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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

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Abstract

A five year survey of the treatment of patients in the United Kingdom suffering from haemophilia and related disorders was carried out on behalf of the directors of haemophilia centres. The survey showed an increase in the number of patients receiving treatment from the centres, a substantial increase in the total amount of therapeutic materials used, and an increase in the average amount of factor VIII or factor IX used yearly per patient. Home treatment became established for severely affected patients and accounted for roughly half of the total amount of material used. Study of the acquisition of factor VIII or factor IX antibodies (inhibitors) in patients with haemophilia A or haemophilia B showed no increase in antibodies during the survey period, despite the increased use of factor VIII and factor IX concentrates. The occurrence of acute hepatitis in treated patients was also studied and no increased incidence was observed. A near normal median expectation of life in patients with severe haemophilia A was found.

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Introduction

ORGANISATION OF TREATMENT

The care of haemophiliacs in the United Kingdom is organised through recognised haemophilia centres situated in National Health Service hospitals throughout the country. The concept of these centres was established in Britain in 1954 to provide specialist diagnostic, registration, and treatment services for haemophilic patients. The present system, which incorporates three types of centres—haemophilia reference centres, haemophilia centres, and associate haemophilia centres—was defined in 1976 by the Department of Health and Social Security in a memorandum (HC(76)4) to regional health authorities and family practitioners. The number of centres gradually increased over the years, and by 1980 there were 10 centres acting as reference centres and nearly 100 other centres.

Each reference centre is responsible for the provision of an advisory clinical and laboratory service to individual haemophilia centres in a wide area (referred to as a "supraregion"). Some centres have staff, laboratory and clinical facilities, and funds specifically allocated for the haemophilia work, but most centres

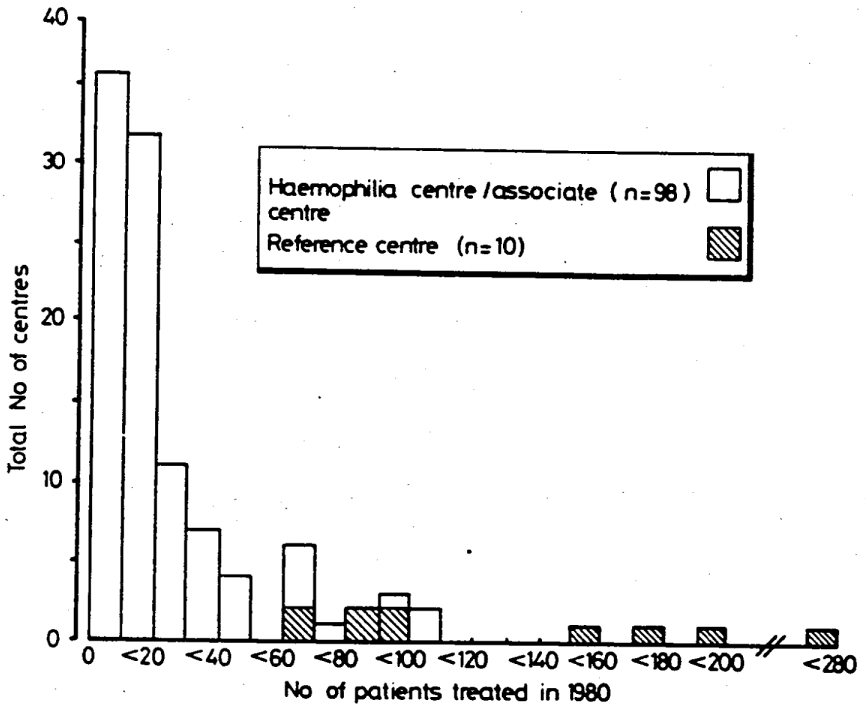

FIG 1—Numbers of patients treated during 1980 at haemophilia centres in United Kingdom.

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are run by the staff of haematology departments, medical departments, or blood transfusion centres as part of their routine service commitment. All haemophilia centres, irrespective of category, are expected to provide 24 hour emergency treatment for haemophilic patients. The number of patients treated each year by centres varies considerably (fig 1). One third of all centres treated fewer than 10 patients in 1980 and two thirds treated fewer than 20.

Since 1969 the directors of the haemophilia centres have collected information about the amount and types of therapeutic materials used to treat patients who have haemophilia A (classical haemophilia: factor VIII deficiency) or haemophilia B (Christmas disease: factor IX deficiency) and about the complications of treatment. In 1976 the directors decided to extend their survey to obtain information on all known patients with haemophilia A or B, including those who had not received treatment, so that more accurate information would be available regarding the total number of patients with the two types of haemophilia in Britain and Northern Ireland. The directors also decided that from 1976 onwards they would collect information on patients receiving home treatment and details about carriers of haemophilia A or B and patients with von Willebrand's disease who required treatment at centres. Reports for the years 1969-75 have been published.[1-4] This report is concerned mainly with the treatment of patients during the five years 1976-80, but information from previous years is included where long term trends are being considered.

