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Haemophilia in Sweden

VII. Incidence, Treatment and Prophylaxis of Arthropathy and other Musculo-skeletal Manifestations of Haemophilia A and B

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I. General Introduction

John C. Otto (1803) is credited with the first fairly detailed description of a disease characterised by a bleeding tendency and affecting only males but transmitted by females. The name 'haemophilia' for this disease was coined in the 1820s by Johann L. Schönlein (Hopff 1828). For a number of years this term was used synonymously with 'haemorrhaphilia' (fondness of bleeding), of which it is probably an abbreviation (Brinkhous 1965). In 1936 Patek and Taylor demonstrated the lack of a certain protein fraction of the plasma in haemophiliacs. They called this factor 'antihaemophilic globulin'. This factor is now known as AHF (antihaemophilic factor) or factor VIII and it is the factor that is deficient in classical haemophilia A. In 1947 Pavlovsky *et al.* (1950) found that blood from one haemophiliac normalised blood from another patient with haemophilia. Similar observations were also reported by Koller *et al.* (1950), Biggs *et al.* (1952) and Aggeler *et al.* (1952), and it was concluded that there existed, besides classical haemophilia, a coagulation defect due to deficiency of another plasma protein. This resulted in the distinction of two types of haemophilia, namely A and B. The new haemophilic factor was called haemophilia B-factor, Christmas factor or factor IX.

In the 1860s Volkmann (Vegas 1914) pointed out that joint symptoms may occur in haemophilia and scurvy. In 1892 König published a detailed report of the joint changes in haemophiliacs. He described 2 patients who died from haemorrhage after operation for what was erroneously believed to be tuberculosis of the knee joint. Feissley (1924) recommended the use of blood and plasma transfusions in the treatment of haemophiliacs. Such infusions have since been widely used and the development of this form of therapy has been reviewed by Brinkhous (1964). But as late as 1956 DePalma and Cotler warned against surgical correction of joint deformities in patients with severe haemophilia.

Haemophilia has been the subject of extensive research in Sweden. Sköld (1944) introduced blood transfusion therapy for treatment of haemophilia in Sweden. He pointed out the value of transfusions of fresh blood as a

Table 1 Earlier investigations of haemophilic arthropathy

Author	Published Year	No. of Cases	Coagulation Studies	Material
Thomas, H. B.	1936	98	Incomplete	Examined at Research and Educational Hospital and the Illinois Surg. Inst. for Children 1930—1935
Ghomley, R. K. and Clegg, R. S.	1948	76	Incomplete	Examined at Mayo Clinic, 1920—1939
Davidson, C. S. *et al.*	1949	40	Not described	Treated at Thorndike Memorial during a period of 10 years
DePalma, A. F. and Cotler, J.	1956	117	Classified in four degrees Not described	Registered at the Jefferson Medical College Hospital
Rodnan, G. P. *et al.*	1957	53	Incomplete	
Jordan, H. H.	1958	110	Not described	Treated at Lenox Hill Hospital, New York City, 1946—1956
Jones, E. W.	1958	110	Not described	Registered at South. California chapter of the Haemophiliac Society
Webb, J. B. and Dixon, A. S.	1960	42	24 completely investigated	Examined following request sent to 77 known haemophiliacs in London and the Home Countries
Crock, H. V. and Boni, V.	1960	21	Incomplete	Treated at Nuffield Orthopaedic Centre, Oxford
Crock, H. V.	1962	30	Incomplete	Treated at Nuffield Orthopaedic Center, Oxford, during a period of 15 years
Arnold, W. D.	1962	25	Not described	Treated at New York Hospital Pediatric Department and the Pediatric Hematology Clinic
Present Study	1965	242	Complete coagulation studies	Representative for all Sweden

prophylaxis in connection with operations and orthopaedic measures on bleeders. He also published an epidemiological study, which was later followed by a similar investigation by Nilsson *et al.* (1961). In the latter publication the haemophiliacs are classified according to the type and severity of the disease. The heredity and symptomatology of haemophilia have also been analysed (Ramgren *et al.* 1962, Ramgren 1962 a).

A method for the production of a concentrated preparation of human antihaemophilic factor (AHF) or fraction I—0 was described by Blombäck and Blombäck (1956), Nilsson (1957), Blombäck *et al.* (1960). This preparation has been used to control haemorrhage in patients with haemophilia A and to enable surgical operations (Blombäck and Nilsson 1958, Nilsson *et al.* 1960, Nilsson *et al.* 1962, Nilsson 1965).

Arthropathy and other musculo-skeletal complications are the commonest causes of disability of haemophiliacs. Previous investigations of the disabling effect of such complications are based on clinical material from various hospitals and collected during a limited period (Table 1). It would appear that so far no attempts have been made to ascertain the incidence of arthropathy in a well defined population.

