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Two decades of haemophilia treatment in the Netherlands, 1972–92

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Summary. Four questionnaire surveys were conducted over a period of 20 years to evaluate long-term effects of haemophilia treatment in the Netherlands. The response to the prestructured questionnaires in 1972, 1978, 1985 and 1992 varied between 70% and 84%. Data concerned treatment modalities, bleeding episodes, hospitalization, absenteeism, joint impairment and employment. Results over the period 1972–92 for patients with severe and moderately severe haemophilia showed that the use of prophylaxis had sharply increased (from 21% to 45%), as was the case for home treatment (from 4% to 62%) Consequently, the annual mean number of bleeds diminished from 19 to 13. Absence from school was markedly reduced (from 32 to 5 days), and sick leave in employed patients had also diminished (from 26 to 22 days). Furthermore, the use of inpatient hospital facilities, as well as employment in haemophilia patients, had nearly equalled that of the general Dutch male population. The self-reported degree of joint impairment showed no overall improvement, but in patients aged under 35 years there seemed to be a slight reduction in severe impairment. Patients aged under 15 years finally had no severe impairment at all. Social participation can only be further improved if arthropathy is prevented from an early age. Therefore adequate prophylactic regimens and close monitoring of joint impairment in young adults are needed.

Keywords haemophilia, prophylaxis, home treatment, hospitalization, absenteeism, joint impairment.

At the end of the 1960s, clotting factor products became available for substitution therapy in haemophilia and a new era in haemophilia care began. Since then the physical, psychological and social condition of haemophilia patients has gradually improved [1–5]. In patients with a high frequency of bleeds, i.e. with severe or moderately severe haemophilia, there has been a shift from on-demand treatment to more prophylactic therapy. Prophylaxis from an early age was expected to be effective in reducing the morbidity of haemophilia, especially in terms of preventing haemarthroses and haemophilic arthropathy [1, 6, 7]. Home treatment was introduced in the early 1970s to optimalize the treatment in patients with a high bleeding tendency. The situation in which patients themselves administer factor concentrates at home or with the help of others, allows for the early treatment of bleeding episodes before the appearance of physical signs [8]. Consequently, arthropathy can be prevented, and this might subsequently lead to a reduction of absenteeism from school or work and a diminished reliance on hospital facilities [8–10].

To evaluate the long-term effects of modern haemophilia treatment on a large scale, we conducted four national questionnaire surveys among haemophilia patients. This article reports on the results collected over a period of two decades (1972–92). By comparing cross-sectional data on the number of bleeding episodes, hospitalization, absenteeism, joint impairment, and social participation, we describe the extent to which a change in treatment modalities contributed to an improvement in the medical and social circumstances of haemophiliacs. Comparisons with national statistics on absenteeism, hospitalization, and social participation will show whether further improvements can be established.

Methods

Patients and procedures. Four nationwide postal surveys were conducted in 1972, 1978, 1985 and 1992. The study population consisted of haemophilia patients who were listed with the Netherlands Hemophilia Society, with the

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haemophilia treatment centres, or on updated mailing lists from our previous survey(s). An extensive search for addresses enabled us to send questionnaires to 639, 1051, 1162 and 1263 patients, respectively. The response was calculated for all questionnaires returned, irrespective of diagnosis (i.e. haemophilia or other bleeding disorders) and whether the received forms were fully completed. Only participants diagnosed with haemophilia A or B were included in the final analyses. The severity of haemophilia was classified according to the residual percentage of factor VIII or IX clotting activity. severe (<1%), moderate (1–5%), or mild (>5%). The self-reported type and severity of haemophilia was verified with data obtained from the treatment centres.

All four prestructured questionnaires covered the following issues the current treatment modality and regimen, the presence of inhibitors, the annual number of bleeding episodes, the use of inpatient hospital care, absence from school or work, degree of joint impairment, employment, and disability. The questionnaires also included new issues raised in haemophilic care, e.g. home treatment (in 1978) and HIV infections (1985 and 1992).

Data analyses. Analyses were conducted according to the severity of haemophilia. Data on the treatment modality, the number of bleeding episodes, the use of hospital facilities, and absence from school or work referred to the year that preceded the questionnaire surveys. The use of prophylaxis refers to a group of patients who predominantly received prophylaxis, from which we excluded patients who predominantly received treatment on demand and short-term prophylaxis at various times.

