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*Review article*

# Hemophilia treatment in historical perspective: a review of medical and social developments

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*"It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way."*
A tale of two cities, Charles Dickens 1859

Hemophilia is a rare hereditary bleeding disorder in which clotting factor VIII (hemophilia A) or factor IX (hemophilia B) is missing. Both hemophilia A ('classic hemophilia') and hemophilia B ('Christmas disease') are caused by defects on the X-chromosome. This implies that, with few exceptions, all patients are men.

In normal hemostasis platelets will adhere and aggregate at the site of a lesion thus forming a platelet plug within minutes. Vasoactive amines released by the platelets cause an arteriolar vasoconstriction that lasts for hours and together with the platelet plug, effectively stops bleeding. The plug needs to be consolidated by a fibrin mesh during this phase of reduced local blood pressure by vasoconstriction. Activation of a cascade of clotting factors will lead to the deposit of fibrin. In hemophilia this fibrin formation by clotting factors activating each other is abnormal, because of a deficiency of factor IX, or its co-enzyme factor VIII, which results in bleeding tendency [80, 117].

## History

Over 1,500 years ago it was written in the Babylonic Talmud that a woman who has lost her first two sons after circumcision shall be exempt from the obligation to have the third son circumcised.

Babylonian Talmud, Tractate Yevamoth 64b: "For it was taught: if she circumcised her first son and he died, and a second one also died, she must not circumcise her third child. These are the words of Rebbe' (Rabbi Judah the Patriarch, redactor of the Mishneh, the second century compilation of Jewish Law). 'Rabban Simeon ben Gamiliel, however, said: she may circumcise the third child but must not circumcise the fourth child" [113] see also [66].

This first description of hemophilia not only shows that hemophilia was recognized in ancient times, but also illustrates the severity of this disease. Early allusions to hemophilia are found in the tenth century medical handbook Al-Tasrif by the Moorish physician Khalaf ibn Abbas Abu-al-Kasim (Albucasis) and in the codification of Talmudic laws by Maimonides. Further references to hemophilia are scarce until John Otto of Philadelphia published his 'An account of a haemorrhagic disposition existing in certain families' in 1803 [27, 94]. Hemophilia became widely known to the layman as the "Royal Disease" during the fin de siècle as it affected members of the English, Prussian, Spanish and Russian Royal houses [60]. In 1911, Bulloch and Fildes compiled the history of hemophilia in a monumental monograph in which they dealt with more than 1,000 references and case reports and set out over 200 extensive pedigrees [27]. This work has been described as "... for students of hemophilia at once their Shakespeare for its drama and its human warmth, and their Bible for its towering authority" [60].

Until only recently, hemophilia remained a crippling disease with a low life expectancy [59, 70], primarily due to the lack of clotting factor preparations of a sufficient concentration to reach adequate hemostatic levels following transfusion. This bleak outlook for hemophilia patients was dramatically improved by the introduction of purified clotting factors in the 1960s.

## Epidemiology

The prevalence of hemophilia in industrialized countries has been reported at 13–18 per 100,000 males [71, 104, 123]. Hemophilia A is five to six times as common as hemophilia B [71, 123]; other clotting factor deficiencies with a bleeding tendency are extremely rare and account for less than one percent of the cases [123].

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The observed occurence of hemophilia is the resultant of the prevalence at birth and the mortality rate. We have estimated the prevalence at birth from data obtained by a survey of all 1,162 hemophilia patients registered in the Netherlands [106]. This is illustrated in Fig. 1, which shows the prevalence per age group. A steady decline of the age-specific prevalence occurs after age 40. This deficit of older patients can only be explained by excess mortality in the past. The plateau of 20.6 per 100,000 males approximates the prevalence at birth, which is 28% more than the observed prevalence in the Netherlands.

Because of the availability of clotting products, hemophilia patients may now expect to live well into their sixties [70, 112]. Inevitably, this will lead to an increase in the number of patients living; with the current small excess mortality (aside from mortalities resulting from AIDS), we estimated an increase in the total number of patients of about 20% to occur in one or two generations [106]. Prenatal diagnosis and selective abortion will not substantially affect these figures, since only a minority of carriers choose for this option, as we found in a survey of 549 female relatives of hemophilia patients [141]. For many of these women hemophilia was no longer a disease of such severity that it warranted an abortion. In the future, the number of patients will increase even further, since more and more patients marry and have families [106].