The present investigation is based on previous work of haemophilia in Sweden. Its main purpose was to ascertain the incidence of arthropathy and other musculo-skeletal manifestations and to devise principles of non-surgical and surgical treatment as well as the prophylaxis of such lesions with the aid of coagulation-correcting preparations.

II. Material and Methods

POPULATION OF SWEDEN AND PUBLIC RECORDS

In 1963 the population of Sweden was 7.6 million, of which about five sixths (6.4 million) were living in the southern half of the country. Sweden is well suited for epidemiological studies because the population is fairly homogenous and because detailed public records have for many years been kept of all births, marriages, deaths (including the main causes of death) and changes of address. Epidemiological surveys on osteogenesis imperfecta (Smårs 1961) and on fracture of the femur (Dencker 1963) may serve as illustrative example of the suitability of Sweden in this respect.

INCIDENCE OF HAEMOPHILIA IN SWEDEN

Nilsson *et al.* (1961) charted the incidence of hameophilia in Sweden and gave a list of all known haemophilic families and individuals classified according to type and degree of the disease. This list has been kept up to date, and on January 1, 1964, it contained 230 families (Addendum p. 99). It is unlikely that this investigation has missed any individuals above 5 years with severe or moderate haemophilia.

CLASSIFICATION OF HAEMOPHILIA

All individuals in the above-mentioned list are classified regarding type and degree of haemophilia in accordance with the principles of Nilsson *et al.* (1961). A distinction is made between haemophilia A and haemophilia B, and within each of these types the degree of the disease is classified according to the plasma content of AHF (haemophilia A) or B-factor (haemophilia B) as *severe*, *moderate* or *mild* (Table 2).

Coagulation tests

All the methods used for collection and preparation of the blood samples and for determination of the different coagulation factors have been described elsewhere (Nilsson *et al.* 1961).

TABLE 2 Classification of haemophilia

Degree	AHF or B-factor in per cent of normal
Severe	< 1
Moderate	1 < 5
Mild	5—25

TABLE 3 Error of tests

Plasma sample	No of determinations	AHF value	
		Mean %	S.D.
1 (O.D.)	24	0.74	± 0.3
2 (P.V.a)	20	0.89	± 0.1
2 (P.V.a)	20	0.93	± 0.1
3 (P.V.b)	24	2.57	± 0.6
4 (B.R.)	24	2.92	± 0.7
5 (P.V.c)	20	5.78	± 1.4
6 (I.R.)	20	21.0	± 4.5
6 (I.R.)	20	19.8	± 5.0
7 (P.G.)	20	37.6	± 5.2

The *AHF activity* of plasma was assessed by its normalizing effect on the recalcification time of platelet-rich haemophilia A plasma containing less than 1 per cent AHF (Nilsson *et al.* 1957, Nilsson *et al.* 1961). The amount of AHF present was expressed in per cent of that found for a normal standard consisting of pooled plasma from 10 normal individuals. New standard plasma was prepared every week, and the plasma of the patients was tested within one week after withdrawal of the blood. A standard curve was plotted for each assay.

The *haemophilia B-factor activity* of the plasma was assessed by its normalizing effect on the recalcification time of haemophilia B plasma (Nilsson *et al.* 1961), and the amount of haemophilia B-factor present expressed in per cent of that found for a normal standard consisting of pooled plasma from 10 normal individuals.

Error of Tests

Repeated AHF determinations were made on different plasma samples with AHF up to about 38 per cent of normal and the standard deviation was calculated (Table 3). At AHF values below 1 per cent of normal the standard deviation was ±0.1— ±0.3 per cent and at AHF values between 2 and 3 per cent it was ±0.6— ±0.7 per cent.

As another example of the reliability and reproducibility of the method, it might be mentioned that when one and the same preparation of frac-

tion I—0 was given to the same patient on two different occasions, remarkably good agreement was noted between the total increase of AHF activity in the plasma of the patient on the two occasions. The standard deviation of a single determination was found to be 11.5 per cent. Good agreement was also found between the increase of AHF in two patients treated on different occasions with the same AHF preparation. The standard deviation of a single determination was found to be 14 per cent (Blombäck *et al.* 1960).

PATIENTS

Selection of Patients

The investigation is based on all haemophiliacs in Sweden registered on Jan. 1, 1964 (Addendum p. 99). The patients were examined (a) clinically by the author, (b) roentgenologically, and/or (c) by questionnaire.

The clinical and roentgenologic examinations were made at twelve hospitals in ten towns (Fig. 1). Of the 157 patients, 76 were examined at Malmö General Hospital and then usually in association with the investigation of their haemophilia. The remaining 81 patients were examined at their local hospitals. Patients with mild haemophilia were requested to present themselves for clinical examination only if they lived near the examination centres.