The prevalence of haemophilia in 1992 was estimated from data of 980 respondents and 240 non-respondents of whom the date of birth and the severity classification were known. The age-specific prevalence was calculated as the number of listed haemophilia patients per 100,000 Dutch males in each age category.

Self-reported measures on joint impairment were obtained for a series of joints, with possible scores of 0 (no impairment), 1 (some impairment without daily problems), 2 (some impairment with daily problems), and a maximum of 3 (severe impairment with complete loss of function). Because shoulder joints and the hips are seldomly affected [1, 11] and patients with the moderate form of haemophilia rarely develop chronic arthropathy [12], scores for ankles, knees and elbows in patients with severe haemophilia were used in assessing the degree of joint impairment. As joint impairment progresses with age and older patients are more likely to have joint damage because of a lack of treatment in the past, the results presented are stratified for age.

The employment status was defined for respondents aged 15–64 years who were either 'active' (i.e. employed, with a paid job) or 'inactive' (administratively registered as unemployed or disabled under the existing Dutch social security laws). To describe social participation in haemophiliacs, an 'inactivity ratio' was calculated by dividing the proportion of 'inactive' patients with severe or moderately severe haemophilia by the proportion of 'inactive' Dutch males [2]. Thus, the percentage of inactive haemophiliacs will be relative to the percentage of inactives in the general male population, and ratios exceeding a value of 1 represent a reduced social participation of haemophilia patients. Descriptive statistics for age, the use of hospital facilities, absence from work, and employment were compared to national figures for the general male population that were provided by Statistics Netherlands.

Results

Response and participants

The response to the questionnaires was 84% ($n=540$) in 1972, 70% ($n=736$) in 1978, 81% ($n=941$) in 1985 and 78% ($n=983$) in 1992. Respondents who were excluded from analyses concerned patients of whom the type of haemophilia remained unknown (1972: $n=48$; 1978: $n=131$), those who were carriers or patients affected with other clotting factor deficiencies (1972: $n=44$; 1978: $n=16$; 1985. $n=2$; 1992: $n=29$), and respondents who returned uncompleted questionnaires with little or no data (1972. $n=1$; 1978: $n=29$; 1985: $n=6$; 1992: $n=3$). A total of 447, 560, 933 and 980 participants, meeting the inclusion criteria of having haemophilia A or B, remained for analyses.

Seventy-five percent ($n=738$) of the patients in 1992 participated in an earlier survey, including 232 patients who responded to all preceding surveys. The mean age of participants increased from 21 years in 1972 to 32 years in 1992, but remained lower than the mean age of Dutch males which had increased from 32 to 36 years over the same period. The distribution of 87% ($n=853$) with haemophilia A and 13% ($n=127$) with haemophilia B in 1992 was similar in all four surveys. Of all participants in 1992, 39% had severe haemophilia ($n=387$), 18% had moderately severe ($n=173$) and 43% had mild haemophilia ($n=420$).

Prevalence

The age-specific prevalence of haemophilia in 1992 is shown in Fig. 1, with separate distributions for the severely and non-severely affected patients. The overall prevalence found in 1992 was 16.3 per 100,000 males. The maximum prevalence of 20.2 per 100,000 males in the age

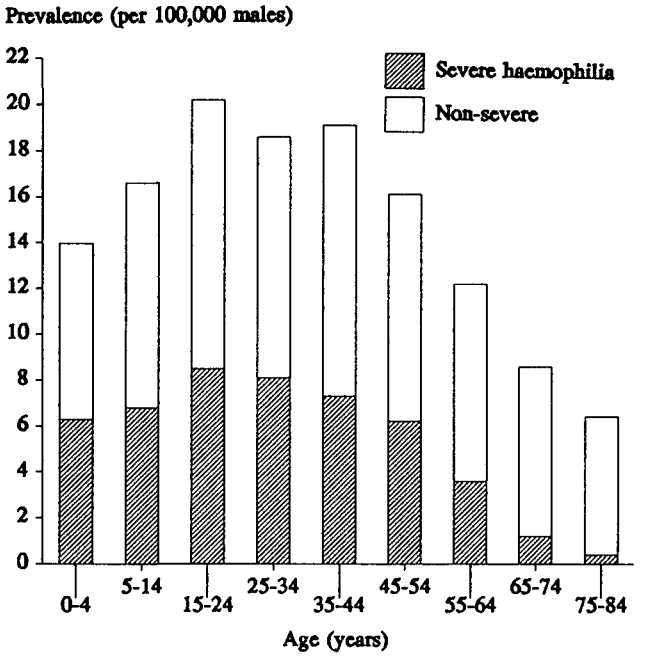

Fig. 1. Prevalence of haemophilia in the Netherlands in 1992 per 100,000 males, with separate distributions for severe and non-severe haemophilia

group of 15–24 years estimates the prevalence at birth, whereas lower values in the younger and older age categories are likely to be the result of delayed diagnoses and excess mortality in the past, respectively.

