REVIEW ARTICLE

The legacy of haemophilia: Memories and reflections from three survivors

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Abstract
Following the publication of a book of personal memories by one of us (CS1,2), 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...
And a thousand flowers (seemed to) bloom:
The seeds of the 1950s bear fruit:

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 British6 and American7 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 plasma23 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 1963,21 was holding bi-annual conferences reporting the latest developments. In 1969, the WFH established official relations...
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. 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 anaphylactic reaction to the cryoprecipitate.

The rapid increases 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. 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.
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 UK36 (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.

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
blood-borne hepatitis followed the discovery of the hepatitis B virus and its associated antigen, permitting the development of a blood screening test and an improvement in the safety of blood transfusions. However, hepatitis B infection continued to occur in haemophiliacs treated with concentrate, despite the screening of the plasma using tests for antigen. A consideration of the limited sensitivity of viral screening tests and the consequences of the large plasma pools used in fractionation 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, 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). Some initial studies suggested that this infection did not lead to progressive progressive liver disease in

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I also met Andrea Buzzi, one of the co-authors of this article. My experiences drove me to work closer as a volunteer for the Society, I started to write articles for their haemophilia magazine.

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.
haemophiliacs. 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 for a comprehensive and objective description of the AIDS epidemic in haemophiliacs by one of the foremost players. Suffice it to record 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. 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, caused chronic liver disease and significant morbidity. 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. These proved to be very effective in eliminating the risk from the established viruses responsible for the epidemics in haemophilia (Figure 2), and also protected patients from the continued emergence of infectious agents in the blood supply. 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, 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.

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. 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 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.
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, an issue which continues to be controversial even after the publication of a randomised clinical trial addressing the issue. 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.

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. 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...
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.\textsuperscript{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.\textsuperscript{74} While this therapy is still experimental and several hurdles remain, it is clear that substantial progress has been made.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{63,84} The efforts of the World Federation of Haemophilia to deliver treatment, even in the form of the most modern of therapies, have achieved magnificant 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. 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. 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. 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. 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.
would not have provided it. 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.

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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.

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