasma derived concentrates had been achieved. A further huge step in therapeutic progression occurred with the cloning of the FVIII gene and the full characterisation of the FVIII protein expressed in recombinant cell culture,[58,59–62] reported through four papers in the issue of nature of 22 November 1984. By the end of the decade, the first clinical studies of recombinant FVIII in patients had been reported.[63]

Albert Farrugia writes

Following my discharge from hospital in September 1976, I re-joined my university in Malta where I was studying for a degree in biology and chemistry. After about six weeks, I started to feel feverish and nauseous, and became ill enough to go back to bed. Soon my eyes turned yellow……yes, I had contracted hepatitis. Testing then and subsequently indicated that this was hepatitis B. Until the infection resolved, and my liver turned to normal capacity, I experienced renewed joint bleeds, which I had not had for some years, and episodes of pain which were probably the result of retroperitoneal bleeding. This required treatment with the same FIX concentrate with which I had been first treated two months before. Moving forward a few years to when I was working in the field, I found that I had also antibody to hepatitis C, but repeated testing for the viral genome over the years has continued to confirm that I spontaneously cleared the virus, as occurs with a minority of patients.[64] In this, as in many other things, I was lucky.

These dramatic events tapered off with the end of 1976, and I made an apparently full recovery. Over the next few years two or three joint bleeds occurred, but nothing to impede me enjoying a reasonably full life. I graduated in science from the University of Malta, undertook post-graduate studies at the University of Edinburgh and embarked on a career in blood transfusion and plasma fractionation. Upon returning to Malta in late 1984 I was appointed head of the blood transfusion service and was immediately plunged in the AIDS crisis, which first impacted on the small haemophilia community. Upon testing the patient population with the first test available, I found 19 out of 21 haemophilia A patients and 0 out of 7 haemophilia B patients had the virus. I consider these results to reflect the therapeutic situation of the community during the crucial period of the late-1970s/early-1980s. During this period the haemophilia A patients had been treated with concentrate sourced from the USA, while the haemophilia B patients had been treated with product from Austria. This purely random allocation because of a bureaucratic tender system made all the difference for the patients involved. And, having had no product in these crucial years, I was, once again, lucky. By the end of 1985, commercial concentrate subjected to viral inactivation was available and was purchased, in lieu of product which was in storage.

In 1987 I was offered a scientific position with the Australian Commonwealth Serum Laboratories (CSL), then a government owned biologicals manufacturer and Australia's sole plasma fractionator. I subsequently held positions in the Australian Red Cross Blood Service and the Royal Children's Hospital in Melbourne. All these positions continued my progression as a transfusion and coagulation scientist.

Cees Smit writes

It was on July 20, 1982, that I read a first article in my daily newspaper 'De Volkskrant' on a new disease in the US, spreading fast in the gay community. But more importantly, it also mentioned haemophiliacs as a risk group for this disease. And the article quoted Harold W. Jaffe from the CDC in Atlanta, mentioning that the cause of the disease should be sought in blood and not in sexual behaviour as had been the working hypothesis until then. As by then I was the secretary of the Netherlands Haemophilia Society, I wrote a letter to the directors of the Central Laboratory of the Blood Transfusion Services of the Netherlands Red Cross for more information. As we had no internet and social media by that time, it took some time for communications between the US and the Netherlands, but by Christmas 1982 all the alarm bells were ringing about the new AIDS virus. In January and February, 1983 we sent two letters to the members of the Dutch haemophilia community to warn them of this new risk associated with the clotting factor products.

Speaking personally, this new virus didn't come out of the blue. In 1979, commercial plasma companies tried to break the monopoly of the Dutch Red Cross – which had its base in the Dutch law on blood and blood products–by going to the Dutch court and requesting a place for their products on the Dutch market. It was at this point that I started – together with my friend Piet J. Hagen – a more thorough investigation of the international market in human plasma. That's how we learned about Richard Titmuss' book 'The gift relationship: From human blood to social policy' published in 1970[65] in which Titmuss had already warned for unknown viruses by studying the higher frequency of hepatitis in paid donors versus unpaid donors. Our research into the trade in human blood has resulted in numerous newspaper publications since 1979 and in Piet J. Hagen's book 'Blood: Gift or merchandise'[66] which was published in the summer of 1982. It was exactly during this summer that I read for the first time about a new virus, causing the then new disease called AIDS.