Report

NUMBERS OF PATIENTS WITH HAEMOPHILIA A AND B

During the study period there was a yearly increase in the numbers of patients known to have haemophilia A and B, and by December 1980 there were 4321 patients with haemophilia A and 777 with haemophilia B known to the directors of the centres (table Im (miniprint)). The incidences of antibody against factors VIII and IX were 6·0% and 0·9% respectively and had changed little during the period or indeed during the past 11 years[2,3] despite more intensive treatment with concentrated preparations of clotting factors in later years.

Tables IIm and IIIm show the age and severity groupings of the patients. To facilitate comparison with other reports these tables also show the total number of haemophiliacs in each age group in December 1974 and the percentage of male subjects in each age group in the normal male population (1971 Census). Of the 4321 known patients with haemophilia A and the 777 with haemophilia B, 1903 (44%) and 276 (36%) were severely affected. There was a preponderance of patients aged 10-40 when compared with normal males but a relative

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MINIPRINT TABLES Im-IVm

Im

TABLE I—*Numbers of patients with haemophilia A and haemophilia B and numbers with factor VIII or IX antibodies detected. Patients known to have died before year specified excluded*

Year	Haemophilia A			Haemophilia B		
	Cumulative No of patients registered	Cumulative No (%) with factor VIII antibodies	No of new antibody cases detected	Cumulative No of patients registered	Cumulative No (%) with factor IX antibodies	No of new antibody cases detected
1975	2839	182 (6·4)	18	663	5 (1·1)	0
1976	3192	195 (6·1)	18	548	5 (0·9)	0
1977	3566	208 (5·9)	20	621	6 (1·0)	1
1978	3916	225 (5·8)	17	686	6 (0·9)	0
1979	4122	245 (5·9)	19	725	7 (1·0)	1
1980	4321	258 (6·0)	13	777	7 (0·9)	0

IIm

TABLE II—*Age distribution and severity of coagulation defect in patients with haemophilia A known to haemophilia centre directors on 31 December 1980*

Age (years)	Factor VIII value (%, average normal)				Total		Figures for 1974		Normal males in UK population (%)*
	<2	2–10	>10	NK	No	%	Total No	%	
5	114	58	30	4	206	4·8	129	5·1	8·4
5–9	194	103	49	16	322	7·4	289	11·4	8·4
10–19	680	260	186	58	838	22·3	646	25·5	15·0
20–29	629	232	144	34	670	19·4	509	20·0	14·8
30–39	322	186	130	32	670	10·2	329	13·0	12·2
40–49	122	139	96	22	443	7·2	222	8·7	12·6
50–59	98	109	69	20	311	5·0	158	6·2	12·0
60–69	67	76	57	15	215	2·8	84	3·3	10·0
≥70	30	45	41	5	121	1·4	42	1·6	5·7
NK	23	28	14	167	232	5·4	130	5·1	—
Total	1903 (44·0)	1236 (28·6)	829 (19·2)	353 (8·2)	4321 (100·0)	100·0	2538	100·0	99·1

NK = Not known. *Figures from 1971 Census.

IIIm

TABLE III—*Age distribution and severity of coagulation defect in patients with haemophilia B known to haemophilia centre directors on 31 December 1980*

Age (years)	Factor IX value (%, average normal)				Total		Figures for 1974		Normal males in UK population (%)*
	<2	2–10	>10	NK	No	%	Total No	%	
5	18	15	6	0	39	5·0	22	5·8	8·4
5–9	25	28	15	0	68	8·8	39	10·3	8·4
10–19	70	60	30	8	168	21·6	107	28·3	15·0
20–29	57	66	37	7	169	19·2	72	19·0	14·8
30–39	54	35	24	10	123	15·8	39	10·3	12·2
40–49	21	34	10	7	72	9·3	36	9·5	12·6
50–59	14	19	10	3	46	5·9	21	5·5	12·0
60–69	8	19	8	7	42	5·4	15	4·0	10·0
≥70	9	13	6	4	28	3·6	10	2·6	5·7
NK	4	4	5	28	41	5·3	18	4·8	—
Total	276 (35·5)	275 (35·4)	151 (19·4)	75 (9·7)	777 (100·0)	100·0	379	100·0	99·1

NK = Not known. *Figures from 1971 Census.

IVm

TABLE IV—*Age at death of patients with haemophilia A and haemophilia B and severity of coagulation defect*

	Age (years)									Total	Total at risk in severity groups
	10	10–19	20–29	30–39	40–49	50–59	60–69	≥70	NK		
	Haemophilia A										
Factor VIII value*											
<2	4	2	12	13	7	7	9	4	—	58	1903
2–10	1	—	—	4	1	2	5	7	—	20	1236
>10	—	1	—	1	—	1	2	3	—	8	829
NK	—	—	—	—	1	—	—	1	1	3	353
Total	5	3	12	18	9	10	16	15	1	89	—
Total at risk in age groups	528	962	890	670	443	311	215	121	232	—	4321
	Haemophilia B										
Factor IX value*											
<2	—	—	—	1	—	2	3	1	—	7	276
2–10	1	1	1	—	2	—	2	—	—	8	275
>10	1	—	—	—	—	—	—	1	—	2	151
NK	—	—	—	1	—	—	—	—	—	1	75
Total	2	1	1	2	2	2	5	3	—	18	—
Total at risk in age groups	108	166	149	123	72	46	42	28	41	—	777

NK = Not known. *Expressed as %, average normal.

deficiency in patients aged less than 10 years or more than 40. When the severely affected patients (factor VIII value <2% of average normal) and mildly affected patients (factor VIII value >2% of average normal) were considered as separate groups there was, as expected, a much smaller proportion of severely affected patients aged above 50 compared with mildly affected patients. On the other hand, there seemed to be proportionately fewer patients aged less than 20

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in the mildly affected group than in the severely affected group. This latter difference may have been due to delay in the diagnosis of the mild form of the condition. Compared to 1974 a larger proportion of haemophiliacs seemed to be reaching middle and old age; a quarter of the patients with haemophilia A in 1980 were more than 40 years of age compared with one fifth in 1974.