A hereditary disease with excess mortality can only be maintained in the population by the arising of new mutations. As J. B. S. Haldane pointed out: if we thought there were no mutations, the present number of hemophilia patients could only be explained by assuming that "all Englishmen at the time of the Norman conquest would have been haemophiliacs" [56]. In hemophilia, about one third of all cases are isolated patients, i.e. the first patient in the family. These patients are likely to be the result of a recent mutation, e.g. in their mothers or grandparents. There are strong indications that the mutation rate in males (producing carrier daughters) is 2 to 10 times as high as the mutation rate in females (producing sons with hemophilia or carrier daughters) [56, 108, 147]. The mean mutation rate for hemophilia has been estimated at 1–5 per 100,000, implying that out of a population of 100,000 homozygous normal individuals, males and females, one to five of the offspring will carry the gene for hemophilia.

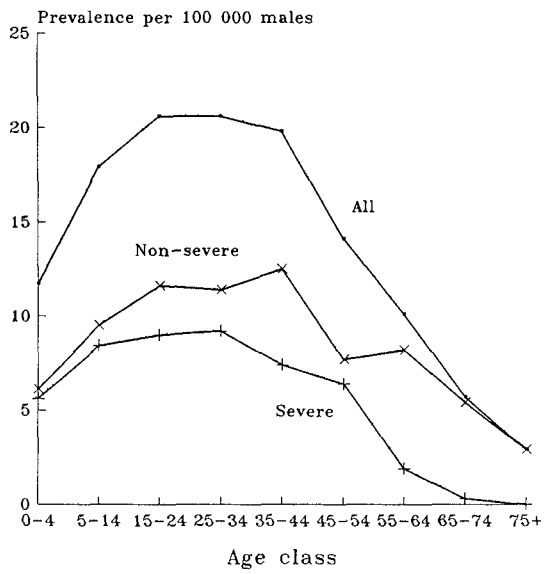


**Fig. 1.** The prevalence of hemophilia. In each age group the number of patients is divided by the total number of men in the Netherlands of that age (data from the Central Bureau of Statistics). Information was available for 80% (935) of the patients, of whom 384 had severe hemophilia; the prevalence data have been extended to all 1,162 (reprinted from [106])

## Signs and symptoms

The severity of the bleeding tendency is determined by the residual clotting factor activity. This residual activity is fairly constant within an individual and breeds true within families. When there is no or less than one percent (i.e. 0.01 IU/ml) clotting factor activity present, the disease is defined as severe hemophilia. Clinically, hemophilia A and B are identical [101].

Most bleedings in severe hemophilia occur spontaneously in the larger joints and in muscles. In mild hemophilia (5–40% FVIII or FIX) bleeding usually does not occur except after trauma; moderately severe hemophilia (1–5% FVIII or FIX) has clinical features in between severe and mild hemophilia and may show the largest individual variation. In severe hemophilia the first signs usually appear at an early age (8 to 12 months) when the child begins to move around. Symptoms will be bruising, nose bleeding, bleedings after minor injuries or joint bleedings. Typically, bleeding does not occur during the neonatal period. Bleeding in the first days of life, notably from the umbilicus, is characteristic of another inherited clotting factor deficiency: homozygous factor XIII deficiency. The diagnosis in the less severely affected patients, who seldom bleed unchallenged, is usually made at an older age after tooth extraction, surgery or trauma [16, 82, 133].

Repeated bleeding in joints causes arthropathy, the major chronic complication of hemophilia. The handicap is often worsened by muscle atrophy because of muscle bleedings. Therefore, the distinguishing features of an older hemophilia patient are posture and gait, far more than evidence of acute bleedings.