Completeness of Survey

Of 116 patients with *severe* haemophilia 95 were examined clinically (Table 4). Seven of the 21 who were not examined were below 5 years of age; they failed to appear for examination because the parents felt either that they were free from arthropathy or that they should not be bothered. Of the remaining 14 above 5 years, information about 7 was obtained by questionnaire. No reply was obtained in the remaining 7 cases.

Of 65 patients with *moderate* haemophilia 38 were examined clinically (Table 4). Another 21 of those 65 answered the questionnaire. Six patients with moderate haemophilia were unavailable for examination and/or failed to answer the questionnaire; 3 of those 6 were below 5 years.

Of 127 patients with *mild* haemophilia 24 were examined clinically (Table 4). Another 57 of those 127 answered the questionnaire.

The age distribution of patients investigated was about the same as that of the entire series (Table 5).

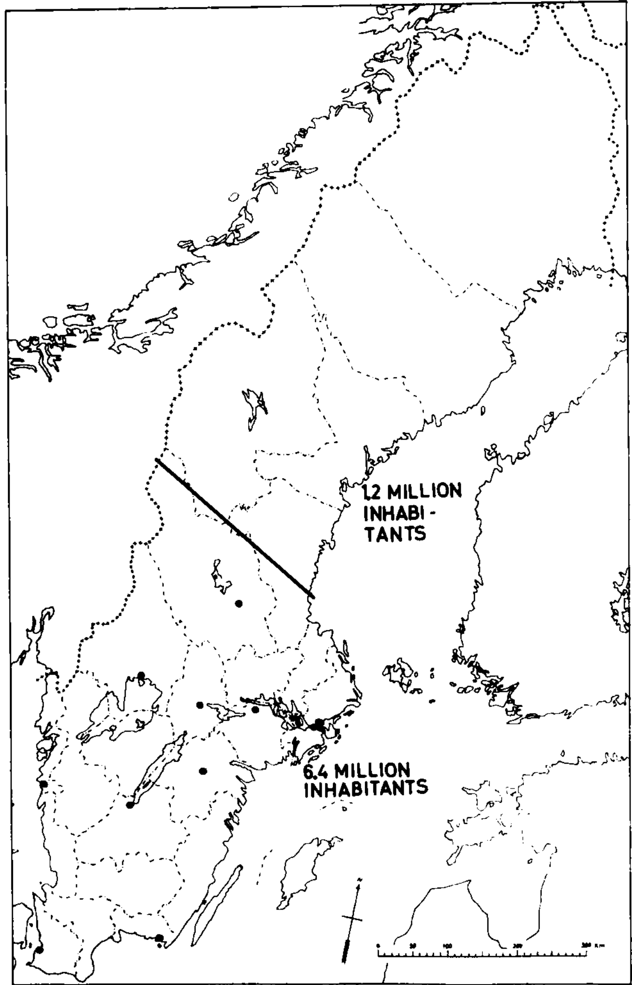


FIGURE 1 Sweden, Hospitals where haemophiliacs were examined.

TABLE 4 Distribution of material

Type of Haemophilia	Haemophilia A			Haemophilia B			Total
	Severe	Moderate	Mild	Severe	Moderate	Mild	
Personally examined	69	28	17	26	10	7	157
Questionnaire only	7	20	45	0	1	12	85
Not evaluated	14	3	38	0	3	8	66
Total	90	51	100	26	14	27	308

TABLE 5 Patients in different age classes

Age in Years	0—9	10—19	20—29	30—39	40—49	> 49	Total
Personally examined	37	42	31	19	15	13	157
Questionnaire only	6	18	19	15	11	16	85
Not evaluated	14	5	14	10	10	13	66
Total	57	65	64	44	36	42	308

METHODS OF INVESTIGATION

Clinical Examination

All clinical examinations were done by the author personally. The examination included the hands and feet, and the following joints: hip, knee, ankle, shoulder, elbow and wrist. The gross configuration was studied and any deformity (valgus, varus, subluxation, rotation defect), increase in breadth of epiphyses, capsular thickening or muscular atrophy was noted. The range of passive motion of the joints was measured. Loss of range of motion was estimated, when possible, by comparison with the mobility of the contralateral joint. The normal ranges of motion published by Hjortsjö (1959) were used as references.

Hip. Flexion was measured with the knee bent. Normal range of extension-flexion according to Hjortsjö 115°—125°.

Abduction and adduction were measured with the hip joint extended. Normal range: about 45° and 25°, respectively.

Outward and inward rotation were measured with the hip joint flexed 90°. Normal range: about 60° and 30°, respectively.

Knee. Extension-flexion was measured. Normal range: about 160°.