Treatment outcomes in severe and moderately severe haemophilia

Table 1 presents an overview of results on treatment modalities, frequency of bleeds, hospital admissions, and absence from school or work for patients with severe or moderately severe haemophilia. Prophylactic treatment was prescribed to 21% ($n=52$) of these patients in 1972, which increased to 45% ($n=251$) in 1992. The application of home treatment in these patients showed an even larger increase from 4% ($n=9$) in 1972 to 62% ($n=349$) administering clotting factor products at home in 1992. The mean number of manifest bleeds per year in patients with severe or moderately severe haemophilia declined from 19 in 1972 to 13 in 1992. The decrease was most prominent in the severely affected patients, who reported 25 bleeds per year in 1972 and 16 in 1992. The most frequent sites of haemorrhages in 1992 were joints (77%), and only three of the 13 bleeds on average were located in muscles or soft tissues.

The total number of days spent in a hospital by patients with severe or moderately severe haemophilia reduced from, on average, 20 days in 1972 to 3 days in 1992, due to a gradual decline in the percentage of patients requiring admission and a diminished duration of stay. Haemophilia patients remained somewhat more dependent on hospital care in comparison with the average hospital usage of the Dutch male population in 1992 (3 days versus 1 day per year). However, their duration of stay per admission had become equal to that of Dutch males (10 days). In addition, the use of hospital facilities in patients with severe haemophilia had become the same as in those who were moderately severely affected.

Absenteeism due to haemophilia, in school-going patients with severe or moderately severe haemophilia, diminished from 32 days per year in 1972 to 5 days in 1992. As national statistics on school-absence are not available, a comparison with Dutch males is not possible.

Table 1. Overview of self reported data obtained from four questionnaire surveys, presented for patients with severe and moderately severe haemophilia, the figures in parentheses only refer to patients with severe haemophilia

	1972	1978	1985	1992
n	242 (159)	351 (245)	559 (384)	560 (387)
Mean age	21 (22)	23 (23)	27 (27)	30 (30)
Treatment modality				
Prophylaxis (%)	21 (30)	33 (40)	36 (48)	45 (59)
Home treatment (%)	4 (5)	25 (30)	53 (67)	62 (77)
No of bleeds per year	19 (25)	19 (23)	13 (17)	13 (16)
Hospital admission per year				
On average (days/patient)	20 (22)	10 (15)	4 (4)	3 (3)
Admitted (%)	47 (51)	37 (40)	23 (25)	22 (22)
Duration of stay (days/patient)	40 (43)	26 (37)	16 (18)	10 (10)
Absenteeism (days/year)				
From school*	32 (40)	15 (17)	9 (10)	5 (6)
From work†	26 (31)	35 (39)	20 (18)	22 (21)

*Due to haemophilia in patients following full daytime education

†Total absence in employed patients aged 15–64 years

Table 2. Patients with severe haemophilia who reported serious impairment in one or more main joints, i e ankles, knees and elbows, with, in parentheses, the mean number of joints severely damaged, stratified by age

Age	1972 (n=159) (% (mean))	1978 (n=245) (% (mean))	1985 (n=384) (% (mean))	1992 (n=387) (% (mean))
0–4 years	8 (0 1)	0 (0 0)	0 (0 0)	0 (0 0)
5–14 years	9 (0 1)	11 (0 2)	6 (0 1)	0 (0 0)
15–24 years	25 (0 4)	17 (0 3)	10 (0 1)	18 (0 2)
25–34 years	50 (0 8)	32 (0 5)	32 (0 6)	32 (0 6)
35–44 years	53 (0 9)	32 (0 6)	47 (0 9)	52 (1 2)
45+ years	82 (1 6)	65 (1 5)	59 (1 4)	54 (1 4)
All	31 (0 5)	23 (0 4)	26 (0 5)	31 (0 7)

Sick leave from work in haemophiliacs aged 15–64 years showed a less marked decline, with a reduction from 26 days in 1972 to 22 days per year in 1992. From the self-reported data in 1992 it was calculated that 15 of the 22 days of absence (68%) were attributable to haemophilia. Absenteeism from work in 1992 was still 9 days higher in employed patients as compared to Dutch males who reported on average 13 days of absence per year.