Both Titmuss and Hagen made a strong plea for blood and plasma collection to be made through voluntary non-remunerated donors. They both criticised the United States for the fact that they permitted plasma donors to get paid for their plasma as well as to give their plasma twice a week. This frequency of around 100 plasma donations a year was much more than the frequency of approximately thirty times yearly recommended by the World Health Organization (WHO) and the international Red Cross societies. In the international congresses of the World Federation of Haemophilia which I attended from 1979 this was certainly not a topic of concern or discussion. More importantly was the supply of factor concentrate to avoid bleeding episodes. I was therefore not surprised that the risk of aids was downplayed at the WFH Congress in Stockholm, May 1983, which was five months after we had alerted the Dutch haemophilia community. In our third national haemophilia survey in The Netherlands in 1985, we could estimate that a total number of 130-170 haemophiliacs out of a total population of 1600 were infected with AIDS. A precise calculation of 152 infected patients was made when compensation for infections with AIDS was applied for in 1996. And even more importantly, almost all infections took place on paid plasma products and less on local products from unpaid donors. A similar result was obtained in Belgium and the Scandinavian countries.[67]

As a result of all the early reports in 1982, I immediately realised that I was at risk. But I was not finally diagnosed with the Human Immunodeficiency Virus (HIV) until the end of 1991, when I was experiencing problems related to thrombocytopenia. In the meantime, it ensued that I was also hepatitis C (HCV) positive. My hepatitis C was treated successfully and my HIV is under control. But in the interim I suffered a lot of side-effects of the HIV medication, amongst them acute renal failure which manifested in France while I was on holiday in France in 2001. And that's why I'm now much more concerned about my renal situation than my haemophilia which is quite under control.

1.5 | The modern era: Triumph from tragedy

With the rapid development of recombinant factor concentrates, and the abeyance of the viral safety threat, haemophilia care from the 1990s entered an era of continuous progress. While plasma-derived products continued to provide an important role in treatment, the role became, increasingly, a niche role in the wealthy countries. The incidence of inhibitors to FVIII, by the 1990s established as the major adverse effect of replacement therapy, appeared to be higher with recombinant concentrates,[68] an issue which continues to be controversial even after the publication of a randomised clinical trial addressing the issue.[69] Plasma-derived Von Willebrand Factor (VWF) concentrates have continued to be used for the treatment of Von Willebrand's Disease (VWD), and a recombinant VWF may disrupt this therapy in the near future.[70]

The recombinant revolution has had profound effects on haemophilia care. The detachment of factor provision from the limitations of the plasma supply has shielded patients with haemophilia from the consequences of chronic shortages in plasma for fractionation. The increase in supply of factor concentrates has allowed treatment to be increased substantially, allowing prophylaxis and tolerisation of patients with inhibitors. Production from cell-culture systems has continued to increase as the efficiency of these systems has been improved.[71] However, the needs of haemophilia patients to the treatment levels representing optimal care cannot be met by substitution therapy, irrespective of its source. The ability to engineer variants

Andrea Buzzi writes

Sometime before AIDS became known, I had been told that the Australia antigen was present in my blood, which meant that hepatitis B, a liver infection had infected my body without significant symptoms and apparently without leaving any trace other than HBsAg (Hepatitis B surface Antigen), also known as the Australia antigen and another hepatitis infection called, bizarrely, non A non B. At the Haemophilia Centre we patients joked amongst ourselves, asking each other: "Do you have Australia?".
Then, on a spring morning in 1983 my doctors communicated to me without any particular emphasis or sympathy that I had contracted or encountered a new infection which was indeed called HTLV III or maybe IV. "You have developed the antibodies, but that doesn't mean you'll get sick", they told me. "And what do I have to do?" I asked. "Nothing," was their reply. Well, I thought, there is no diagnosis, there is no disease, there are no therapies. I accepted the news without particular stress or grief.

I don't know how and why I continued my life without interruption, even if the expected survival was no more than five years and many, as I saw, were gone sooner. Maybe I was too trivial, perhaps I was too young, I wanted to live and thanks to a lifetime of hospital visits and the other consequences of my condition I had already made contact with the frailty of existence. Somehow, I had experienced life to the limit of adversity, through forces that cannot be opposed, including disease. Or maybe I thought, then as in the rest of my life, that you have face challenges like the river bed holds flowing water: it is contained, channelled, held in a loop and it modifies, digs, changes our course.

I have no particular memories related to HIV during those five years, but I certainly did not spend them counting the days until my assumed death.

At a certain point, those of us who continued to defy prognosis and epidemiology and exceeded the five years life expectation without getting sick began to be referred to as "long survivors".
Many years later, I realised that those like me who were born in the era of no therapy and then had made it through only to be faced with the era when therapy became lethal think of themselves as survivors.

of the coagulation factors which have improved pharmacokinetic profiles has allowed the development of prophylactic regimens with decreased infusion frequencies. Another major development has been the provision of non-factor therapies, with the ability to mimic or bypass the coagulation factors, or to modulate the coagulation system through impeding its natural inhibitors. These developments are all the subjects of excellent reviews.[72,73] The availability of improved presentations, allowing less frequent and subcutaneous administration, has revolutionised the treatment of many patients, particularly those with inhibitors.

The hope for a cure for haemophilia is, at this moment, approaching reality through gene therapy.[74] While this therapy is still experimental and several hurdles remain, it is clear that substantial progress has been made.[75] For the majority of the world's haemophiliacs, born in countries where these expensive treatments are unaffordable, solidarity with the more fortunate members of the global community continues to be effected through the donation programs organised by the WFH.[76] The development of a universally accessible form of gene therapy is crucial for these patients, and the funding of gene therapy continues to be a subject of debate.[77]

1.6 | Final reflections

In many ways, the authors of this paper consider themselves to be fortunate. Having been dealt with the bad card of being born with haemophilia in a time when no treatment was available, we have by luck and by coincidence survived problems others have not survived. All by all, this created circumstances in which we could play a modest role in active engagement in advocacy and awareness of haemophilia and contribute to patient organizations in the world of haemophilia and that of other rare diseases.