Ankle (including the talo-crural and subtalar joints). Dorsal and plantar flexion as well as pronation and supination were noted. Normal ranges: dorsal flexion about 20°, plantar flexion about 40°, pronation-supination about 45°.

Shoulder. The purpose of the examination was to assess the mobility of the humeroscapular joint. Abduction with the scapula fixed normally about 90°. Rotation was measured with the arm abducted 90°. Normal range: about 110°.

Elbow (including the distal radio-ulnar joint with which it forms a functional unit). Normal extension-flexion: 130°—140°. Pronation and supination was measured with the elbow flexed 90°. Normal range: about 150°.

Wrist. Volar and dorsal flexion as well as radial and ulnar deviation were studied. Normal ranges: volar 80°—90°, dorsal 50°—60°, radial about 20°, ulnar about 45°.

Roentgen Examination

As a rule, the patients were also examined roentgenologically (Chapter IX). The examinations were done at 12 hospitals (Fig. 1), and no attempt was made to standardise the exposure conditions. The roentgenologic

TABLE 6 Questionnaire used in examination for disability in haemophilia

Draw circle round correct answer:	Right		Left	
Can you put your hand behind your neck?	yes	no	yes	no
Can you reach your back with your hand?	yes	no	yes	no
Can you reach your mouth?	yes	no	yes	no
Can you use knife and fork?	yes	no	yes	no
Can you open a water faucet?	yes	no	yes	no
Can you turn a key?	yes	no	yes	no
Can you put on stocking and shoe?	yes	no	yes	no
Can you walk upstairs?	yes		no	
Can you walk downstairs?	yes		no	
Can you climb a chair with				
(a) right leg first?	yes		no	
(b) left leg first?	yes		no	
Can you walk more than 100 meters without stopping?	yes		no	
Can you walk more than 1000 meters without stopping?	yes		no	
Can you walk out of doors without a cane?	yes		no	
Do you use one cane out of doors?	yes		no	
Do you use two canes out of doors?	yes		no	
Do you use crutches out of doors?	yes		no	
Do you use braces?	yes		no	
Do you use orthopaedic shoes?	yes		no	
Do you use a wheelchair?	yes		no	
Are you always confined to bed?	yes		no	
Can you dress without help?	yes		no	
Can you eat without help?	yes		no	
Can you do your toilet without help?	yes		no	

examination included the regions which were clinically examined. In some cases, roentgenologic examination was not done either because the joints were clinically normal and there was no history of joint haemorrhage, or because the patients would not consent to such an examination. When possible, films were taken in two perpendicular planes. Contractures and deformities, especially of the knee and elbow joints, sometimes made it impossible to place the patient in the proper position for antero-posterior and lateral views. The films were checked in Malmö in cooperation with Lars Andrén, M. D. (Roentgen-diagnostic Department, Malmö General Hospital).

Interview Examination and Questionnaire

The functional ability of the patients was assessed with the aid of a questionnaire (Table 6), which contained specific questions concerning

their ability to walk, use of braces, activity of daily life, etc. The same questionnaire was mailed to patients over 5 years of age who had failed to come for examination, or to their parents.

CLASSIFICATION OF HAEMOPHILIC ARTHROPATHY

König (1892) distinguished between haemarthrosis, panarthritis, and the regressive stage, and Key (1932) simplified this classification to comprise only two stages; acute haemarthrosis, and chronic arthritis. None of these classifications were based on the degree of chronic arthropathy. DePalma and Cotler (1956) and Jordan (1958) recognised four degrees of chronic haemophilic arthropathy. These two classifications were largely the same, with the exception that Jordan based his classification largely on the roentgenograph, whereas DePalma and Cotler based their classification on a combination of the clinical and roentgenographic findings. Largely the latter classification was used in this investigation.

DePalma and Cotler distinguished four grades of arthropathy with grade 1 as the earliest form. Joints belonging to this grade have no functional impairment, and classification is therefore made largely on the basis of very slight roentgenologic changes, such as "some slight generalized decreased density of the bone ends", and "some increased density of the capsular tissues". These roentgenologic changes proved too subtle to serve as a basis for classification in the present investigation. This was partly because the roentgenographs had been taken at different hospitals and not under standardized exposure conditions. Therefore, in this investigation only three grades of arthropathy were used corresponding largely to DePalma's grades 2, 3 and 4. In order to facilitate direct comparison DePalma's terms were used.

The classification was based on the findings listed in Table 7.

Grade 2. Slightly reduced range of mobility not interfering with the function of the joint. Increase in breadth of epiphyses, subchondral cyst formation and/or increased trabeculation of the bone ends (Fig. 2).

Grade 3. Reduced range of mobility interfering with the function of the joint. Occurrence of valgus, varus, subluxation or rotation deformity. Roentgenologically demonstrable narrowing of the joint space, osteophytes and/or incongruence of the joint surfaces. Sclerosis of the ends of the bones (Fig. 3).