Joint impairment

Table 2 shows percentages of severe haemophilia patients who reported serious joint impairment (score 3) in at least one of their ankles, knees or elbows, and the mean number of joints affected (range 1–6), stratified by age. No severe joint impairment was reported in patients aged 0–4 and 5–14 years in 1992. In the age category of 15–24 years there was no obvious improvement over the years in the percentage affected with severe joint impairment. In respondents aged 25–34 years this percentage initially dropped, from 50% to 32%, but showed no further change. The overall joint status in the age category 35–44 years had not changed over 20 years, although the mean number of severely-impaired joints had somewhat increased. Older patients (45+) had gradually reported less severe impairment. Altogether, the proportion of severe haemophilia patients having at least one severely impaired joint had not changed over 20 years (31% in 1972 and 1992). Meanwhile, overall scores on the average number of affected joints had increased from 0.5 to 0.7. Finally, 19% of all patients with severe haemophilia reported no joint impairment in 1992. This percentage was directly related to age no joint impairment at all in 1992 was reported by 86% of the patients aged 0–4, 61% of those aged 5–14, 15% of the young adults (15-24 years), and <2% of those aged 25 years and over.

Employment and social participation

The figures for participation in the national labour force of patients with severe or moderately severe haemophilia aged 15–64 years are shown in Table 3. Those listed as 'active' participators had a paid job, and the category 'inactive' included those who were unemployed, disabled, early retired, or who participated in voluntary work. The percentage of patients with severe or moderately severe haemophilia listed as 'inactive' had increased over the 20 years. However, as national statistics for the same time showed an even larger increase in the number of inactive individuals, the excess of inactivity among patients compared to Dutch males decreased from 130% in 1972 to 30% in 1992.

HIV infections

To assess HIV-related changes in outcome on hospitalization, absenteeism and employment, we estimated firstly the prevalence of HIV infections based on answers to the

Table 3. Participation in the national labour force of patients with severe and moderately severe haemophilia aged 15–64 years who did not follow full daytime education, as compared to Dutch males, corrected for age

	1972 (n=113)	1978 (n=168)	1985 (n=330)	1992 (n=352)
No of active patients (%)	89 (79)	116 (69)	215 (65)	227 (64)
(% active Dutch males)	(91)	(85)	(77)	(73)
No of inactive patients (%)	24 (21)	52 (31)	115 (35)	125 (36)
(% inactive Dutch males)	(9)	(15)	(23)	(27)
Inactivity ratio (haemophiliacs/Dutch males)	2 3	2 1	1 5	1 3

Table 4. Prevalence of HIV antibodies in 1992 according to severity and for all

	Severe (n=378)	Moderate (n=173)	Mild (n=420)	All (n=980)
At risk (n)*	328	136	243	707
At risk and tested (n)	278	112	138	528
Seropositive for HIV (n)	43	10	2	55
Seropositivity if at risk (%)	16	9	1	11

*Patients who probably have been exposed to HIV infection during 1979–85

questionnaire in 1992 (Table 4). The percentage of HIV-seropositive patients was calculated for those 'at risk', i.e. those who were born before June 1985 and had received treatment with blood products in the period 1979–85. Altogether, of 707 patients who had been exposed to untested blood products 528 (75%) were tested for HIV. 11% (n=55) of these 528 patients were reported to be seropositive for HIV antibodies. The highest prevalence of 16% (43/278) was found among patients with severe haemophilia.

No excess of hospital admissions was observed in seropositive patients. 17% of the seropositive patients had to be admitted in 1992 and 22% of the seronegative patients with severe or moderately severe haemophilia. However, once admitted, the average duration of stay in hospital was more than twice as high in seropositive patients as in seronegative patients with severe or moderately severe haemophilia (32 versus 14 days). Seropositive patients with severe or moderately severe haemophilia who were undergoing full daytime education, reported on average 10 days of absence from school. This was twice as high as in seronegative patients with severe or moderately severe haemophilia (5 days). Sick leave from work in employed seropositive patients was not higher: 18 days versus 23 days per year in the seronegative patients with severe or moderately severe haemophilia. The inactivity ratio for seropositive patients was calculated at 1.4 (38% versus 27% in Dutch males), whereas in seronegative patients this ratio was 1.2.