In this context, we continue to be sobered by the realisation that 70% of the world's population of haemophiliacs is minimally or inadequately treated, and we have focussed our efforts beyond our immediate, somewhat privileged, geographies, to attempt to improve the lives of people in the emerging economies. We attribute our own survival during the years of no or minimal treatment to the fact that we were diagnosed with haemophilia and, to a greater or lesser extent, were aligned to specialised centres where attention could be focussed specifically on our condition. This is important for patients where specific treatment options in the form of replacement therapy are still limited.

This review has included the history of the development of factor therapy to its current level of safety and availability in the wealthy countries, but most of these developments are still not accessible by less developed countries, where the consequences of lack of treatment result in problems similar to those experienced by us in our early lives. Notably, the use of unmodified plasma and cryoprecipitate continues to cause infections in patients in emerging countries, decades after this problem was eradicated in the Western world.[83,84] The efforts of the World Federation of Haemophilia to deliver treatment, even in the form of the most modern of therapies, have achieved magnificent results in embedding a level of care in countries which, otherwise,

Albert Farrugia writes

My career in blood products continued while in the Australian regulatory authority (the Therapeutic Goods Administration [TGA]), where I worked for a formative period of fifteen years from 1994. This made me familiar with the global blood industry, and the need to keep a constant oversight on safety issues. During much of this period, my haemophilia was quiescent, and I lived a normal life with increasing international engagement. In 2000, I became a volunteer for the WFH, serving as its Blood Safety Advisor for eight years and writing a Guide, now in its 3rd edition, for the use by government agencies charged with accessing therapeutic haemophilia products in the absence of regulatory provision.[78] Between 2008 and 2021 I worked for the commercial sector, which, if anything, cemented my view that the presence of a strong regulatory environment is pivotal in ensuring the safety of patients who are dependent on life-long therapies.

My phenotype continued to be moderate in these years, and I collaborated in the delineation of my defect as a mutation of the FIX promoter region, possibly explaining the improvement at puberty.[79] My engagement with the new therapies was limited, but one of my nephews achieved a good outcome with the first successful gene therapy trial for haemophilia B.[80] I am happy that, besides two normal sons, I am the uncle of four men with haemophilia B, all of them born in the era of safe and adequate treatment, with successful careers and every prospect of a full and normal life.

Moderate haemophilia does present challenges. An episode of painless haematuria in 2009 (subsequently repeated about five times in the succeeding years) led to a severe crisis requiring surgery, when I was "triaged" into a day long wait at the emergency department, by which time I required urgent attention. I continue to be struck at the resistance to the patient's experience by medical workers unfamiliar with rare chronic disorders. It is for this reason that those of us born in the 1950s are ingrained in the need for constant alertness and apprehension. Thankfully, those who were born later do not experience these feelings, at least not to the same extent.

Cees Smit writes

As I'm now entering my 71th birthday, my life lasted much longer than my parents expected. Both have now died and luckily, they were not aware of my HCV and HIV infections through my treatment with plasma products. That was absolutely one of the most awesome things I experienced amongst all those who died because of HIV and HCV: parents who had to bury their children and often with feelings of guilt that they had administered the contaminated products.

At the end of 2021, I switched from a factor VIII plasma product to a prolonged half-life product and now I can handle my treatment with one infusion of 2.000 units a week (55/kg). I'm most concerned now about my renal situation and the more general, possibly geriatric, care which I will need in the future. Where discussions within the haemophilia community focus around hub and spoke models because of gene therapy, I'm wondering why we also shouldn't focus more on expert care for ageing haemophiliacs with comorbidity problems. In the illustration, I have put my circle of health care contacts within my own hospital (Figure 3). The 'fear' factor behind this illustration is who can take care when I'm no longer capable of taking responsibility for coordination of this care complex and as well what will happen when I have to go to a nursing home for the elderly.

Another of my concerns is the highly commercialized care for haemophilia: a worldwide market of 10 billion USD in 2018 will grow to a 14 billion USD market in 2024. A market that serves only 30% of the worldwide haemophilia population, a figure that has hardly changed over the past half century since the beginning of the era of modern treatment of haemophilia. Around sixty companies are active in this market and despite the factor product donations mentioned earlier there is little or no willingness to develop a strategy to treat those who are untreated. This always gives me a feeling of living in a privileged liberal country with good public health service and insurance at the cost of those who can't survive.