## Treatment

A succesful effect of blood transfusion for postoperative bleeding in a hemophilic boy has been described as early as 1840 by Lane [69]. The yield of whole blood or plasma transfusion, however, usually proved insufficient for control of bleeding and the transfusion easily led to circulatory overload. Attempts to increase the factor VIII activity in preparations made from human plasma came about in the 1950s [14, 67, 126]. In 1964, Judith Pool and coworkers reported a simple and reliable method to purify

clotting factor VIII as a cryoprecipitate from human plasma [96]. At approximately the same time blood products rich in factor IX, as well as factors II, VII and X, became available for the treatment of patients with hemophilia B [10, 13, 125]. Dutch factor VIII and IX preparations were used from 1967 on [79, 88]. These developments opened the possibilities of modern hemophilia treatment by adequate replacement therapy and revolutionalized hemophilia care.

Replacement therapy in hemophilia A consists of the intravenous infusion of cryoprecipitate or factor VIII concentrate; for hemophilia B, prothrombin complex concentrate is used (PPSB; which contains factor II, VII, IX, X). In little more than 20 years, the use of clotting factor preparations for the treatment of hemophilia has increased greatly. In 1969 the average yearly consumption of factor VIII in the UK was 7,000 IU per patient [12]. By 1974 this had almost doubled [12] and increased again by 30% from 1976 to 1980 [104]. In 1988 in the Netherlands the Central Laboratories and bloodbanks of the Dutch Red Cross produced almost 40 million IU Factor VIII, i.e. 30,000 IU per patient [30]. This growth reflects the increasing number of patients as well as the increasing intensity of treatment, with a shift from on-demand treatment to prophylactic treatment for patients with a high frequency of bleeding.

Refinements in the manufacturing process have led to clotting preparations becoming more and more concentrated. The recent development of Factor VIII extracted from plasma by monoclonal antibodies has made available a product of unparalleled purity [23, 136]. This increase in purity has its price: in Europe, the products manufactured by the monoclonal antibody technique are about 30% more expensive than 'conventional' Factor VIII concentrates. Theoretical advantages of these ultrapure products that might counterbalance the high costs have been postulated, e.g. a beneficial effect on the immune system; however, neither this effect nor its possible clinical relevance have been convincingly demonstrated.

Presently, the first Factor VIII products made by recombinant DNA techniques are being used to treat hemophilia patients [144]. These preparations are not made from human blood and are therefore free of human viruses. Theoretically, this new technique also opens the possibility to manufacture a modified clotting factor, with properties differing from those of natural Factor VIII or IX (e.g. an extended half-life or high activity after oral intake).

Successful laboratory experiments on the transfer of genes [58] makes one hopeful for the more distant future, when gene therapy will one day be the final step from lifelong substitution treatment to a real cure for hemophilia.

## Prophylactic treatment

Clotting factor administration for the prevention rather than treatment of bleedings was first applied in the late 1960s, although prophylactic plasma transfusions had been reported much earlier [2, 61, 90, 105, 137]. Using data from the Dutch hemophilia surveys we estimated that the number of patients receiving prophylaxis in the Netherlands had almost doubled between 1972 and 1985, as shown in Fig. 2 [123]. In prophylactic treatment, the patient receives clotting factor product infusions two (hemophilia B) or three (hemophilia A) times a week, aimed at maintaining a clotting factor level of more than 1% of the normal value (0.01 IU/ml) at all times. Since joint damage is absent or mild in patients with moderate or mild hemophilia, it has been suggested that prophylactic therapy started at an early age could prevent joint damage altogether [2, 8, 91, 95, 137]. In prophylactic therapy, bleedings probably are not truly prevented, but arrested at the earliest, subclinical phase. It has been shown that prophylaxis reduces the number of manifest bleedings by as much as 60% [8, 9].

Although common sense dictates that prophylaxis prevents or slows the progression of arthropathy, this has not convincingly been demonstrated. It has been suggested that early treatment of all joint bleedings (at the first sign, and at least within 2 h after onset) may also be highly effective [1, 24, 25, 34]. This remains an important issue, since prophylactic treatment usually implies a large increase in clotting factor consumption.