Discussion

As modern haemophilia treatment aims to prevent arthropathy, by keeping the clotting factor activity above 1% of its normal value [1, 6] it can be expected that successful prevention is reflected in a decrease of the frequency of bleeds and a diminished degree of joint impairment in severe haemophilia. Therefore, if comprehensive care methods were effective, the situation in severe haemophiliacs would equal that of patients with moderately severe haemophilia. Subsequently, the social participation, absenteeism and hospitalization of haemophilia patients would gradually become similar to that of the general male population.

The true prevalence of haemophilia in the Netherlands in 1992 was estimated at a value between the overall prevalence of 16.3 and the estimated maximum of 20.2 per 100,000 males (see Fig. 1). With a total of 7.48 million Dutch male inhabitants in 1992, the total number of haemophilia patients was approximately 1365 (range 1219–1511). Consequently, we reached about 93% of the Dutch haemophilia population in 1992, and approximately 72% of all patients participated in the questionnaire survey. In 1985 these two percentages were estimated at 95% and 75% [2]. By reaching a large majority of the haemophilic population, the reported data can be generalized for each severity category.

Since 1972 the use of prophylaxis in (moderately) severely affected patients more than doubled and the application of home treatment ended up 15 times higher. This shift in treatment modalities contributed to a decrease in the annual number of bleeds, especially in patients with severe haemophilia. Nonetheless, in the perspective of preventing all joint damage by preventing bleeds, the number of bleeds in patients with severe or moderately severe haemophilia was still disconcertingly high. As home treatment allows for prompt treatment, it is probable that home therapy contributed to the 'quality' of bleeds by reducing the severity of accompanying symptoms.

Modern haemophilia treatment succeeded in reducing the dependence on inpatient hospital care, as hospitalization in 1992 almost equalled that of the male population. Nonetheless, in 1992 the absence from school in patients with severe or moderately severe haemophilia was on average still 2–3 days higher than in patients with mild haemophilia, and sick leave from work remained higher in employed patients than in Dutch males. The participation of haemophilia patients in the national labour force in 1992 nearly equalled that of the Dutch male population, although the absolute number of unemployed and disabled haemophiliacs had increased over the years.

The consequences of HIV infections were reflected most obviously in the duration of hospital admission and absence from school in 1992. Although we must be careful in interpreting the analyses with regard to the self-reported HIV test status in 1992, we tend to conclude that seropositivity did not result in any clear changes in the

outcome measures used for assessing the effects of modern treatment. However, the 11% seropositivity for haemophilia patients in the Netherlands may have an impact that goes beyond the outcome reported in this article. The same might hold true for hepatitis infections, but because no self-reported test results on hepatitis were available we cannot report on the consequences of hepatitis in this article. In a recent study we showed the impact of virus infections on mortality, with AIDS and liver disease becoming the main causes of death [13].

Contrary to expectation, the overall percentage of patients reporting severe joint impairment had not changed over 20 years. Despite the fact that factor preparations were readily available at an early age in patients born in the 1960s, no obvious improvement in the joint status was observed for patients aged under 35 years in 1992. It can be questioned whether the self-rated degree of joint impairment used in the four questionnaire surveys is an accurate measure for assessing the effects of modern treatment methods. The Orthopedic Advisory Committee of the World Federation of Hemophilia recommended using the orthopaedic and radiological score system proposed by Pettersson [14]. However, as there is no clear relationship between radiological scores and clinical observations [15–17] there might also be a discrepancy between such clinical measures and self-reported or subjective scores. According to Johnson & Babbit [18], factors such as motivation, drive and personality traits might influence the perception of disability. In our self-assessment method it is likely that amongst temporary physical effects (e.g. recent acute bleeds) the reported degree of joint impairment was subject to person-related factors. Otherwise we would have to conclude that treatment modalities are still failing to prevent arthropathy. A more adequate prophylactic treatment regimen, starting at an earlier age or with higher doses, will then be needed to produce better functional state. From our cross-sectional data for 1992 it seems unlikely that the treatment method is inadequate in the Netherlands with respect to the onset of prophylaxis. Already 48% of patients with severe haemophilia aged 0–4 years receive prophylaxis, 83% of those aged 5–9, and 89% of patients aged 10–14. After the age of 15 years the use of prophylaxis declined, from 72% in patients aged 15–24 years to 69% in those aged 20–24 years. Since we did not enquire about the number of bleeds preceding the onset of prophylaxis, we cannot be sure whether young patients received prophylactic treatment in time, i.e. when a process of arthropathy had not yet been initiated.