AGE AT DEATH AND CAUSES OF DEATH

Eighty nine patients with haemophilia A and 18 with haemophilia B died during 1976-80. Table IVm shows the age at death and severity of the haemophilia and table Vm lists the causes of death. Sixty six of the 107 deaths reported (62%) were in patients suffering from severe haemophilia A or B. Twenty of the patients with haemophilia A who died (22%) had factor VIII antibodies in their blood, and one of the patients with haemophilia B who died had factor IX antibodies. The average ages of the patients who died were 46·7 years in the haemophilia A group and 48·3 years in the haemophilia B group. Comparable figures for 1969-74 were 42·3 years and 33·6 years, respectively.

A more useful statistic was the median expectation of life. This was calculated from life tables derived from the information on the number of deaths in each age and severity group and total numbers at risk in each age and severity group during the five years of the survey. Surprisingly the calculations yielded a median life expectancy of 69·1 years for severely affected haemophiliacs as compared with 72·8 years for normal males (appendix Im (miniprint)). Those figures must clearly be viewed with caution, since the numbers in the calculations were relatively small and also because of the possibility that deaths in haemophiliacs may not all be reported to haemophilia centre directors. Median expectation of life for the group of patients with factor VIII values greater than 10% of average normal were not calculated because of the small number of deaths which had occurred. Also many such patients probably go undetected owing to the mildness of their clinical symptoms. It is therefore difficult to be sure of the total number in the group "at risk" for the purpose of calculating "probability of death" rates.

Cerebral haemorrhage was the commonest cause of death in haemophilia A and accounted for 26 of the 89 deaths (29%). Two thirds of the cerebral haemorrhages occurred in severely affected patients. Other types of haemorrhage accounted for 11 deaths (12%). Hepatitis was recorded as the cause of death in one patient with haemophilia A and one with haemophilia B, and there were five suicides. In 11 cases (12%) the cause of death was not known. As expected, there was a greater incidence of death from haemorrhage in patients with antibodies than in those without antibodies: bleeding accounted for 55% of deaths in patients with antibody and 38% of deaths in patients without antibody.

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AMOUNT AND TYPES OF THERAPEUTIC MATERIAL USED

Figures 2 and 3 show the long term changes in usage of the different blood products, and tables VIm and VIIm show in more detail the type and amount of the various therapeutic materials used in the management of haemophilia A and B during 1976-80. The total amount of factor VIII used steadily increased each year from $33{\cdot}716 \times 10^6$ units in 1976 to $57{\cdot}0 \times 10^6$ units in 1980. In 1976 nearly half of the factor VIII used was in the form of cryoprecipitate. Usage of this material decreased during the survey period and in 1980 accounted for only 14% of the total number of factor VIII units given. The use of commercial factor VIII concentrate, on the other hand, showed a steady increase each year and in 1980 represented 60% of the total factor VIII used.

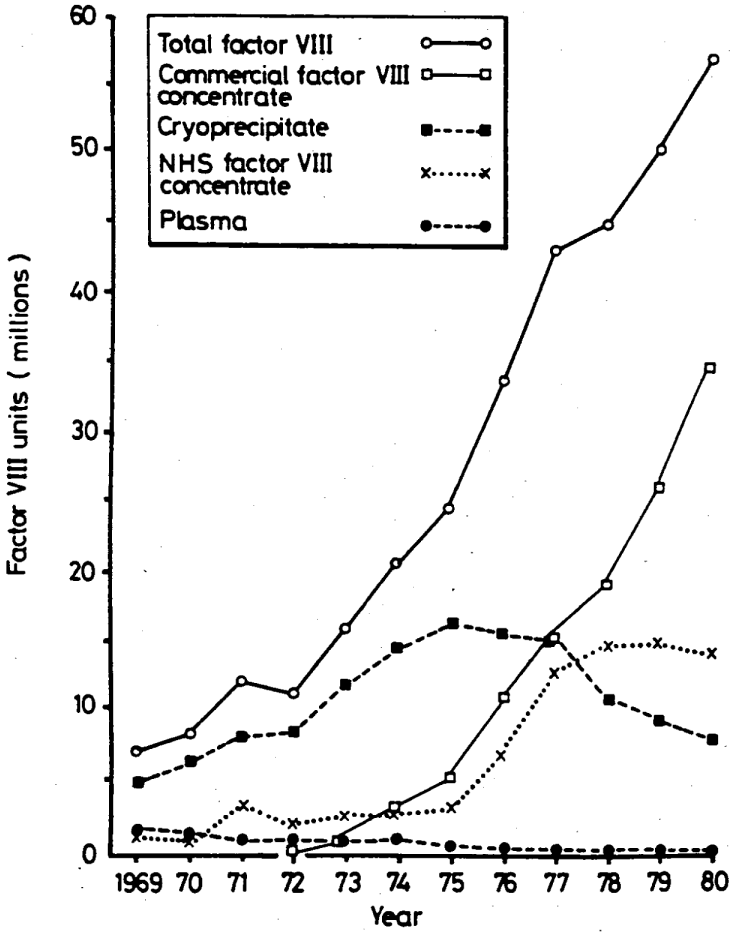

FIG 2—Amount of different types of materials containing factor VIII and total amount of factor VIII activity units used each year during 1969-80 by haemophilia centres in United Kingdom to treat patients for haemophilia A.

