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Life expectancy of Swedish haemophiliacs, 1831–1980

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SUMMARY. Life expectancy of Swedish haemophiliacs has been estimated for the period 1831–1980. The data were derived from 948 haemophiliacs of whom 580 survived throughout 1980. Applying standard demographic techniques, median life expectancy of patients with severe haemophilia was found to have increased fivefold, from a mere 11 years during the period 1831–1920 to 56·8 years during 1961–80. The corresponding estimates for patients with moderate haemophilia were 27·5 and 71·5 years, respectively. The limited data on patients with mild haemophilia did not indicate any significant improvements in mortality. From the beginning of this century to 1980 median life expectancy for Swedish males increased from 61·7 years to 75·6 years, an increase of 23%. Analysing the last 12 years of the study (1969–80), death rates for patients with severe haemophilia below the age of 45 were not much different from those of Swedish males in the population as a whole. The investigation implies that the mortality of haemophiliacs in Sweden is approaching that of the total male population.

Factor concentrate for haemophilia A treatment has been available in Sweden since 1956 (Nilsson *et al*, 1957). The prognosis for Swedish haemophiliacs in terms of age at death did not improve until the end of the 1960s when a salient increase was found (Larsson & Wiechel, 1983). At this time, factor concentrate also became available for treatment of haemophilia B (Nilsson *et al*, 1971). A better way, however, to assess the prognosis is to estimate the life expectancy which also takes into consideration the distribution of ages of living haemophiliacs. Very few papers on life expectancy in haemophilia have previously been published (Stafford *et al*, 1980; Kamps & Blanco, 1981; Ikkala *et al*, 1982; Rizza & Spooner, 1983).

Sweden established national registration in the 1750s, thus providing a sound basis for population research. Therefore it was regarded worthwhile investigating life expectancy for all known haemophiliacs in Sweden since 1831.

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MATERIALS AND METHODS

Study group

Only patients with haemophilia A (factor VIII:C deficiency) and haemophilia B (factor IX deficiency) were included in the study. Previous Swedish surveys of haemophiliacs served as sources (Sköld, 1944; Ramgren, 1962; Ahlberg, 1965; Larsson *et al*, 1982; Larsson & Wiechel, 1983). Patients diagnosed in 1981 and 1982 were also included if born no later than 31 December 1980.

Definitions

Severity. In Sweden, laboratory testing of clotting factor activity was not possible until 1956 (Nilsson *et al*, 1957). The severity of haemophilia in patients who died before 1956 could only be ascertained if the clotting factor activity of another affected family member was tested after 1956. The severity of patients in families who had become extinct was based on clinical symptoms and/or on available laboratory procedures such as coagulation time.

The bleeding disorder was classified as *severe* if the factor activity was less than 1% of the activity in normal plasma, *moderate* if it was 1–4% and *mild* if it was 5–25%.

Periods. The period of study was divided into four sub-periods, 1831–1920, 1921–40, 1941–60 and 1961–80.

Statistics

Estimation of death rates and of median life expectancy. To estimate central death rates, 5-year age groups were employed and the assumption was made that the deaths were uniformly distributed within each age group. The survival function was estimated using standard demographic techniques (Colton, 1974). The median life expectancy was defined as the age to which half the members of a synthetic cohort survived. Ancillary data for the Swedish male population were obtained from the official publications of Statistics Sweden.

RESULTS

The total number of patients traced was 948 of whom 580 were alive on 31 December 1980. The allocation into different subperiods is given in Table I. The percentage allocation of living haemophiliacs into the different severity groups remained constant during the period of study. The percentages who died of the total number of patients registered in each sub-period as well as the severity are given at the bottom of the table. During the first three sub-periods the percentage of patients with mild haemophilia who died was only 6·3–9·8%. There was a continuous decrease in the percentage of patients with severe haemophilia among the deceased with a corresponding increase in patients with mild haemophilia.