The question arises whether further improvements in the overall condition of haemophilia patients can be made. Our findings over a period of two decades suggest that the annual number of bleeds, absence from work and the degree of joint impairment can be diminished, and that social participation can be improved in (severe) haemophiliacs. With respect to joint status, a reduction is desirable in the degree of joint impairment reported by patients who were born at a time when substitution therapy already existed. In conclusion, the outcome measures over 20 years show that modern haemophilia treatment has led to improvements in the medical and social condition of patients. However, figures on the frequency of bleeds, absenteeism, joint impairment, and social participation can be improved further. Unless more attention is given to the prevention of (initial) joint damage, especially in adolescents and young adults, social inactivity in terms of disability and unemployment will remain higher in haemophiliacs than in the general male population. We stress the importance of closely monitoring young adults in whom initial joint damage may occur or progress.

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References

1 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H Twenty-five years experience of prophylactic treatment in severe haemophilia A and B *J Intern Med*, 1992, **232:** 25–32

2 Smit C, Rosendaal FR, Varekamp I, Brocker-Vriends A, Van Dijck H, Suurmeijer TPBM, Briet E Physical condition, longevity, and social performance of Dutch haemophiliacs, 1972-85. *Brit Med J*, 1989, **298:** 235–238.

3 Rosendaal FR, Smit C, Briet E Hemophilia treatment in historical perspective a review of medical and social developments *Ann Hemat*, 1991, **62:** 5–15

4 Rosendaal FR, Smit C, Varekamp I, Brocker-Vriends AH, Van Dijck H, Suurmeijer TP, *et al.* Modern haemophilia treatment· medical improvements and quality of life *J Intern Med*, 1990, **228:** 633–640.

5 Rizza CR, Spooner RJD. Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976–80: report on behalf of the directors of haemophilia centres in the United Kingdom. *Brit Med J*, 1983, **286:** 929–33.

6 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Prophylactic treatment of severe hemophilia A and B can prevent joint disability. *Semin Hemat*, 1994, 31 (Suppl. 2) 5–9.

7 Petrini P, Blomback M, Lindvall N. Prophylaxis with factor concentrates in preventing hemophilic arthropathy. *Am J Paediatr Hemat Oncol*, 1991, **13:** 280–287.

8 Jones P Haemophilia home therapy. *Haemostasis*, 1992; **22:** 247–50.

9 Rizza CR, Spooner RJD. Home treatment of haemophilia and Christmas disease. five years experience. *Brit J Haemat*, 1977; **37:** 53–66

10 Bohn RL, Avorn J. Cost-effectiveness, can it be measured? *Semin Hemat*, 1993; **30** (Suppl 2) 20–23.

11 Hoskinson J, Duthie RB. Management of musculoskeletal problems in the hemophilias. *Orthop Clin North Amer*, 1978, **9:** 455–480.

12 Ahlberg A. Haemophilia in Sweden. VII. Incidence, treatment and prophylaxis of arthropathy and other musculoskeletal manifestations of haemophilia A and B. *Acta Orthop Scand*, 1965, **Suppl. 77:** 7–80.

13 Triemstra AHM, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Changes in mortality among haemophilia patients. (Submitted).

14 Pettersson H, Gilbert M. *Diagnostic Imaging in Hemophilia; Musculoskeletal and Other Hemorrhagic Complications.* Berlin: Springer, 1985 56–65.

15 Pettersson H. Can joint damage be quantified? *Semin Hematol*, 1994· **31** (Suppl. 2) 1–4.

16 Gilbert MS. Prophylaxis· musculoskeletal evaluation. *Semin Hemat*, 1993, **30** (Suppl. 2). 3–6.

17 Gamble JG, Bellah J, Rinsky LA, Glader B. Arthropathy of the ankle in hemophilia. *J Bone Joint Surg*, 1991; **73A:** 1008–1015

18 Johnson RP, Babbitt DP. Five stages of joint disintegration compared with range of motion in hemophilia. *Clin Orthop*, 1985, **201:** 36–42.

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