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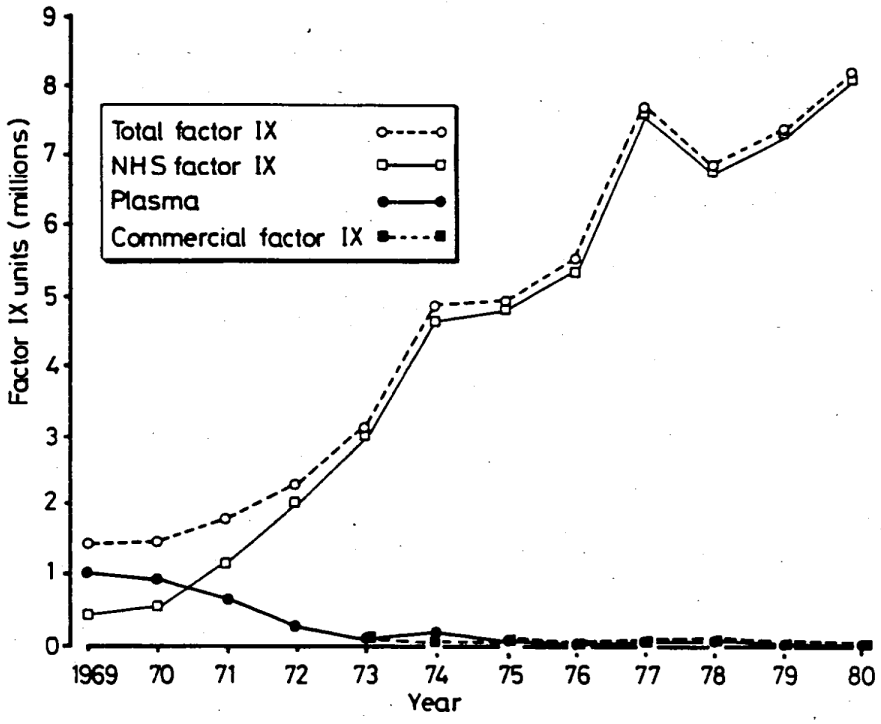

FIG 3—Amount of different types of materials containing factor IX and total amount of factor IX activity units used each year during 1969-80 by haemophilia centres in United Kingdom to treat patients for haemophilia B.

Usage of factor VIII manufactured by NHS laboratories doubled from 1976 to 1977 but the amount used each year then changed very little and in 1980 represented a quarter of all factor VIII used. This low usage almost certainly reflected the relatively low output from the NHS fractionation laboratories and not a preference for commercially prepared concentrates. The average amount of factor VIII used yearly per patient increased each year and in 1980 was 27 181 units. In 1977-80 some centres reported that desmopressin (DDAVP) had been used to treat mild haemophilia A. The numbers of patients treated with this drug were 8, 10, 20, and 12 in successive years from and including 1977.

With regard to amounts of factor IX used in the treatment of haemophilia B this also showed a trend upwards, rising from $5{\cdot}563 \times 10^6$ units in 1976 to $8{\cdot}272 \times 10^6$ units in 1980 (table VIIm). This increase was accounted for in part by the increase in number of patients treated but also by an increase in the yearly amount received per patient. Some 99% of the factor IX concentrate used was prepared by NHS fractionation laboratories. Enough factor IX is made by those laboratories to meet the needs of patients with haemophilia B in Britain and there seems little if any need to purchase factor IX from commercial companies.

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MATERIALS USED FOR TREATMENT OF PATIENTS WITH ANTIBODY AGAINST FACTOR VIII OR FACTOR IX

Information on the use of factor VIII or IX replacement was available only for 1977, 1978, 1979, and 1980 (table VIIIm). The therapeutic material used included human factor VIII concentrate, activated and non-activated human prothrombin complex concen-

MINIPRINT TABLES Vm–IXm

Vm

TABLE V—*Causes of death in patients with haemophilia A and haemophilia B (1976–80). Figures are numbers of patients (numbers with antibodies given in parentheses)*

Causes	Haemophilia A	Haemophilia B
Cerebral haemorrhage/"stroke"	26 (5)	4 (1)
Other types of bleeding	11 (6)	1
Postoperative complications	6 (2)	—
Suicide	5	—
Neoplasm	7	3
Pulmonary embolism	2	—
Pneumonia	4	—
Hepatitis	1 (1)	1
Myocardial infarct	1	3
Accidents	4	2
Not known	11 (1)	4
Miscellaneous non-haemorrhagic conditions	11 (5)	—
Total	99 (20)	18 (1)