This issue also relates to all kinds of conflicts of interest within the international haemophilia community: almost no independent research, commercial sponsorship of haemophilia societies as well as haemophilia centres and almost no external audits of clinical trials of haemophilia treatments. It was these same conflicts of interest that was also a main cause of timely warnings within the international haemophilia community forty years ago with the onset of HIV. The Lancet wrote six years ago about the 'long shadow of past mistakes' when the use of contaminated blood products was mentioned as the 15th biggest peacetime disaster in British history.[81] It's thanks to the Fatherless Generation that there is now an Independent Blood Inquiry in the UK, but it would be wise to extend this inquiry into an international one to get for everyone in the world hurt by this tragedy a truthful narration of the ins and outs of what happened then.

Andrea Buzzi writes

The shock and grief haemophilia community suffered during the years of the viral epidemics someway triggered my engagement with advocacy, an involvement which started in 1993 and which was to become, increasingly, my second, uncompensated, job.

In 2004, following an initiative carried out with two friends who were, like myself, volunteers, an agreement was signed with one of the companies that produced and distributed factor products during the years of factor-borne infections in Italy. Thus was born, after a negotiation starting in 2000, a solidarity fund in favour of haemophiliacs with HIV infection and the heirs of those who had died in the meantime. The 40 thousand euros paid to each applicant was modest, but what was pivotal for the success of the initiative was the prospect of setting up a non-profit foundation managed by patients and intended for the assistance of other patients. Upon reaching the agreed subscription quota, payments to beneficiaries would commence. The foundation would have been endowed with the sum of 5 million euros to be dedicated to social and health projects for the benefit of the entire community. The goal was achieved in 2006. The solidarity fund paid benefits to 500 applicants, of which half were still living and half were the heirs of deceased patients.

The massive inclusion in the agreement by those who had lost a son, a father, a brother, or a husband, shows that the people affected by the most appalling pharmacological catastrophe of medical history sought, beyond the material aspects, an element of recognition and a lasting benefit. By joining the solidarity fund they accepted a small sum which in many cases was divided between all the heirs (four, five, six or seven that they were) in reparation for the irreparable harm to their lives, thus allowing the birth of an organisation that has since worked in favour of other haemophiliacs.[82]

With their gesture, they converting it to a tangible and ongoing benefit for the whole afflicted community, separating the institution from individual consumerism and investing it with a symbolic role in the complicated and laborious task of grappling and making sense of great adversity.

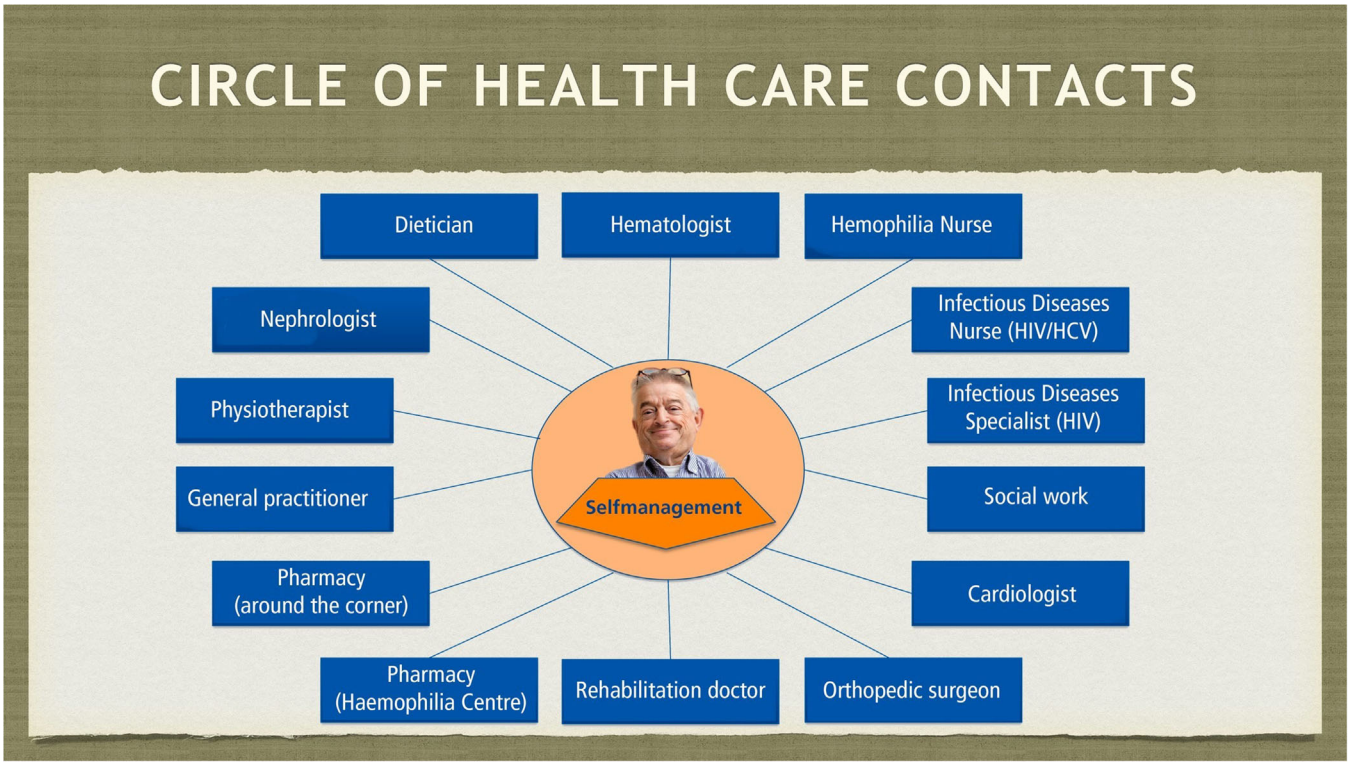

FIGURE 3 Network of health care providers involved in personalised haemophilia care. By Cees Smit