## Home treatment

Home treatment, first introduced in the early 1970s, has become one of the cornerstones of modern hemophilia care [75, 99, 100]. In our latest survey we saw that the majority of patients in the Netherlands now received their

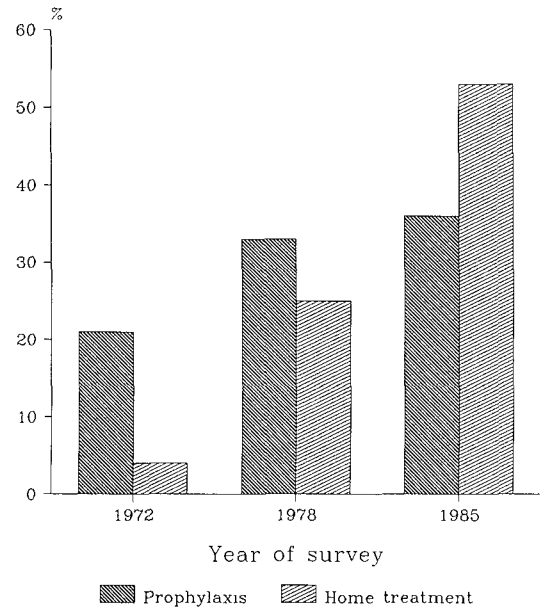


**Fig. 2.** Home treatment and prophylaxis in the Netherlands. The percentage of patients receiving prophylactic treatment and home treatment are shown, for patients with severe and moderately severe hemophilia. The 1972 figures refer to a survey of 242 patients, the 1978 figures to 351 patients, while 559 patients with severe and moderate hemophilia participated in the 1985 survey [110, 123]

infusions at home, administered either by themselves or by household members (Fig. 2) [123]. Home treatment has been shown to combine several advantages. First, bleedings can be treated without delay, which may help in preventing the development and progression of joint damage. We found that the average delay between the onset of bleeding and the administration of a transfusion is less than 2 h for patients on home treatment as compared to 3–4 h for patients who have to travel to a hospital [109, 143]. In countries less densely populated than the Netherlands the time gain in home treatment will be even higher.

Home treatment leads to a reduction in the days spent as hospital inpatients, with large savings in hospital fees [76, 122]. Home treatment apparently does not lead to a higher consumption of Factor VIII or IX [76, 100]. We estimated for the Netherlands that the number of transfusions performed at home rose from 996 in 1972 to 29,680 in 1985, which implies an enormous decrease in outpatient visits [123].

The most important benefit of home treatment is that it greatly enhances the patient's possibilities to lead as normal a life as possible. The independence offered by home treatment leads to increased self-regard of hemophilia patients, a greater mobility in job and vocation choices and an increased participation in social activities [100]. Home treatment has been reported to substantially decrease days lost from school and work [73, 77, 100]. We have shown that this even leads to differences in opportunities for employment: when we compared patients who were employed and patients who were unemployed and received disablement pensions, we noted that home treatment as much as doubled the chance of employment [111].

## Mortality and life expectancy

Before 1960 patients with severe hemophilia had a life expectancy of only 25 years [59, 70, 119]. The availability of clotting factor preparations has greatly increased the expected life span almost to normal (Table 1). We observed 43 deaths in a group of 117 hemophilia patients we followed from 1973 to 1986 (mean follow-up 11 years), while 21 deaths were expected in a hypothetical cohort of non-hemophiliacs of the same age distribution (Fig. 3). Mortality in hemophilia is now twice as high as in the non-hemophilic population [62, 112], aside from AIDS mortality which differs from country to country, dependent on the number of patients infected. The relative increase in mortality by two is approximately the same as that caused by smoking cigarettes and implies an eight-year reduction in life expectancy.

During this century, the number of living hemophilia patients has increased fourfold because of the higher life expectancy. In Western-Europe, just before World War II there were only four hemophilia patients per 100,000 males [6, 55]. In 1960 there were 6.6 patients per 100,000 males [102], while now the prevalence is 13–18 per 100,000, much closer to the prevalence at birth of 21 per 100,000 males [71, 104, 106, 123]. When patients live longer, the average age of the living patients increases. This was seen in the Netherlands: in 1972 the average age was still 11 years lower than that of the general male population; in 1985 the difference was no more than 5 years (29 as compared to 34 years for the general male population) [110]. The most common cause of death in hemophilia still is hemorrhage, although it no longer constitutes the sole death cause: in our study it accounted for half of the deaths [78, 93, 102, 112, 129, 148]. In a recent report on almost a thousand deaths of hemophilia patients in the USA from 1968 to 1979, it was observed that the ratio of the number of deaths by ischemic heart disease over the