VIm

TABLE VI—*Human factor VIII preparations used by haemophilia centres during 1976–80 to treat patients with haemophilia A and number of patients treated each year with these products*

Material	Factor VIII units									
	1976		1977		1978		1979		1980	
	Amount	%, Total	Amount	%, Total	Amount	%, Total	Amount	%, Total	Amount	%, Total
Plasma	15 000	< 0·1	1 000	< 0·1	5 000	< 0·1	32 000	< 0·1	1 000	< 0·1
Cryoprecipitate	15 717 000	46·6	15 226 000	35·3	10 980 000	24·4	9 414 000	18·1	8 153 000	14·2
NHS factor VIII concentrate	6 915 000	20·5	12 949 000	30·0	14 800 000	32·9	15 092 000	30·0	14 368 000	25·1
Commercial factor VIII concentrate	11 089 000	32·8	15 017 000	34·8	19 273 000	42·8	26 178 000	51·9	34 749 000	60·7
Total	33 716 000	100·0	43 193 000	100·0	45 058 000	100·0	50 716 000	100·0	57 271 000	100·0
No of patients treated	3 886	—	1 975	—	2 048	—	2 053	—	2 107	—
Average amount of factor VIII used per patient	17 877	—	21 870	—	22 000	—	24 703	—	27 181	—

VIIm

TABLE VII—*Factor IX preparations used by haemophilia centres in 1976–80 to treat patients with haemophilia B and number of patients treated each year with these products*

Material	Factor IX units									
	1976		1977		1978		1979		1980	
	Amount	%, Total	Amount	%, Total	Amount	%, Total	Amount	%, Total	Amount	%, Total
Plasma	16 000	0·3	31 000	0·4	28 000	0·4	3 000	< 0·1	1 000	< 0·1
NHS factor IX concentrates	5 533 000	99·5	7 621 000	98·9	6 799 000	99·4	7 362 000	100·0	8 194 000	99·1
Commercial factor IX concentrates	12 000	0·2	52 000	0·7	11 000	0·2	Nil	—	77 000	0·9
Total	5 563 000	100·0	7 704 000	100·0	6 827 000	100·0	7 365 000	100·0	8 272 000	100·0
No of patients treated	296	—	332	—	330	—	344	—	355	—
Average amount of factor IX used per patient	18 796	—	23 205	—	20 688	—	21 410	—	23 301	—

VIIIm

TABLE VIII—*Type and amount (activity units) of material used to treat patients with antibodies against factor VIII or IX*

	1977	1978	1979	1980
	Haemophilia A			
No of patients with antibodies treated	116	131	124	121
Human factor VIII	2 589 000	3 249 000	4 011 000	4 491 000
Porcine factor VIII	16 000		279 000	378 000
NHS factor IX	266 000	124 000	50 000	214 000
Commercial factor IX (Prothromplex*)	10 000	12 000	5 000	
Activated prothrombin complex concentrates				
FEIBA*	2 329 000	1 928 000	821 000	647 000
Proplex*	2 667	149 000		
Autoplex*				81 000
	Haemophilia B			
No of patients with antibodies treated	3	2	1	2
NHS factor IX concentrate	37 000	34 000	36 000	85 000

*Units of activity as defined by manufacturers concerned.

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IXm

TABLE IX—*Numbers of patients with haemophilia A treated by haemophilia centres during 1980, showing severity of coagulation defect, age, and proportion receiving home treatment (HT)*

Age (years)	Factor VIII value (%, average normal)								Total	
	<2		2–10		>10		Not known			
	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT
<5	84	7 (8·3)	27	2 (7·4)	4	0 —	0	0 —	115	9 (7·8)
5–9	119	69 (58·0)	58	13 (22·4)	18	1 (5·6)	3	2 (67·0)	198	85 (42·9)
10–19	388	293 (75·6)	138	31 (22·5)	47	2 (4·3)	4	0 —	587	326 (55·5)
20–29	322	208 (64·6)	94	18 (19·2)	29	0 —	4	0 —	449	226 (50·3)
30–39	234	154 (65·8)	59	7 (11·9)	31	2 (6·5)	1	0 —	325	163 (50·2)
40–49	137	73 (53·3)	41	4 (9·8)	14	0 —	4	0 —	196	77 (39·3)
50–59	75	31 (41·3)	42	6 (14·3)	19	0 —	2	0 —	138	37 (26·8)
60–69	33	8 (24·2)	18	2 (11·1)	8	0 —	2	0 —	61	10 (16·4)
≥70	15	3 (20·0)	12	0 —	5	0 —	0	0 —	32	3 (9·4)
NK	2	1 (50·0)	5	1 (20·0)	1	0 —	8	0 —	16	2 (12·5)
Total	1419	847 (59·7)	496	84 (17·0)	176	5 (2·8)	28	2 (7·1)	2117	938 (44·3)
Total treated as % of total known*	74·6	— —	40·0	— —	21·2	— —	7·9	— —	69·0	— —

NK = Not known. *See table IIm.

trates, and porcine factor VIII. Prothrombin complex concentrates were on the whole used less in 1980 than in 1977.

The few patients with antibody against factor IX who were treated all received human factor IX concentrates prepared by NHS fractionation laboratories.