would not have provided it.[85] In addition, the inclusion of many patients from such countries in the clinical trials for such products has also contributed greatly. However, if the world's population of haemophilia is to be treated, current efforts towards a cure through gene therapy need to be continued, as it is difficult to envisage a sufficiency of products from the several efforts of biotechnological manufacture, and impossible to contemplate through the plasma supply.

We reflect, with satisfaction, on the growth in the importance of haemophilia in the medical and scientific community, in contrast to the situation in our childhood when this condition was still ignored by other than a few, very notable, specialists. Haemophilia has evolved into a major sub-speciality contributing to many brilliant careers and has also assumed a significant role in the viability and profitability of many pharmaceutical companies. These are positive developments overall, but we suggest that more needs to be done by the companies to make their products accessible by our community in the less developed countries. We recall the episodes during our lives when we encountered difficulties from the lack of timely interventions from producers of haemophilia products and national health authorities with respect to viral transmission. Within the haemophilia community there was also a period of doubt on what was ensuing and as a result precious time to act was lost. The eighties and nineties were a very difficult time leading to feelings of guilt and regret on what were appropriate actions in the treatment of haemophilia for haemophiliacs and their parents and but also the physicians nurses and other health care workers who had to deal with an unprecedented catastrophe. We wrote this paper for all those stakeholders to remind them of a period in history that should be remembered and considered when all the difficult decisions in haemophilia treatment are made in future.

In summary, we attribute our ability to survive and age with haemophilia to correct diagnosis, access to specialised care even in the earliest years of minimal treatment and eventual access to full care, as well as the medicines to overcome the adverse effects of concentrates. As we survey our lives, we experience satisfaction at the current excellent situation of haemophiliacs in the generations succeeding ours, in our respective countries. Many of the hurdles we have described are unknown to them, and we feel it would be of use if the history of the progression of our generation was to be more widely known, and if our experiences could contribute to a template for the evolution of haemophilia care worldwide. Above all, we encourage our brothers and sisters in the global community of patients with bleeding disorders to become their own advocates, to get involved, as we did, in the landscape of haemophilia, and to use the massive resources of the internet to become aware and expert in their condition. And to never, ever, give in. That is how we have survived.

ACKNOWLEDGEMENTS

Albert Farrugia wrote the background on the development of haemophilia care and his own experiences over this period. Cees Smit and Andrea Buzzi wrote their own experiences and edited the paper. This review is dedicated to the memory of John Farrugia (1960–1968), to all those others of our generation who did not survive, and to all who labour to provide treatment for our community globally.

Open access publishing facilitated by The University of Western Australia, as part of the Wiley - The University of Western Australia agreement via the Council of Australian University Librarians.

[Correction added on 4 July 2022, after first online publication: Funding statement has been added.]

CONFLICT OF INTEREST

We have no conflicts to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Albert Farrugia https://orcid.org/0000-0003-0804-7463

REFERENCES

1. Smit C. Seventy years of haemophilia care: A personal perspective. Available from: http://onlinelibrary.wiley.com/doi/abs/10.1111/vox.13173
2. Smit C. *Surviving Hemophilia: A Road Trip Through the World of Healthcare* [Internet]. Levi M, editor. Eburon Academic Publishers; 2021 [cited 2022 Jan 21]. p. 240. Available from: https://press.uchicago.edu/ucp/books/book/distributed/S/bo85954476.html
3. Biggs R, Douglas AS, Macfarlane RG, Dacie JV, Pitney WR, Merskey null. Christmas disease: a condition previously mistaken for haemophilia. *Br Med J*. 1952;2(4799):1378-82.
4. Merskey C. The laboratory diagnosis of haemophilia. *J Clin Pathol*. 1950;3(4):301-20.
5. Wright IS. Nomenclature of blood clotting factors. *Can Med Assoc J*. 1959;80(8):659-61.
6. Macfarlane RG. An enzyme cascade in the blood clotting mechanism, and its function as a biochemical amplifier. *Nature*. 1964;202:498-9.
7. Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. *Science*. 1964 Sep;145(3638):1310-2.
8. Biggs R. Thirty years of haemophilia treatment in Oxford. *Br J Haematol*. 1967;13(4):452-63.
9. Nilsson IM, Blombäck M, Ahlberg Å. Our experience in Sweden with prophylaxis on haemophilia1. *Hemoph His World*. 1970;34:111-24.
10. Nilsson IM, Hedner U, Ahlberg åke, Larsson SA, Bergentz S-E. Surgery of hemophiliacs—20 years' experience. *World J Surg*. 1977;1(1):55-66.
11. Ingram GI. The history of haemophilia. *J Clin Pathol*. 1976;29(6):469-79.
12. Jones PK, Ratnoff OD. The changing prognosis of classic hemophilia (factor VIII 'deficiency'). *Ann Intern Med*. 1991;114(8):641-8.
13. Biggs R. Witnessing medical history: an interview with Dr Rosemary Biggs. Interview by Christine Lee and Charles Rizza. *Haemoph Off J World Fed Hemoph*. 1998;4(5):769-77.
14. Tansey E, Christie D. Haemophilia: Recent history of clinical management. In: Welcome Seminar on the History of Medicine [Internet]. 1998. Available from: http://www.histmodbiomed.org/sites/default/files/44826.pdf
15. Hawgood BJ. Rosemary Biggs MD FRCP (1912-2001) and Katharine Dormandy MD FRCP (1926-78): from laboratory to treatment and care of people with haemophilia. *J Med Biogr*. 2013;21(1):41-8.
16. Brinkhous KM. Physiopathology of Hemophilia. *Acta Haematol*. 1958;20(1-4):125-30.
17. Bidwell E. The purification of antihaemophilic globulin from animal plasma. *Br J Haematol*. 1955;1(4):386-9.