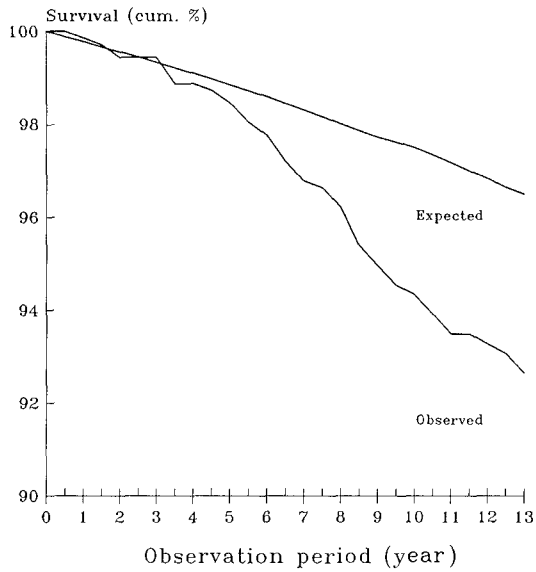


**Fig. 3.** Mortality in hemophilia 1973–1986. Cumulative survival over time is shown. The *lower line* ('observed') is the survival of the cohort of 717 hemophilia patients; the *upper line* ('expected') is the survival in a hypothetical cohort from the general male population, adjusted for age. The distance from 100% is the mortality, 7.4% observed and 3.5% expected (redrawn from [112])

**Table 1.** Life expectancy in hemophilia

| Study period | Country | Author(s) | Severity | Life expectancy (years) |
|---|---|---|---|---|
| 1830–1920 | Sweden | Larsson [70] | severe | 11 |
| 1921–1940 | Sweden | Larsson [70] | severe | 23 |
| –1940 | Finland | Ikkala et al. [59] | severe | 17 |
| –1940 | Denmark | Sjölin [119] | severe | 18 |
| 1941–1960 | Sweden | Larsson [70] | severe | 28 |
| 1931–1957 | Sweden | Ramgren [102] | severe | 25 |
| | | | moderate | 38 |
| | | | mild | 50 |
| 1961–1980 | Sweden | Larsson [70] | severe | 57 |
| 1976–1980 | United Kingdom | Rizza, Spooner [104] | severe | 69 |
| 1973–1986 | The Netherlands | Rosendaal et al. [112] | severe | 63 |
| | | | moderate | 65 |
| | | | mild | 69 |

number of cancer deaths was much smaller than in the general population [7]. It was not possible from this study to conclude whether this was caused by an increased mortality from cancer or a decreased mortality from ischemic heart disease, since this was not a follow-up study: the number of deaths could only be compared relative to each other [proportional mortality ratios (PMR)]. In our follow-up study on 717 hemophilia patients we found that the mortality from malignancies was increased (2.5 fold), while mortality from ischemic heart disease was substantially (80%) lower than in the non-hemophilic population [112]. Several other studies on mortality in hemophilia also seem to show a deficit of deaths by myocardial infarction [62, 104, 129], although this is clearly not reflected in one Swedish study [72].

Subsequently, we showed that the low mortality of ischemic heart disease could not be attributed to differences in other risk factors in hemophilia patients, e.g. blood pressure, smoking and serum cholesterol [107]. These results led us to the conclusion that the low activity of the factor VIII–IX complex in hemophilia offers protection against ischemic heart disease. The protection is not complete, for autopsy series have shown that hemophilia patients develop atherosclerosis [37, 120], while myocardial infarctions in hemophilia patients have been reported occasionally [18, 19]. It is interesting to note that the protection against ischemic heart disease occurs even while hemophilia patients have higher blood pressures than non-hemophilic males. In our study on risk factors for ischemic heart disease we found that the hemophilia patients were hypertensive twice as often as non-hemophilic men (defined according to WHO standards), and also more often used antihypertensive medication [107]. Presently, no explanation can be offered for this high prevalence of hypertension among hemophilia patients, although a high frequency of renal disorders among hemophilia patients has been reported [36, 39, 74, 97, 121, 152].