In Fig 1 the increase in the number of known haemophiliacs in Sweden is illustrated. It

Table I. Number of patients, living and deceased, in the sub-periods of study

	1831–1920				1921–40				1941–60				1961–80			
Patients	Sev	Mod	Mild	Total	Sev	Mod	Mild	Total	Sev	Mod	Mild	Total	Sev	Mod	Mild	Total
Living at the end of the period	66	33	129	228	92	53	209	354	126	82	290	498	169	94	317	580
(%)	(28·9)	(14·5)	(56·6)	(100·0)	(26·0)	(15·0)	(59·0)	(100·0)	(25·3)	(16·5)	(58·2)	(100·0)	(29·1)	(16·2)	(54·7)	(100·0)
Deceased during the period	71	13	14	98	47	9	14	70	63	10	29	102	30	12	56	98
(%)	(72·4)	(13·3)	(14·3)	(100·0)	(67·1)	(12·9)	(20·0)	(100·0)	(61·8)	(9·8)	(28·4)	(100·0)	(30·6)	(12·3)	(57·1)	(100·0)
Subtotal	137	46	143		139	62	223		189	92	319		199	106	373	
Total		326				424				600				678		
Percentage dead of subtotal	51·8	28·3	9·8		33·8	14·5	6·3		33·3	10·9	9·1		15·1	11·3	15·0	

Sev = severe; Mod = moderate.

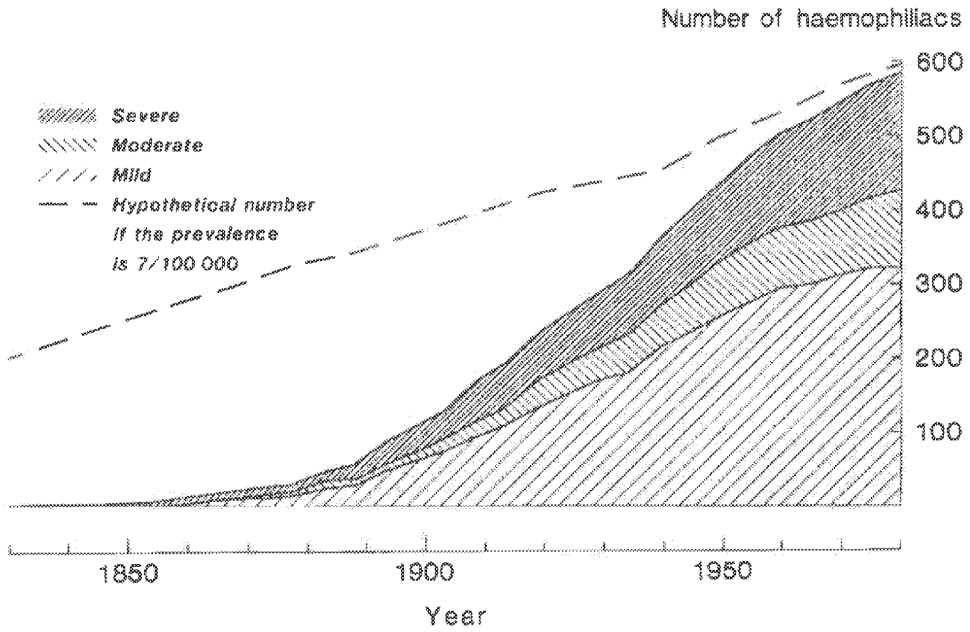

Fig 1. Number of known haemophiliacs in Sweden, allocated into severities, 1831–1980.

has been proposed that the 'true prevalence' of haemophilia should be 7(–8) per 100 000 population (Biggs, 1979). This hypothetical number of haemophiliacs is also given in the figure.

In 1940 Sköld (1944) described 101 living haemophiliacs in Sweden and in 1960 Ramgren (1962) published case reports on 253 patients. Using the case reports in Ramgren's dissertation, the number of living haemophiliacs in Sweden was estimated to have been about 205 in 1940. The present investigation demonstrated that the number of haemophiliacs was at least 354 in 1940 and 498 in 1960.

No difference in longevity was found between haemophilia A and B. Hence, no distinction between the two types was made in the investigation.