18. Macfarlane RG, Biggs R, Bidwell E. Bovine antihaemophilic globulin in the treatment of haemophilia. *Lancet Lond Engl*. 1954;266(6826):1316-9.
19. Remigy E. *Donnees Actuelles Sur Le Diagnostic Blologloue De L'hemophilie – Essais De Traitement Par Plasma Cryoconcentre*. University of Nancy, France; 1955.
20. Sibinga CT. Emile Rémigy and the discovery of anti-haemophilic activity in cryoprecipitate. *Haemoph Off J World Fed Hemoph*. 1996;2(1):56-60.
21. Hemophilic arthropathies /by Henry H Jordan. [Internet]. Wellcome Collection. [cited 2021 Nov 27]. Available from: https://wellcomecollection.org/works/v7tuvysa
22. Biggs R, Bidwell E, Macfarlane RG. The mode of action and aetiology of antihaemophilic globulin inhibitors. *Le Sang*. 1959;30:340-51.
23. Pool JG, Robinson J. Observations on plasma banking and transfusion procedures for haemophilic patients using a quantitative assay for antihaemophilic globulin (AHG). *Br J Haematol*. 1959;5(1):24-30.
24. Pool JG, Shannon AE. Production of High-Potency Concentrates of Antihemophilic Globulin in a Closed-Bag System. *N Engl J Med*. 1965;273(27):1443-7.
25. Hershgold EJ, Pool JG, Pappenhagen AR. The potent antihemophilic globulin concentrate derived from a cold insoluble fraction of human plasma: characterization and further data on preparation and clinical trial. *J Lab Clin Med*. 1966;67(1):23-32.
26. Larrieu MJ, Caen J, Soulier JP, Bernard J. [Treatment of hemophilia B with a plasma fraction rich in antihemophilic B factor (P.P.B.)]. *Pathol Biol*. 1959;7:2507-13.
27. Biggs R, Bidwell E, Handley DA, Macfarlane RG, Trueta J, Elliot-smith A, et al. The preparation and assay of a christmas-factor (factor IX) concentrate and its use in the treatment of two patients. *Br J Haematol*. 1961;7(3):349-64.
28. Turpin R. The therapeutic consequences of the sensitivity of hemophiliacs to certain hormones. *Gaz Med Fr*. 1946;53(6):145-7.
29. World Federation of Hemophilia. History – World Federation of Hemophilia [Internet]. 2021 [cited 2021 Nov 29]. Available from: https://www.wfh.org/en/about/history
30. Larsson SA, Wiechel B. Deaths in Swedish hemophiliacs, 1957-1980. *Acta Med Scand*. 1983;214(3):199-206.
31. Farrugia A. Factor VIII manufactured from plasma—the ups and downs, and the up again: a personal journey—part 1: history of the development of plasma-derived factor VIII therapies. *Ann Blood [Internet]*. 2018;3(2). Available from: http://aob.amegroups.com/article/view/4328
32. Farrugia A. Factor VIII manufactured from plasma—the ups and downs, and the up again: a personal journey—part 1: history of the development of plasma-derived factor VIII therapies. *Ann Blood [Internet]*. 2018 [cited 2019 Sep 17];3(2). Available from: http://aob.amegroups.com/article/view/4328
33. Dike GW, Bidwell E, Rizza CR. The preparation and clinical use of a new concentrate containing factor IX, prothrombin and factor X and of a separate concentrate containing factor VII. *Br J Haematol*. 1972;22(4):469-90.
34. Bruning PF, Loeliger EA. Prothrombal: a new concentrate of human prothrombin complex for clinical use. *Br J Haematol*. 1971;21(4):377-98.
35. Barrowcliffe TW, Stableforth P, Dormandy KM. Small scale preparation and clinical use of factor IX-prothrombin complex. *Vox Sang*. 1973;25(5):426-41.
36. UK Dept of health. Self-Sufficiency in Blood Products in England and Wales A Chronology from 1973 to 1991 [Internet]. 2006 [cited 2021 Nov 29]. Available from: https://haemophilia.org.uk/wp-content/uploads/2017/05/Self-sufficiency-in-blood-products-in-England-and-Wales-A-chronology-from-1973-to-1991.pdf