Grade 4. Changes of the same type as grade 3, but more advanced, *e.g.*, ankylosis or marked loss of mobility, pronounced deformity and severe sclerosis of the bone ends (Fig. 4).

TABLE 7 Classification of haemophilic arthropathy

Grade	2	3	4
Range of motion	Slightly reduced No impairment of function	Reduced with impairment of function	Greatly reduced
Increased breadth of epiphyses	+	+	+
Subchondral cyst formation	+	+	+
Increased trabeculation	+	+	+
Narrowing of joint space	—	+	+
Osteophytes	—	+	+
Deformity (valgus, varus, subluxation, rotation)	—	+	++
Incongruence of articular surfaces	—	+	++

CLASSIFICATION OF GENERAL DISABILITY

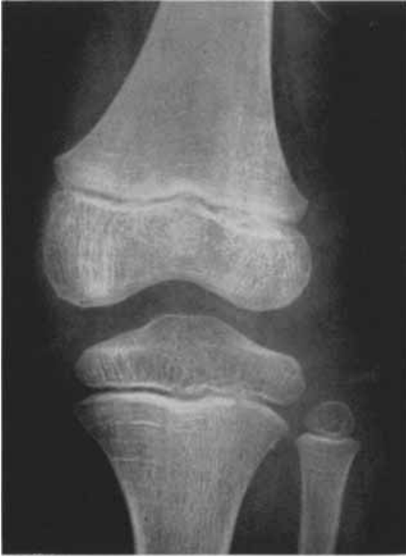
Classification according to disability was based on (a) clinical examination of the joints and (b) data from the questionnaires. Patients not examined clinically were classified according to the notes made in the questionnaires. The patients were informed that the questions referred to their condition when they were free from acute bleeding.

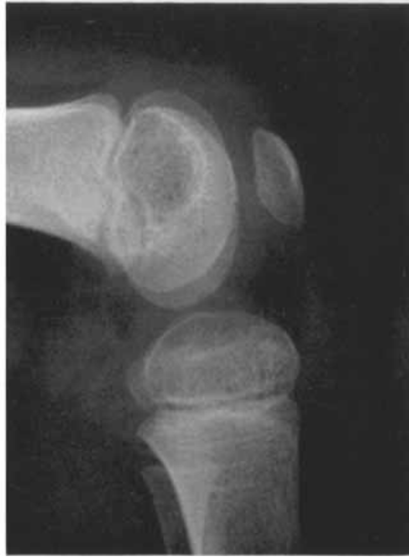
Patients (a) without arthropathy of more than grade 2 and (b) without loss of function according to the questionnaire were said to be free from disability. Three grades of disability were distinguished.

1. *Mild general disability* (a) One or more joints with grade 3 arthropathy, (b) impairment of one of the joint functions included in the questionnaire. Can manage activity of daily life. No need of orthopaedic appliances. Can walk 1000 metres without stopping.

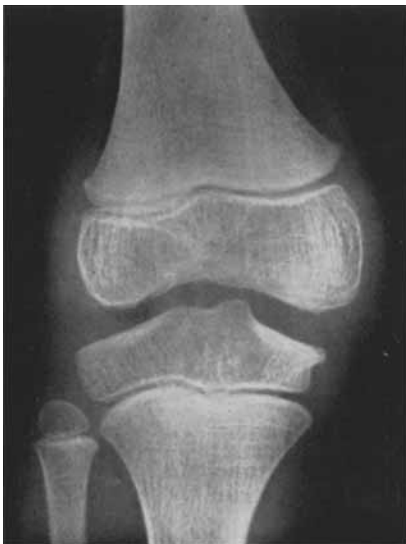
2. *Marked general disability* (a) One or more joints with arthropathy of grade 3 or 4, (b) uses orthopaedic shoes, splints and/or stick. Can walk 100 metres but not 1,000 metres without stopping.

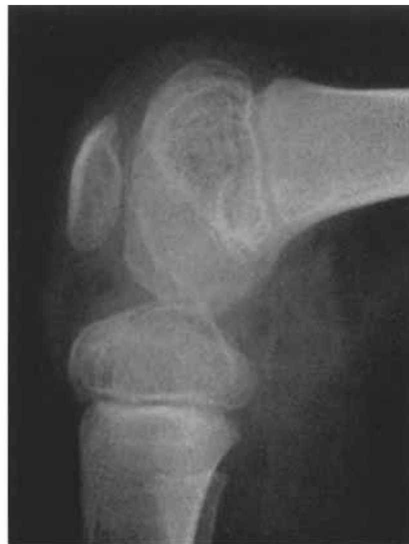
3. *Severe general disability.* (a) One or more joints with arthropathy of grade 3 or 4, (b) uses crutches, wheelchair or is bedridden. Cannot walk 100 metres without stopping. Requires help to manage activity of daily life.





a. Left knee, normal





b. Right knee, grade 2

FIGURE 2 Knee joint, grade 2, S.P., fam. 215, 7 years old.