The increase in median life expectancy in severe haemophilia was fivefold, from 11·4 years (1831–1920) to 56·8 years in the most recent sub-period of study. Moderate haemophilia experienced more than a doubling of median life expectancy, from 27·5 years to 71·5 years. No calculation was made for mild haemophilia for the periods 1831–1920 and 1921–40 owing to the small number of patients diagnosed. For the same reason the data on moderate haemophilia are less reliable for these periods. In the last 90 years, the median life expectancy of Swedish men increased from 61·7 years to 75·6 years, i.e. by 23%. The median life expectancy is given in Table II. Corresponding data for Swedish men from the general population are also given in the table.

The life expectancy of severe, moderate and mild haemophilia in the different sub-periods is shown in Figs 2–4. The mortality for three control groups of Swedish males, 1891–1900, 1936–40 and 1976–80, is also shown in Figs 2–4.

It has previously been shown that the main achievements in haemophilia treatment did not appear until the end of the sixties (Larsson & Wiechel, 1983). If only the last 12 years,

Table II. Median life expectancy (years)

	1831–1920			1921–40			1941–60			1961–80		
	Sev	Mod	Mild	Sev	Mod	Mild	Sev	Mod	Mild	Sev	Mod	Mild
Haemophiliacs	11·4	27·5*	—	23·3	41·5*	—	26·4	56·6	70·1	56·8	71·5	72·1
Swedish men (period)	61·7 (1891–1900)			71·7 (1936–40)			75·3 (1956–60)			75·6 (1976–80)		

Sev = severe; Mod = moderate. * Unreliable data due to a small number of patients.

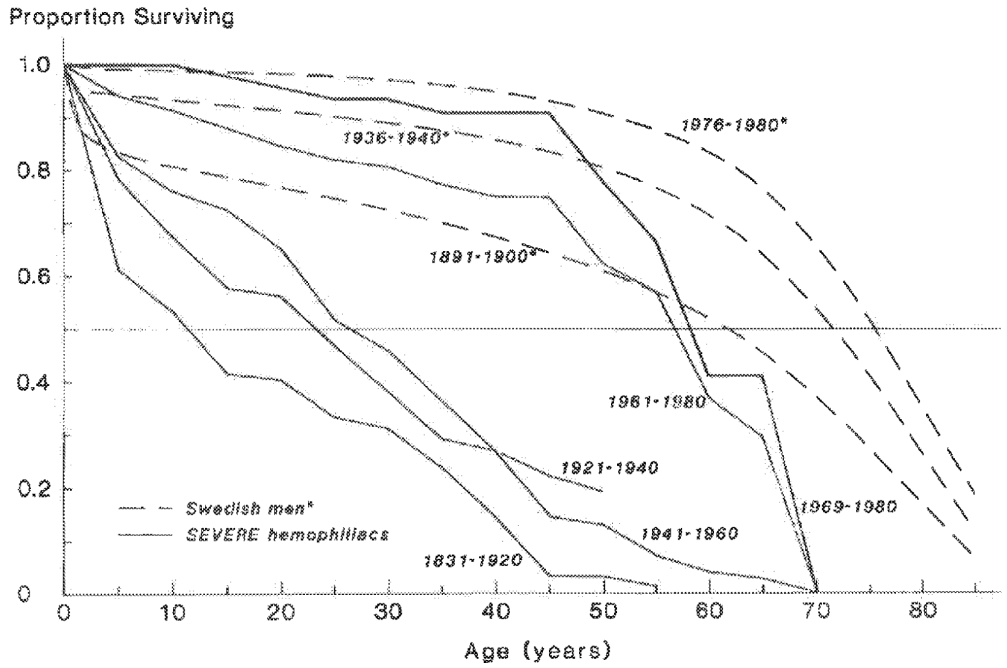

Fig 2. The proportion of surviving severe haemophiliacs in the periods 1831–1920, 1921–40, 1941–60, 1961–80 and 1969–80. Corresponding curves for Swedish men, 1891–1900, 1936–40 and 1976–80 are given for comparison.

1969–80, are considered (Fig 2), it will be observed that the death rates were almost the same in severe haemophilia as for Swedish males from the population up to the age of 45. The median life expectancy of patients with severe haemophilia was 58·2 years in 1969–80. The overall death rate was 6·5 per thousand. Only 10% of the Swedish haemophiliacs were above the age of 45 in 1980 (Larsson *et al*, 1982).