37. Britten AF, Ala F, Carman C, Smit Sibinga CT. Worldwide overview of plasma procurement and fractionation. *Scand J Haematol Suppl*. 1984;40:479-84.
38. Högman CF. To what extent can plasma supply for factor VIII production, be obtained within the frame of a blood component program? *Scand J Haematol Suppl*. 1984;40:485-90.
39. Rizzo-Naudi J, Griscti-Soler N, Ganado W. Human brucellosis: an evaluation of antibiotics in the treatment of brucellosis. *Postgrad Med J*. 1967;43(502):520-6.
40. Edsall JT. Stabilization of Serum Albumin to Heat, and Inactivation of the Hepatitis Virus. *Vox Sang*. 1984;46(5):338-40.
41. Soulier JP, Pe G. [Study of the frequency of transfusion hepatitis after transfusion of plasma in hemophiliacs]. *Presse Med*. 1958;66(52):1207-10.
42. Blumberg BS, Alter HJ, Visnich S. *A 'new' Antigen In Leukemia Sera*. *JAMA*. 1965;191:541-6.
43. Aach RD, Kahn RA. Post-transfusion hepatitis: current perspectives. *Ann Intern Med*. 1980;92(4):539-46.
44. Lewis JH. Hemophilia, Hepatitis and HAA. *Vox Sang*. 1970;19(3-4):406-9.
45. Lynch TJ, Weinstein MJ, Tankersley DL, Fratantoni JC, Finlayson JS. Considerations of pool size in the manufacture of plasma derivatives. *Transfusion (Paris)*. 1996;36(9):770-5.
46. Iwarson S, Kjellman H, Teger-Nilsson AC. Incidence of viral hepatitis after administration of factor IX concentrates. *Vox Sang*. 1976;31(2):136-40.
47. Hruby MA, Schauf V. Transfusion-related short-incubation hepatitis in hemophilic patients. *JAMA*. 1978;240(13):1355-7.
48. Skidmore SJ, Jones TE, Boxall EH. Non-A, non-B hepatitis in patients receiving blood products. *J Med Virol*. 1980;6(1):85-9.
49. Mannucci PM, Colombo M, Rizzetto M. Nonprogressive course of non-A, non-B chronic hepatitis in multitransfused hemophiliacs. *Blood*. 1982 Sep;60(3):655-8.
50. Stevens RF, Cuthbert AC, Perera PR, Whitwell HL, Haboubi NY, Warnes TW, et al. Liver disease in haemophiliacs: an overstated problem? *Br J Haematol*. 1983;55(4):649-55.
51. Evatt BL. The tragic history of AIDS in the hemophilia population, 1982-1984. *J Thromb Haemost JTH*. 2006;4(11):2295-301.
52. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*. 1989;244(4902):359-62.
53. Hay CR, Preston FE, Triger DR, Underwood JC. Progressive liver disease in haemophilia: an understated problem? *Lancet Lond Engl*. 1985;1(8444):1495-8.
54. Makris M, Preston FE, Triger DR, Underwood JC, Choo QL, Kuo G, et al. Hepatitis C antibody and chronic liver disease in haemophilia. *Lancet Lond Engl*. 1990;335(8698):1117-9.
55. Evatt BL. The AIDS epidemic in haemophilia patients II: pursuing absolute viral safety of clotting factor concentrates 1985-1988. *Haemophilia*. 2012;18(5):649-54.
56. Soucie JM, Richardson LC, Evatt BL, Linden JV, Ewenstein BM, Stein SF, et al. Risk factors for infection with HBV and HCV in a largecohort of hemophiliac males. *Transfusion (Paris)*. 2001;41(3):338-43.
57. Kreil TR. Building blocks of the viral safety margins of industrial plasma products. *Ann Blood [Internet]*. 2018;3(2). Available from: http://aob.amegroups.com/article/view/4316
58. Brownlee GG, Rizza C. Clotting factor VIII cloned. *Nature*. 1984;312(5992):307.
59. Gitschier J, Wood WI, Goralka TM, Wion KL, Chen EY, Eaton DH, et al. Characterization of the human factor VIII gene. *Nature*. 1984;312(5992):326-30.
60. Wood WI, Capon DJ, Simonsen CC, Eaton DL, Gitschier J, Keyt B, et al. Expression of active human factor VIII from recombinant DNA clones. *Nature*. 1984;312(5992):330-7.