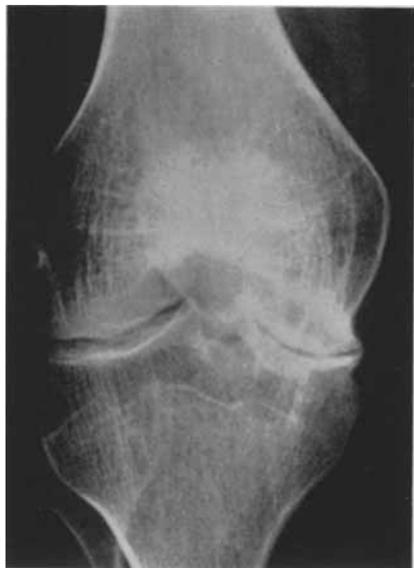
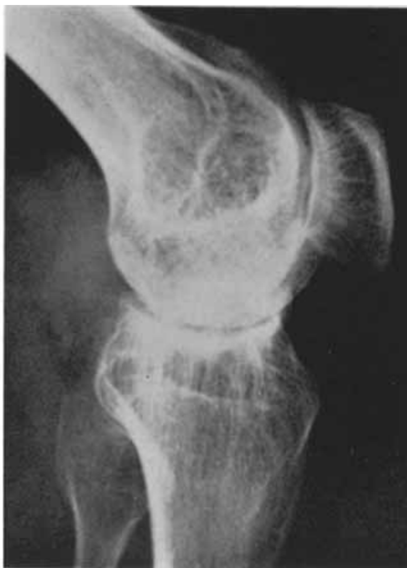



FIGURE 3 Knee joint, grade 3, S.W., fam. 28, 28 years old.

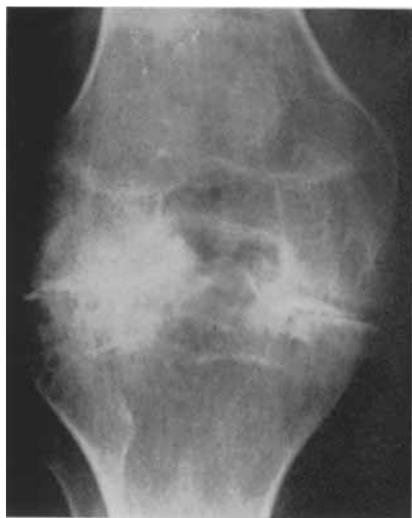
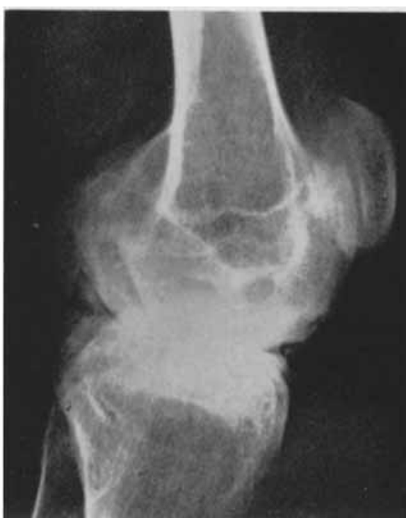



FIGURE 4 Knee joint, grade 4, L.L., fam. 36, 33 years old.

III. Incidence of Musculo-skeletal Manifestations in Haemophilia A and B

ARTHROPATHY

Arthropathy in Haemophilia A and B

Ramgren (1962 a) was unable to show any difference between the symptomatology of haemophilia A and B. Most of the patients in the present investigation were included in Ramgren's material, but the incidence of arthropathy is analysed in greater detail.

In the present material the distribution of the patients with haemophilia A according to degree of the disease and according to age was the same as that of the patients with haemophilia B (Tables 4 and 8). The two groups could therefore be compared regarding the incidence and degree of arthropathy (Table 9 and 10). No certain difference in either respect was found. Patients with haemophilia A and those with haemophilia B were therefore pooled in the following analysis.

Individual Joints (Table 11 and 12)

Hip

Of 157 patients, 1 hip joint was involved in 11 and both in 1. Haemophilia was severe in 11 of these patients and moderate in 1. Hip arthropathy thus occurred in 1 out of every 9 patients with severe haemophilia, and hardly ever in patients with moderate or mild haemophilia.