HOME TREATMENT

Home treatment programmes have been introduced by most haemophilia centres in Britain and in 1980, 44% of all haemophiliacs treated and 60% of severely affected haemophiliacs treated were receiving home treatment (table IXm). Slightly less than half of all the factor VIII used in 1980 was used for home treatment; some 26×10^6 units of factor VIII was used to treat 938 patients. Four per cent of the material was in the form of cryoprecipitate, 28% was NHS factor VIII, and 67% was commercial factor VIII. Roughly 28 000 units per patient per year was used in home treatment (table Xm).

Tables XIm and XIIm give data on home treatment of patients with haemophilia B in 1980. Of the 208 patients severely affected by the disease, 116 (56%) were receiving home treatment and roughly half of all the material used to treat haemophilia B was used for home treatment. The amount of factor IX used per patient per year for treatment at home was 30 000 units. This is similar to the amount of factor VIII used in home treatment by patients with haemophilia A.

CARRIERS OF HAEMOPHILIA A OR B AND PATIENTS WITH VON WILLEBRAND'S DISEASE

Information about carriers and patients with von Willebrand's disease treated by haemophilia centres has been collected since 1976. Table XIIIm gives the total numbers of carriers of haemophilia A and patients with von Willebrand's disease treated during 1976-80 and the amounts and types of blood products used. With regard to types of material used to treat carriers of haemophilia A, the use of cryoprecipitate and NHS factor VIII fluctuated greatly from year to year but there was a steady increase in the use of commercial factor

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VIII. In addition to the patients treated with blood products, four mildly affected carriers of haemophilia A were treated with desmopressin only. The total amount of factor VIII used in any one year for the treatment of carriers of haemophilia A accounted for less than 1% of the total factor VIII used in Britain. Throughout the period of the survey cryoprecipitate was the therapeutic material most used for the treatment of von Willebrand's disease, accounting for 75-90% of the factor VIII given to those patients. Besides preparations containing factor VIII other materials were infrequently used: in 1977 a patient with von Willebrand's disease and antibodies against factor VIII was treated with an activated prothrombin complex concentrate (FEIBA; "factor eight inhibitor bypassing activity") and porcine factor VIII, and in 1977, 1978, 1979, and 1980 desmopressin was given to two, four, nine, and nine patients, respectively. The total amount of factor VIII used in any one year to treat carriers of haemophilia A and patients with von Willebrand's disease accounted for only 3-4% of the total factor VIII used in Britain.

Very few carriers of haemophilia B required treatment during the survey period, the numbers fluctuating between five and 12 a year. Those patients were mainly treated with NHS factor IX concentrates, though fresh frozen plasma was occasionally used. The total amount of factor IX used in any one year ranged from 7000 to 115 000 units and accounted for 0·1-1·4% of the total amount of factor IX used in Britain in that year.

HEPATITIS

Table XIVm shows the number of patients treated each year and the number and percentage of those treated who developed acute hepatitis. The diagnosis was based on clinical and laboratory data and did not include patients known previously to have had persistent abnormalities in liver function values. In the five years 1976-80 the incidence in patients with haemophilia A varied between 1·7% and 3·5% of those treated in any year and was very little different from that seen in the period 1969-74. In 1974-5, however, with the first use of US commercial factor VIII concentrates on a wide scale in British haemophilia centres, the overall incidence of hepatitis in patients with haemophilia A rose from 2·3% to 5·2% in 1974, and then declined to 3·1% in 1976. The yearly attack rate has remained about the same since then.

At the time of reporting there had been remarkably few sequelae of acute hepatitis. Over the six years only two patients had died from illness related to the complications of acute hepatitis. The problem of chronic hepatitis remains unresolved. Several patients have been seen with symptomatic evidence of chronic liver disease, but only further studies of these patients as a whole over the next 10 years will disclose the true incidence.

A working party of haemophilia centre directors has been set up to look into the incidence of both acute and chronic post-transfusion hepatitis. A separate report on the incidence of acute hepatitis in haemophiliacs in Britain is in preparation.

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Discussion

The number of haemophiliacs known and treated at haemophilia centres in Britain continues to rise, as does the amount of factor VIII used in their treatment.

If the amount of factor VIII used continues to increase at the present rate some 120×10^6 units of the factor will be required by 1990. Should there be any major change in treatment policy

MINIPRINT TABLES Xm-XIVm

Xm

TABLE X—*Materials used for home treatment of patients with haemophilia A during 1989*

Material	Total factor VIII units used for all patients	Factor VIII units used for home treatment only	% of material used for home treatment
Plasma	1 000	Nil	—
Cryoprecipitate	8 153 000	1 043 000	12·8
NHS factor VIII concentrate	14 368 000	7 456 000	51·9
Commercial factor VIII concentrate	34 749 000	17 679 000	50·9
Total units	57 271 000	26 180 000	45·7
No of patients treated	2 107	938	44·5
Average amount used per patient	27 181	27 918	—

In addition 11 900 units factor eight inhibitor bypassing activity (1·7% of total FEIBA used) was supplied for home treatment.