In myocardial infarction, coronary thrombosis is the final event after many years of atherosclerotic coronary disease [149]. For the general population, it has been shown that low levels of fibrinogen [63, 146] and factor VII [87], protect from coronary disease. In the Northwick Park study [87] it was also found that individuals in the general population in the highest tertile of factor VIII levels had a 40% higher risk of myocardial infarction than those in the lowest tertile. Although this association was non-significant ($p = 0.2$), when viewed together with our observations in hemophilia patients, it seems likely that also in the non-hemophilic population, low factor VIII levels protect against myocardial infarction.

## Clinical and social progress

Our consecutive hemophilia surveys have provided us with an overview of the improved life expectancy, physical status and social opportunities of hemophilia patients since the early 1970s, brought about by the availability of clotting products and the implementation of prophylaxis and home treatment. Table 2 shows the tremendous decrease in hospital use and absenteeism from school and work [123]. In 1972 one out of every two patients needed to be hospitalized, as compared to only one out of every five in 1985, while the number of days spent in hospital decreased threefold.

**Table 2.** Trends in hospital admissions and sick leave

| | Patients with severe and moderately severe hemophilia | | |
|---|---|---|---|
| | 1972 (n = 242) | 1978 (n = 351) | 1985 (n = 559) |
| *Inpatient hospital use* | | | |
| Average use (days a year)[a] | 23 (2) | 10 (2) | 4 (1) |
| Admissions (%) | 47 | 37 | 22 |
| Duration of stay (days per year)[b] | 49 (20) | 26 (15) | 16 (13) |
| *Sick leave* | | | |
| Absenteeism from school (days per year) | 36 | 19 | 9 |
| Absenteeism from work (days per year) | 32 (18) | 34 (18) | 20 (15) |

Data from national hemophilia surveys in the Netherlands [123]. In brackets the figures for the general male population

[a] Average of all patients

[b] Average for those patients who were admitted to a hospital throughout one year

Before clotting factor products were available, many hemophilia patients did not receive adequate education, because of frequent long absences due to bleedings [102]. Many hemophilia patients were unemployed, since they were at a disadvantage due to their disability and lack of education [65, 83, 84]. The consequences of poor educational opportunities have been shown in studies from Scotland, where a high percentage of patients was unemployed, while those who were employed were mainly engaged in manual labor (55%, as compared to 28% in the Netherlands) [83, 84, 140]. It was also noted that the more severe the hemophilia, the more often the patient was engaged in manual labor.

In the Netherlands nowadays hemophilia patients are less often unemployed for economical reasons only, than the average Dutch male [140]. Furthermore, the patients who are employed have obtained positions that are appropriate for the education they have received and they do not have to perform jobs below their capacities. In this respect it is important to note that in the Netherlands hemophilia patients have achieved the same educational level as the general male population [123, 139]. Table 3 shows the sharp decline in sick leave from school, that has undoubtedly contributed to the high educational level of Dutch hemophilia patients [123]. A similar positive trend has been observed in the United Kingdom: the younger patients showed better academic achievements than the older patients [134].

In spite of these positive trends, many hemophilia patients still are not employed because of their physical status and depend on benefits from one of the social security funds. In the Netherlands the percentage of patients who received a disability pension even slightly increased

from 17% in 1972 to 22% in 1985, although this implied a decline when related to the increase in the number of these persons in the general population, which more than doubled in the same period [38, 123, 124].

### Antibodies to factor VIII or IX

Some patients respond to treatment by the development of antibodies to clotting factors, the so-called inhibitors. Treatment of these patients in case of a bleeding may prove extremely difficult, since infused clotting factors will be neutralized by these antibodies. Inhibitor development occurs mainly in patients who themselves produce no clotting factor at all, i.e. patients with severe hemophilia, although antibodies to factor VIII in mild hemophilia have been reported [20, 35]. Antibodies to the missing clotting factor are far more often seen in hemophilia A than in hemophilia B [11, 26]. It is likely that inhibitor development is to some extent genetically predisposed [49]. About 5–15% of the patients with severe hemophilia have antibodies to Factor VIII or IX [11, 26, 50, 64, 123]. Since these prevalence data do not take into account the high mortality risk of inhibitor patients [12, 59, 104, 112], the acutal risk of developing an inhibitor before age 20 is probably as high as 15–24% [86, 132].