Winston (1952) pointed out that the roentgenographic appearance of haemophilic arthropathy of the hip joint depends on whether the joint was initially affected before or after puberty. In the former situation the appearance may resemble that seen in Legg-Perthes disease and in the latter that of non-specific coxarthrosis. Peterson (1923) has described three cases with a Legg-Perthes-like affection of hip joint in haemophiliacs, and, like Caffey and Schlesinger (1940), he believed haemorrhage in the femoral capital epiphysis to be the cause of this appearance. He pointed out that the appearance of haemophilic arthropathy of the hip joint may differ from Legg-Perthes disease by presence of changes also in the acetabulum.

Most of the affected joints in the present material belonged to grade 3. Four hips belonged to grade 4. Of these, 3 were seen in patients below 20

TABLE 8 Age distribution of haemophilia A and B

Age in Years	Haemophilia A	Haemophilia B	A/B
0— 9	24	13	1.8
10—19	35	7	5.0
20—29	22	9	2.4
30—39	13	6	2.2
40—49	12	3	4.0
> 49	8	5	1.6
Total	114	43	2.6

TABLE 9 Incidence of arthropathy in haemophilia A and B

Type of Haemophilia	A	B	A/B
Number of patients	114	43	2.6
Joints affected			
Hip	10	3	3.3
Knee	127	45	2.8
Ankle	68	28	2.4
Shoulder	21	7	3.0
Elbow	106	39	2.7
Wrist	17	3	5.7
Total	349	125	2.8

TABLE 10 Degree of arthropathy in haemophilia A and B

	Number of Joints affected		
Type of Haemophilia	A	B	A/B
Grade 2	104	27	3.9
Grade 3	170	70	2.4
Grade 4	75	28	2.7
Total	349	125	2.8

Table 11 Incidence of arthropathy as a function of degree of haemophilia

Degree of Haemophilia Number of patients examined	Severe 95	Moderate 38	Mild 24	Total 157
Patients with arthropathy of				
hip	11(1)*	1	0	12(1)
knee	77(58)	21(13)	2(1)	100(72)
ankle	45(31)	12(7)	1	58(38)
shoulder	19(5)	2(2)	0	21(7)
elbow	66(49)	20(10)	0	86(59)
wrist	8(5)	5(2)	0	13(7)
Total number of joints affected	375	95	4	474

* Bracketed figures indicate number of bilateral cases.

Table 12 Incidence of arthropathy as a function of age in severe and moderate haemophilia

Age in years		0—9		10—19		20—29		30—39		40—49		> 49		Total	
Haemophilia		Se	Mo	Se	Mo	Se	Mo	Se	Mo	Se	Mo	Se	Mo	Se	Mo
Number of patients examined		26	6	27	8	22	6	11	5	5	8	4	5	95	38
Number of joints affected															
Hip	grade 2			1		1								2	
	3			1		1		4				1		7	
	4			2	1			1						3	1
Knee	2	5	4	13	3	8	2	1			1		2	27	12
	3	6		20		27	4	9	6	6	4			68	14
	4	1		10		6		11		4	4	8	4	40	8
Ankle	2	4	1	7		16		7			7		1	34	9
	3	1		5		10	1	7		3	5	6	4	32	10
	4			3		2		2		1		2		10	
Shoulder	2			2		2		1		1			2	6	2
	3	1		1		2		4		1	2	3		12	2
	4					1		3		1		1		6	
Elbow	2	1	1	8	2	8	3	1		2	2		1	20	9
	3	5		19	2	23	1	13	4	2	5	5	4	67	16
	4			3		9		7		6	5	3		28	5
Wrist	2	1				4	1			1	1			6	2
	3							3		1	1	2	3	6	4
	4			1			1							1	1
Total	grade 2	11	6	31	5	39	6	10		4	11		6	95	34
	3	13		46	2	63	6	40	10	13	17	17	11	192	46
	4	1		19	1	18	1	24		12	9	14	4	88	15

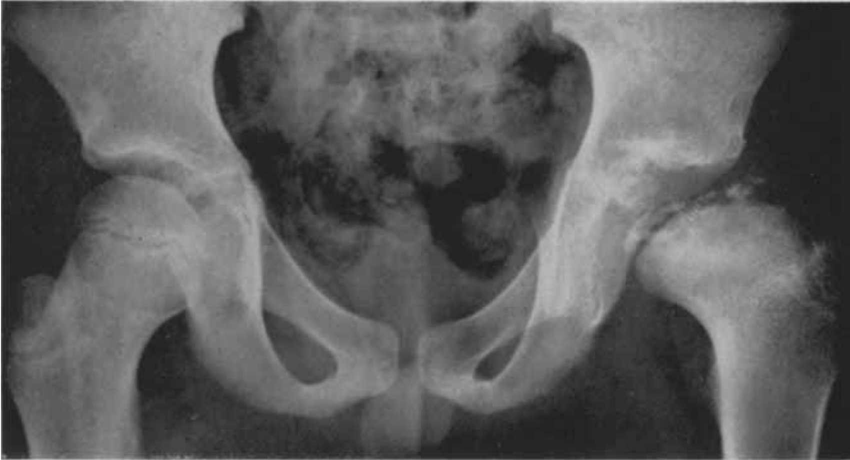


FIGURE 5 Hip joint with Legg-Perthes-like roentgenogram, U.J., fam. 81, 10 years old.

years of age. In one of these cases the appearance of the affected hip, in which the change was detected when the patient was 8 years old, resembled that seen in Legg-Perthes disease (Fig. 5). Advanced atypical destruction of the joint was demonstrated in the other 2 cases (Figs. 6 and 7).