XIm

TABLE XI—*Numbers of patients with haemophilia B treated by haemophilia centres during 1989, showing severity of coagulation defect, age, and proportion receiving home treatment*

Age (years)	Factor IX value (% average normal)								Total	
	< 2		2–10		> 10		Not known			
	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT	No treated	No (%) on HT
< 5	14	1 (7·1)	8	0	1	0	0	0	23	1 (4·4)
5–9	28	14 (70·0)	13	2 (15·4)	4	0	0	0	37	16 (43·2)
10–19	38	29 (67·4)	32	12 (37·5)	7	1 (14·3)	1	0	98	52 (53·1)
20–29	45	29 (95·6)	19	3 (15·8)	0	0 (12·5)	0	0	72	29 (40·3)
30–39	37	24 (64·9)	7	2 (28·6)	0	0	0	0	55	26 (47·3)
40–49	18	9 (50·0)	13	3 (23·1)	1	0	2	1 (50·0)	34	12 (35·3)
50–59	9	2 (22·2)	7	1 (14·3)	0	0	2	0	18	3 (16·7)
60–69	6	1 (25·0)	4	0	0	0	0	0	9	1 (11·1)
>70	3	1 (33·3)	3	2 (66·7)	0	0	1	0	7	3 (42·9)
NK	0	0	0	0	1	0	1	0	2	0
Total	208	116 (55·8)	106	24 (22·6)	28	2 (7·1)	13	1 (7·7)	355	143 (40·3)
Total treated on % of total known*	75·6		30·0		10·5		17·3		65·7	

NK = Not known. *See table IIIm.

XIIm

TABLE XII—*Materials used for home treatment of patients with haemophilia B during 1989*

Material	Total factor IX units used for all patients	Factor IX units used for home treatment only	% of total of each material used for home treatment
Plasma	1 000	Nil	Nil
NHS factor IX concentrate	6 196 000	4 170 000	39·6
Commercial factor IX concentrate	77 000	75 000	97·4
Total units	8 272 000	4 245 000	51·3
No of patients treated	395	143	40·3
Average amount used per patient	23 301	29 689	

XIIIm

TABLE XIII—*Type and amount of materials used by haemophilia centres in 1976–90 to treat patients with von Willebrand's disease and carriers of haemophilia A*

Human blood products used	Factor VIII units									
	1976		1977		1978		1979		1980	
	Total used	% total	Total used	% total	Total used	% total	Total used	% total	Total used	% total
Patients with von Willebrand's disease										
Plasma	9 000	1·1	10 000	0·6	16 000	1·2	9 000	0·6	6 000	0·3
Cryoprecipitate	674 000	86·7	1 619 000	89·1	1 030 000	79·5	984 000	63·5	1 076 000	74·1
NHS factor VIII concentrate	41 000	5·2	86 000	5·4	171 000	13·2	221 000	14·3	113 000	7·8
Commercial factor VIII concentrate	72 000	9·1	78 000	4·9	79 000	6·1	335 000	21·6	256 000	17·8
Total	796 000	100·0	1 593 000	100·0	1 296 000	100·0	1 549 000	100·0	1 449 000	100·0
No of patients treated	185		231		240		247		244	
Average amount used per patient	4 300		6 895		5 400		6 271		5 936	
Carriers of haemophilia A										
Plasma			1 000	1·6	3 000	1·5				
Cryoprecipitate	16 000	28·1	26 000	46·4	141 000	71·9	61 000	45·5	31 000	21·7
NHS factor VIII concentrate	36 000	63·2	22 000	39·3	25 000	12·8	43 000	32·1	24 000	16·8
Commercial factor VIII concentrate	5 000	8·8	7 000	12·5	27 000	13·8	30 000	23·4	88 000	61·5
Total	57 000	100·0	56 000	100·0	196 000	100·0	134 000	100·0	143 000	100·0
No of patients treated	19		42		30		28		28	
Average amount used per patient	3 000		1 333		6 533		3 526		5 107	

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XIVm

TABLE XIV—*Incidence of acute hepatitis in patients treated by haemophilia centres in 1976–80*

Coagulation defect	1976			1977			1978			1979			1980		
	Total No of patients treated	Cases of hepatitis		Total No of patients treated	Cases of hepatitis		Total No of patients treated	Cases of hepatitis		Total No of patients treated	Cases of hepatitis		Total No of patients treated	Cases of hepatitis	
		No	% of treated patients		No	% of treated patients		No	% of treated patients		No	% of treated patients		No	% of treated patients
Haemophilia A	1886	61	3·2	1973	70	3·5	2048	57	2·8	2053	34	1·7	2107	52	2·5
Haemophilia B	298	7	2·4	332	8	2·4	330	3	0·9	344	3	0·9	355	3	0·8
von Willebrand's disease	186	4	2·2	231	4	1·7	208	10	4·8	247	8	3·4	230	8	3·5
Haemophilia A carrier	10	1	9·5	62	1	1·4	30	Nil		28	Nil		28	Nil	
Haemophilia B carrier	5	Nil		9	Nil		7	Nil		9	Nil		12	Nil	
Total	2382	73	3·1	2580	83	3·2	2695	70	2·6	2681	46	1·7	2737	63	2·3

such as the administration of larger doses for the management of haemarthroses or the widespread use of prophylactic treatment the total amount of factor VIII used will be still greater.