Inhibitor patients have profited least from the availability of clotting factor preparations. In our follow-up study over the period 1973–1986 the death risk of inhibitor patients was five times as high as that of non-inhibitor patients, i.e. a quarter of the inhibitor patients (average age only 20 years at the begin of the study) died within ten years of follow-up [112]. Since joint bleedings cannot be adequately treated because of the inhibitor, these patients are often severely handicapped. Therefore, while prospects for employment have improved for hemophilia patients, we saw in the same study that the presence of an inhibitor very often led to unemployment [111].

In the treatment of a bleeding episode in an inhibitor patient, activated prothrombin complex concentrate (FEIBA, Factor Eight Inhibitor Bypassing Activity) and porcine factor VIII have proved useful [22, 68, 98, 116, 118]. The inhibitor titer can be brought down by the infusion of high doses of factor VIII, as well as by cyclophosphamide treatment [21, 81, 92, 145]. Recently, is has been shown that in some patients the inhibitor response itself may be eradicated by the repeated infusion of low doses of Factor VIII [103, 138].

### Transfusion-transmitted disease

The clotting factor products used to treat hemophilia patients are prepared from donated human blood and may therefore transmit infectious diseases. Transmission of hepatitis (B as well as non-A non-B) and the acquired immunodeficiency syndrome (AIDS) are the most threatening.

Very few of the hemophilia patients who have ever received clotting factor products are free of markers of hepatitis B infection [128]. The large majority of hemophilia patients has also been infected with non-A non-B hepatitis [43, 47]. The number of infected patients, as well as the percentage of patients demonstrating elevated liver enzymes, may be somewhat lower in those treated with cryoprecipitate than in those treated with large pool concentrates [127]. Evidence of cirrhosis has been reported in 15–38% of hemophilia patients [4, 57]. In the USA liver disease accounted for 9% of the deaths in hemophilia patients between 1968 and 1979 [7]; surprisingly, in our more recent study of mortality over the period 1973–1986 no deaths from liver disease were noted [112].

In 1982 it became apparent that the acquired immunodeficiency syndrome (AIDS) can be transmitted by blood transfusions [29]. The first case of AIDS in a hemophiliac was reported in 1982 in the United States and since then more than 2,000 cases among hemophiliacs have been reported worldwide [29, 150, 151], of whom many have died.

The percentage of patients infected with the human immunodeficiency virus (HIV) differs widely from country to country. The highest prevalence is found in countries that predominantly used clotting products manufactured from the plasma of paid donors in the United States [17, 89, 114]. In the United States itself 90% of severely affected hemophilia patients are seropositive, in West Germany 53%, in the United Kingdom 39% [3, 42, 52]. In countries that predominantly used products manufactured from local donors, the numbers of seropositive patients are much lower: Belgium 7% [54], Norway 8% [44], the Netherlands 17% [109] and Finland 1% [Ikkala, personal communication]. In France, 50% of hemophilia patients have become HIV positive in spite of a blood product supply predominantly of local origin [5].

Steps have been taken to reduce the risk of HIV transmission from infected donors to hemophilia patients: donors are asked to withdraw if they belong to one of the risk groups of AIDS (i.e. male homosexuals or bisexuals, intravenous drugusers, sexual partners of someone belonging to a risk group), all donations are tested for anti-HIV antibodies, and in the production of clotting factor products a virus-inactivation step has been introduced. By adequate heat-treatment, pasteurization or solvent-detergent inactivation techniques Factors VIII and IX products can be manufactured that are free from the risk of HIV transmission [40, 115, 130]. Since pasteurization also inactivates hepatitis viruses [131], products inactivated by this method should be used in treating virgin patients (patients who have not received any transfusions previously).

No other group has been hit as hard by AIDS as the hemophilia patients, of whom in many countries the majority is HIV-seropositive. AIDS has had a profound effect on the lives of many if not all hemophilia patients, who often form closely knit groups, within families and within treatment centers [53, 109]. There are many instances in which several members of one family became infected with AIDS.

Among the HIV infected hemophilia patients are many children. This poses additional problems, since these boys have to live through puberty and adolescence not only hindered in establishing relationships by their

hemophilia and its hereditary nature, but also by the burden of carrying an infectious and dreaded disease.