61. Toole JJ, Knopf JL, Wozney JM, Sultzman LA, Buecker JL, Pittman DD, et al. Molecular cloning of a cDNA encoding human antihaemophilic factor. *Nature*. 1984;312(5992):342-7.
62. Vehar GA, Keyt B, Eaton D, Rodriguez H, O'Brien DP, Rotblat F, et al. Structure of human factor VIII. *Nature*. 1984;312(5992):337-42.
63. Schwartz RS, Abildgaard CF, Aledort LM, Arkin S, Bloom AL, Brackmann HH, et al. Human recombinant DNA-derived antihemophilic factor (factor VIII) in the treatment of hemophilia A. recombinant Factor VIII Study Group. *N Engl J Med*. 1990;323(26):1800-5.
64. Maor Y, Schapiro JM, Bashari D, Martinowitz U. Survival of hepatitis C-infected haemophilia patients is predicted by presence of cirrhosis but not by anti-viral treatment. *Ann Hepatol*. 2014;13(6):753-61.
65. Titmuss R. *The Gift Relationship – From human blood to social policy*. The New Press. 1970. p. 360.
66. Hagen PJ. Blood: Gift Or Merchandise : Towards an International Blood Policy. A.R. Liss; 1982. 231 p.
67. Hagen P, Council of Europe. Blood Transfusion in Europe: A 'white Paper'. *Council of Europe*; 1993. 204 p.
68. Goudemand J, Rothschild C, Demiguel V, Vinciguerrat C, Lambert T, Chambost H, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. *Blood*. 2006;107(1):46-51.
69. Peyvandi F, Mannucci PM, Garagiola I, El-Beshlawy A, Elalfy M, Ramanan V, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med*. 2016;374(21):2054-64.
70. Gill JC, Castaman G, Windyga J, Kouides P, Ragni M, Leebeek FWG, et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood*. 2015;126(17):2038-46.
71. Hong JK, Lakshmanan M, Goudar C, Lee D-Y. Towards next generation CHO cell line development and engineering by systems approaches. *Curr Opin Chem Eng*. 2018;22:1-10.
72. Kizilocak H, Young G. Emerging drugs for hemophilia A: insights into phase II and III clinical trials. *Expert Opin Emerg Drugs*. 2021;1-14.
73. Okaygoun D, Oliveira DD, Soman S, Williams R. Advances in the management of haemophilia: emerging treatments and their mechanisms. *J Biomed Sci*. 2021;28(1):64.
74. Batty P, Lillicrap D. Gene therapy for hemophilia: Current status and laboratory consequences. *Int J Lab Hematol*. 2021;43(S1):117-23.
75. Páramo JA. Treatment of haemophilia: From replacement to gene therapy. *Med Clin (Barc)*. 2021; S0025-7753(21)00336-5.
76. Pierce GF, Haffar A, Coffin D. Impact of humanitarian aid linked prophylaxis in Côte d'Ivoire (Ivory Coast). *Haemoph Off J World Fed Hemoph*. 2021;27(1):9-11.
77. Batty P, Lillicrap D. Hemophilia gene therapy: approaching the first licensed product. *HemaSphere*. 2021;5(3):e540.
78. Farrugia A. Guide For The Assessment Of Clotting Factor Concentrates 3rd Edition [Internet]. World Federation of Hemophilia; 2017. Available from: https://www1.wfh.org/publications/files/pdf-1271.pdf
79. Lannoy N, Lambert C, Farrugia A, Van Damme A, Hermans C. Usual and unusual mutations in a cohort of Belgian patients with hemophilia B. *Thromb Res*. 2017;149:25-8.
80. Nathwani AC, Tuddenham EGD, Rangarajan S, Rosales C, McIntosh J, Linch DC, et al. Adenovirus-associated virus vector-mediated gene transfer in hemophilia B. *N Engl J Med*. 2011;365(25):2357-65.
81. The Lancet. The long shadows of past mistakes. *Lancet HIV*. 2015;2(2):e33.
82. Buzzi A. The projects and initiatives of Fondazione Paracelso. *Blood Transfusion*. (2011);9(6):S4.
83. Ghosh K, Joshi SH, Shetty S, Pawar A, Chipkar S, Pujari V, et al. Transfusion transmitted diseases in haemophilics from western India. *Indian J Med Res*. 2000;112:61-4.
84. Yaqoob M, Khan S, Atta S, Khan SN. Current trends of Hepatitis C virus genotypes and associated risk factors in hemophilia patients in Pakistan. *Trop Biomed*. 2020;37(4):1000-7.
85. Lambert C, Meité N, Sanogo I, Lobet S, Hermans C. Feasibility and outcomes of low-dose and low-frequency prophylaxis with recombinant extended half-life products (Fc-rFVIII and Fc-rFIX) in Ivorian children with hemophilia: Two-year experience in the setting of World Federation of Haemophilia humanitarian aid programme. *Haemophilia*. 2021;27(1):33-40.

How to cite this article: Farrugia A, Smit C, Buzzi A. The legacy of haemophilia: Memories and reflections from three survivors. *Haemophilia*. 2022;28:872–884. https://doi.org/10.1111/hae.14587