During 1980 commercial factor VIII constituted 60% of the total factor VIII used and cost the NHS some £2·5 million. If the proportion of commercial factor VIII used in 1990 remains the same as today the cost at today's prices will be of the order of £5 million. But if, as seems likely from recent trends, there is an increase in the proportion of commercial factor VIII used the cost will be even higher. It is unlikely that the upward trend in the use of commercial factor VIII will be reversed before the middle to late 1980s, when the NHS fractionation laboratories are expected to increase greatly their output of factor VIII.

As in other reports intracranial bleeding is the commonest cause of death in patients suffering from haemophilia A. Other types of bleeding constituted the second largest cause of death. The finding of a near normal median expectation of life in severely affected haemophiliacs and a greater than normal expectation in mildly affected patients is interesting and encouraging. The numbers concerned are relatively small, so that the above results must be interpreted with caution. Clearly there has been a noticeable improvement in the management of haemophilia since factor VIII has become widely available and bleeding to death from trivial injury—so common in the past—is now rarely seen. We should therefore not be surprised at some increase in life expectation, but whether the improvement observed in this survey is an overestimate will remain to be seen. The directors of haemophilia centres in Britain are continuing with their collaborative studies, and it is hoped that further information collected over the next few years will answer this question.

In view of the widespread concern about the transmission of hepatitis viruses by giving blood products it is interesting to note that only two deaths were attributed to hepatitis during the five year period. There have been several reports recently of persistently abnormal liver function values and abnormal histological findings in liver tissue from haemophiliacs treated with blood products. Most of these patients are asymptomatic

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MINIPRINT APPENDICES I AND II

APPENDIX Im

APPENDIX I—*Life tables and expectation of life for patients with haemophilia A in Britain during 1976-80*

In preparing the life tables for patients with haemophilia A (tables XVm-XVIIIm) the "not knowns" were assigned proportionately throughout the age and severity groupings. Person-years at risk were calculated from the number of patients in the register at the mid-point of each year. Also the assumption was made that mortality operated constantly through the age bands. See Hill[3] and Armitage[4] for further details of methods used.

XVm

TABLE XV—*Person-years at risk (mid-1976 to mid-1980 inclusive). (Haemophilia A)*

Age group (years)	Factor VIII value (average normal)			
	< 2	2–10	> 10	Total
< 10	1479	780	315	2 574
10–19	2518	1271	782	4 572
20–29	2184	1028	620	3 833
30–39	1543	848	439	2 830
40–49	868	614	419	1 901
50–59	558	510	323	1 392
60–69	282	309	251	843
≥ 70	98	181	129	408
Total	9531	5542	3280	18 354

XVIm

TABLE XVI—*Deaths during 1976-80 inclusive ("not knowns" apportioned). (Haemophilia A)*

Age group (years)	Factor VIII value (average normal)			
	< 2	2–10	> 10	Total
< 10	4	1	—	5
10–19	2	—	1	3
20–29	13	—	—	13
30–39	13	4	1	18
40–49	8	1	—	9
50–59	7	2	1	10
60–69	9	5	2	16
≥ 70	4	8	3	15
Total	60	21	8	99

XVIIm

TABLE XVII—*"Probability of death" rates for haemophilia A in Britain (1976-80 inclusive)*

Age group (years)	Factor VIII value (average normal)	
	< 2	2–10
10	0 0027	0 0013
10–19	0 0008	*
20–29	0 0060	*
30–39	0 0084	0 0047
40–49	0 0092	0 0016
50–59	0 0125	0 0039
60–69	0 0319	0 0162
≥ 70	0 0608	0 0442
All age groups	0 0063	0 0038

*No deaths in group.

XVIIIm

TABLE XVIII—*Life table for haemophilia A in Britain (1976-80) and for normal males in England and Wales (1977-9)*

Age (years)	Haemophilia A (factor VIII value as average normal)		Normal males*
	< 2	2–10	
0	10 000	10 000	10 000
10	9 733	9 871	9 813
20	9 656	9 871	9 754
30	9 092	9 871	9 667
40	8 356	9 417	9 547
50	7 619	9 267	9 207
60	6 718	8 912	8 200
70	4 858	7 569	5 983
75	3 945	6 038	4 363
80	3 203	4 816	2 953
Median life	69·1	79·2	72 8

Columns 2, 3, and 4 show number of 10 000 born who would survive to ages in column 1 when subjected to recorded age death rates for survey periods shown. Median life is age at which 5000 of original 10 000 had died.

*From table 23 of *Mortality Statistics 1978*, series DH1 No 8, Office of Populatoon Censuses and Surveys, London.

APPENDIX IIm

APPENDIX II

The following directors of haemophilia centres contributed data to the survey Dr W S A Allan, The Royal Hospital, Wolverhampton. Dr S Ardeman, Edgware General Hospital, Edgware, Middlesex, Dr A Aronstam, Treloar Haemophilia Centre, Alton, Hants, Dr B Attock, North Devon District Hospital, Barnstaple, Dr P Barkhan, Guy's Hospital, London SE1 9RT, Dr A M Barlow, Huddersfield Royal Infirmary, Huddersfield, Yorks. 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but it remains to be seen how many will develop severe chronic liver disease with the passage of time.

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