The World Federation of Hemophilia has recognized the need for financial assistance for HIV infected hemophilia patients by establishing a committee to this effect. In several countries some sort of financial support has been awarded based on pre-existing legislation, i.e. product liability laws, as in West Germany and Sweden, or no-fault compensation, as in Norway and Denmark. Special support foundations, partly supported by government funds, have been established in several other countries, such as the United Kingdom, Austria and Australia. Lawsuits have been brought against governments, clotting factor producers (pharmaceutical companies, the Red Cross) and hospitals by individual plaintiffs as well as by groups, sometimes of hundreds of patients, as in the compensation claims against the government in the United Kingdom. Few of these litigations have proven successful in court, although several are still undecided. Out of court settlements have been an indirect success of (possible) legal action in a few individual cases in the United States, and for all infected hemophilia patients in Germany, by an agreement between patients' organisations and clotting factor producers [15, 31–33].

The prognosis for seropositive hemophilia patients appears to be no different than that of individuals from other risk groups: 25% of seropositive individuals will progress to AIDS within eight to nine years [51]. In spite of the tremendous research efforts of the past years, the outlook for those infected with HIV has improved only very little. A benificial effect has been demonstrated for the antiviral agent zidovudine (formerly called AZT), that decreases the occurrence of opportunistic infections and improves survival time in patients with AIDS [46]. In one study zidovudine was also shown to reduce the rate of progression in asymptomatic HIV infected individuals, especially those with low CD4-positive cell counts [142]. It is still unclear whether this implies a true benefit in long-term survival [41, 48].

Since often the first manifestation of AIDS is a *Pneumocystis carinii* pneumonia (PCP), prophylaxis in asymptomatic individuals seems recommendable [45, 85]. This PCP prophylaxis consists of co-trimoxazol orally or pentamidine spray inhalation.

## Conclusion

The introduction of products rich in factor VIII or IX in the late 1960s, and the subsequent implementation of home treatment and prophylaxis have greatly improved the physical status and the social opportunities of hemophilia patients. At present, feelings of optimism are overshadowed by the tragedy of AIDS that has befallen so many hemophilia patients. Nevertheless, this AIDS epidemic will pass, be it after it has taken a large toll.

The future of hemophilia treatment holds many promises and many challenges. The newest clotting factor products offer a purity unprecedented, but are expensive and require more plasma per unit of Factor VIII produced. One of the challenges for the future will be to secure treatment of hemophilia patients that is safe, adequate and affordable for society. In this respect, history has shown us not to place all our trust in the newest products, for new products carry new risks. It is also noteworthy that the improvements in physical status and quality of life of hemophilia patients over the past two decades were mostly achieved with simple and unpure cryoprecipitate.

In 1975, the World Health Organization urged all countries to develop a self-sufficient blood system, with voluntary and unpaid donors. In Europe nowadays, there are only a few, small self-sufficient countries, like Belgium, Finland and the Netherlands, while most countries more or less depend on the import of blood products from the United States, which are commercially manufactured from plasma of paid donors. Although the European Committee has declared itself in favor of self-sufficiency, this may be threatened when Europe becomes a common market in 1992. The use of plasma obtained locally from voluntary and unpaid donors, which offers a safeguard against the international spread of transfusion-transmitted diseases, is also often preferred out of motives of principle [135].

Hemophilia treatment is expensive, but the investment pays. In this respect, hemophilia offers an excellent example of a disease in which the benefits outweigh the costs to a high extent. These gains that have emerged over a period of only twenty years are to a large extent nonmaterial in nature. Nevertheless, the increase in opportunities for employment on the one hand, and the reduction of hospital admissions and chronic physical ailments on the other, will also lead to material gains that in due course may outweigh the costs.

The life expectancy of hemophilia patients has become almost normal, and therefore the group of hemophilia patients is now ageing and rapidly catching up with the general population. This implies that even though the progression of joint damage is slower than in the past, it may accumulate over many years. Treatment of arthropathy in a growing group of older hemophilia patients will be one of the challenges in the years to come.

It was the best of times, it was the worst of times. While on the one hand the prospects of hemophilia patients never have been better, on the other hand they have never been worse for those who have been infected by HIV. It is difficult to express confidence and hope for the future, when for some the perspective is filled with despair. We expect that the hemophilia patients born in the present era will be able to lead lives no different than other people.

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