An abridged life table for severe, moderate and mild haemophilia for the period 1961–80 is presented in Table III.

During the period 1961–80 five patients with inhibitors died. Twenty-five patients had inhibitors and were alive at the end of the study. The death rates were higher than for severe

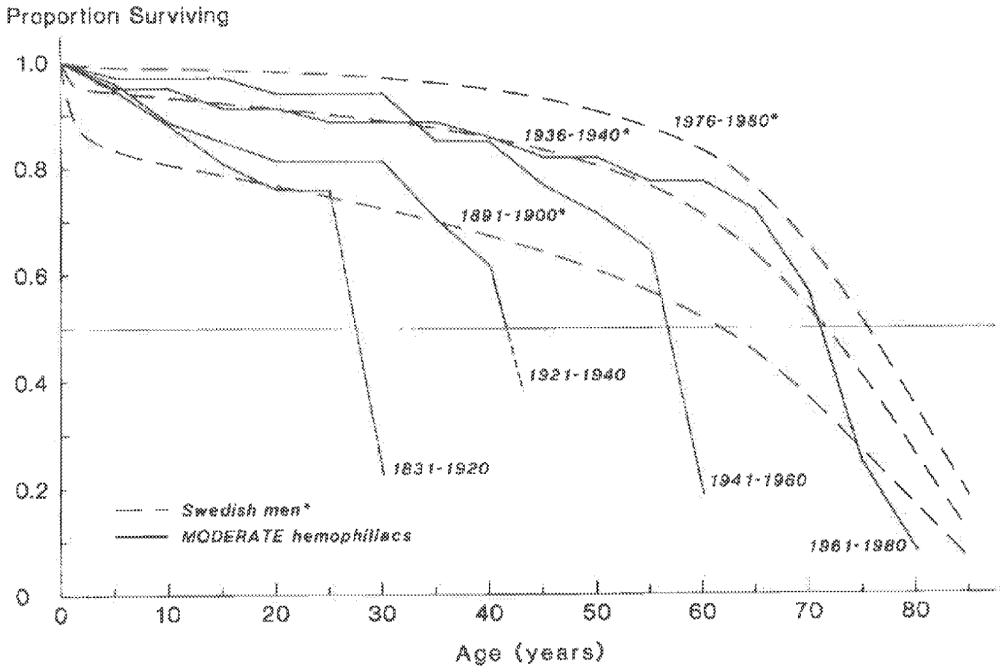

Fig 3. The proportion of surviving moderate haemophiliacs in the periods 1831–1920, 1921–40, 1941–60 and 1961–80. Corresponding curves for Swedish men, 1891–1900, 1936–40 and 1976–80 are given for comparison.

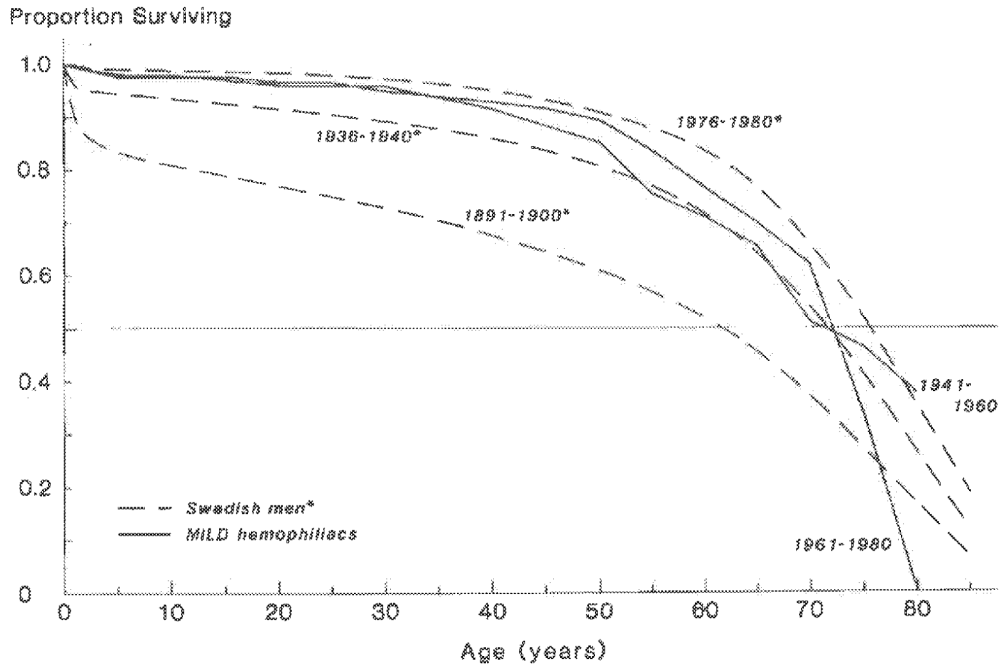

Fig 4. The proportion of surviving mild haemophiliacs for the periods 1941–60 and 1961–80. Corresponding curves for Swedish men, 1891–1900, 1936–40 and 1976–80 are given for comparison.

Table III. Abridged life table for Swedish haemophiliacs, 1961–80

Age group (1)	Severe				Moderate				Mild				Swedish men 1976–80 Death rate per thousand
	Deaths (2)	Person years at risk (3)	Death rate per thousand (2)/(3)	Surviving of 100 000	Deaths (2)	Person years at risk (3)	Death rate per thousand (2)/(3)	Surviving of 100 000	Deaths (2)	Person years at risk (3)	Death rate per thousand (2)/(3)	Surviving of 100 000	
0–4	4	331·5	12·07	93967	1	102·0	9·80	95098	2	403·0	4·96	97519	2·08
5–9	2	391·0	5·13	91564	0	126·0	0	95098	0	524·0	0	97519	0·30
10–14	3	376·5	7·99	87916	1	124·5	8·03	91279	0	535·0	0	97519	0·27
15–19	3	389·5	7·70	84530	0	148·0	0	91279	1	515·5	1·94	96573	0·77
20–24	2	353·0	5·67	82135	1	179·5	5·57	88736	0	539·0	0	96573	1·08
25–29	1	298·5	3·35	80759	0	184·0	0	88736	2	524·0	3·82	94730	1·20
30–34	2	232·0	8·62	77278	0	184·0	0	88736	1	497·5	2·01	93778	1·35
35–39	1	175·5	5·70	75077	1	146·5	6·83	85708	1	468·5	2·13	92777	1·87
40–44	0	131·0	0	75077	1	113·5	8·81	81932	1	452·5	2·21	91752	2·83
45–49	3	87·5	34·29	62207	0	92·0	0	81932	2	406·0	4·93	89492	4·33
50–54	1	61·5	16·26	57149	1	91·5	10·93	77455	5	369·5	13·53	83437	6·85
55–59	3	42·5	70·59	36979	0	98·0	0	77455	5	306·5	16·31	76631	10·77
60–64	1	25·5	39·22	29728	1	70·5	14·18	71962	4	225·0	17·78	69820	17·07
65–69	3	10·5	285·71	—	2	47·0	42·55	56651	4	176·0	22·73	61886	27·32
70–74	0	5·0	0	—	2	25·0	80·00	33990	10	110·0	90·91	33756	43·20
75–79	1	1·5	666·67	—	1	6·5	153·85	7844	11	55·5	198·20	304	65·81
80–84									3	27·5	109·09	138	94·48
85–89									4	14·0	285·71	—	127·02
All	30	2912·5	10·30		12	1737·5	6·91		56	6149·0	9·11		12·05

haemophiliacs without inhibitors and median life expectancy was estimated to approximately 45 years.

DISCUSSION

Two shortcomings of the present study group should be briefly commented on.

Firstly, during the first one hundred years of study only a minor fraction of all haemophiliacs in Sweden were diagnosed (Fig 1), indicating a pronounced under-reporting. This was further illustrated when comparison was made with previous Swedish surveys. Sköld (1944) was aware of only half of the haemophiliacs alive in 1940 according to Ramgren in 1962. However, the present investigation revealed that Ramgren underestimated the prevalence in 1940 and 1960 by half. This underestimation was largely found among the mild cases (Larsson *et al*, 1982). Only the future will tell whether the present estimate is correct or not. As can be seen in Fig 1, the increase in the number of known haemophiliacs is levelling off. This might indicate that the number of known patients was close to the true number of haemophiliacs in Sweden, though a number of patients with mild haemophilia were no doubt undiagnosed as these patients rarely have any symptoms before the age of 5.

Secondly, it can be seen from the survival curves (Figs 2–4) that the infant mortality in mild and moderate haemophilia was grossly understated in relation to the total male population, but of course the haemophiliacs as a sub-population in Sweden faced at least the same infant mortality as the rest of the population. Several infant deaths were simply not recognized as having been caused by haemophilia.

In a survey of 490 patients treated at the Haemophilia Centre in Portland, Oregon, Stafford *et al* (1980) found 105 deaths and an increase in life expectancy from 50·5 years in 1930 to 64·9 in the 1970s. Kamps & Blanco (1980) reported the life expectancy in Chilean haemophiliacs to be 35 years in 1965 and 43 years in 1975. The corresponding age for Chilean males was 58·3 years in 1970. No information about type and severity of the patients was supplied in these two papers. Since the study groups and the statistical methods used were incompatible with the present investigation, no further comparison was possible.

In Finland Ikkala *et al* (1982) analysed all known patients with severe haemophilia A 1930–79. In the youngest age group, 0–9 years, the annual death rate decreased from 56·3 in 1930–39 to 4·8 per thousand in 1970–79. The overall death rate for severe haemophilia decreased during the same periods from 39·2 to 6·5 per thousand, being less than the annual death rate of the population, which was 10·6 per thousand in 1979. It must still be remembered, however, that the haemophilic population had a much lower median age than the general population.

Recently, Rizza & Spooner (1983) published data from the haemophilia centres in the United Kingdom. This compilation of 5098 haemophiliacs is probably the largest one presented in the literature. The annual death rate for haemophilia A was based on 89 deaths and 18 354 'patient years at risk'. The overall annual death rate for severe haemophilia A (VIII:C $<2\%$) was 6·3 per thousand for the period 1976–80. The same death rate was observed by Ikkala *et al* (1982) and in this investigation. The median life expectancy was

69·2 years for patients with less than 2% VIII:C and 79·2 years for those with 2–10% VIII:C. English males faced a median life expectancy of 72·8 years in 1977–79.

There are at least two pitfalls when predicting future achievements:

The prevalence of elevated liver enzymes among haemophiliacs receiving repeated treatments with concentrates is increasing and might be an indicator of a widespread occurrence of chronic liver disease caused by different types of hepatitis (Jones, 1983; Schulman & Wiechel, 1984). So far, no one knows the long-term prognosis for patients with 'chronic liver dysfunction' caused by repeated exposure to (contaminated?) blood products (Hadziyannis, 1981). A future increase in the number of haemophiliacs with liver cirrhosis and subsequent portal hypertension might altogether change the favourable development of life expectancy (Lesesne *et al*, 1982; Jones, 1983; Woodcock & Lilleyman, 1983).

The appearance of AIDS in the spectrum of treatment complications may lead to some reconsideration (Curran, 1983; Daly & Scott, 1983; Jones, 1983). So far, however, no haemophiliac in Sweden has contracted AIDS.

The present investigation showed a substantial improvement in the longevity of Swedish haemophiliacs over the past 150 years. The increment in median life expectancy was much greater among haemophiliacs than among Swedish males. The main improvement, particularly in severe haemophilia, coincided with the introduction of adequate prophylaxis during the last 20 years. In moderate and mild haemophilia, median life expectancy was just a few years less than that of Swedish males but patients with severe haemophilia still experienced excess mortality. They will, however, benefit from future advances in haemophilia treatment. If the trend found in this investigation persists, it seems likely that the prognosis of haemophilia in terms of life expectancy should gradually approach that of the general population.

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HIGH-POTENCY ANTIHAEMOPHILIC FACTOR CONCENTRATE PREPARED FROM CRYOGLOBULIN PRECIPITATE.

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