Knee

One hundred patients had knee joint arthropathy, which was bilateral in 72. This condition was found in 4 cases out of every 5 patients with severe haemophilia, in every other one with moderate haemophilia, and only occasionally in patients with mild haemophilia. In severe and moderate haemophilia the arthropathy, when present, was predominantly of grade 3 or 4. The joint changes were bilateral in three fourths of the patients with severe haemophilia and in half of those with moderate haemophilia.

In severe haemophilia arthropathy of grades 3 and 4 was seen in 7 children out of 26 below 10 years and in 1 of 6 below 5 (L. C. S. fam. 37). In moderate haemophilia grade 3 arthropathy was never seen below the age of 20 and grade 4 never below 40 years. Of patients with mild haemophilia, only 3 knees were affected; the most severe affection (grade 3) was seen in a 14-year-old boy (K. A. fam. 123), who had had a supracondylar fracture of the femur. A 7 year old boy (R. H., fam. 145) had bilateral changes of grade 2.

There is general agreement that haemophilic arthropathy involves the knee more often than any other joint (Ghormley and Clegg 1948, Fonio

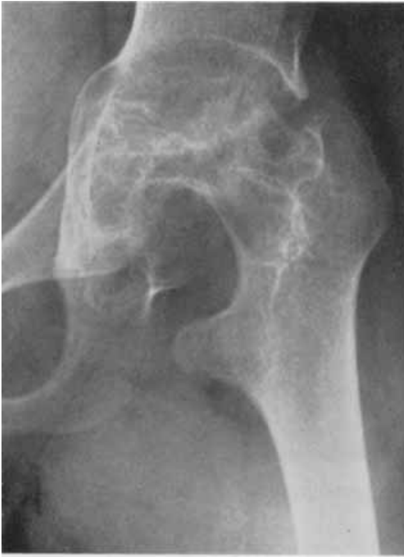


FIGURE 6 Hip joint, grade 4, L.-G.J., fam. 103, 15 years old.

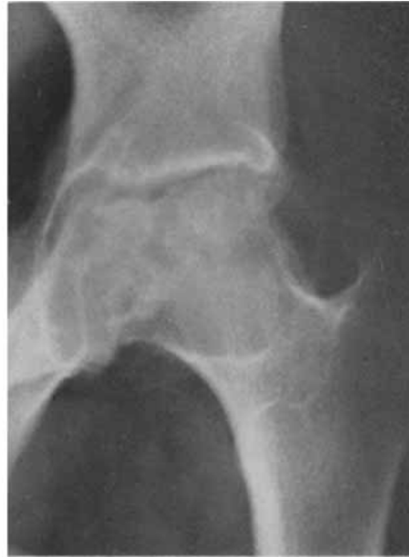


FIGURE 7 Hip joint, grade 4, A.J., fam. 73, 18 years old.

and Bühler 1952, DePalma and Cotler 1956, Jordan 1958, Ramgren 1962 a and others). It might therefore be convenient briefly to describe the roentgenographic appearance of the most important changes seen in this joint. The description applies also largely to the other joints. The roentgenographic changes in haemophilic arthropathy have been described by several authors (Fonio and Bühler 1952, DePalma and Cotler 1956, Stiris 1958, Jordan 1958, Tengberg *et al.* 1960, Holstein 1960, 1961, Mosley 1963, and others). Favre-Gilly (1964) published a roentgenologic investigation of the knee joints in 100 haemophiliacs, aged 7 to 15 years.

Changes in the epiphyses occur early: the trabeculation is increased and the epiphyses are enlarged. Cysts of varying size appear periarticularly. Disturbed development of the epiphyses can lead to deformation of the femoral and tibial condyles. The patella increases in size, especially in thickness, and its lower pole becomes squared off. Erosion of the joint cartilage often occurs early. In later stages the cartilage undergoes destruction with narrowing of the joint space and the formation of osteophytes.

Developmental changes of the epiphyses and secondary degenerative changes can together result in severe destruction of the joint. Differences in the rate of growth of the femoral condyles can cause valgus or varus deformity (Caffey and Schlesinger 1940). Webb and Dixon (1960) stated

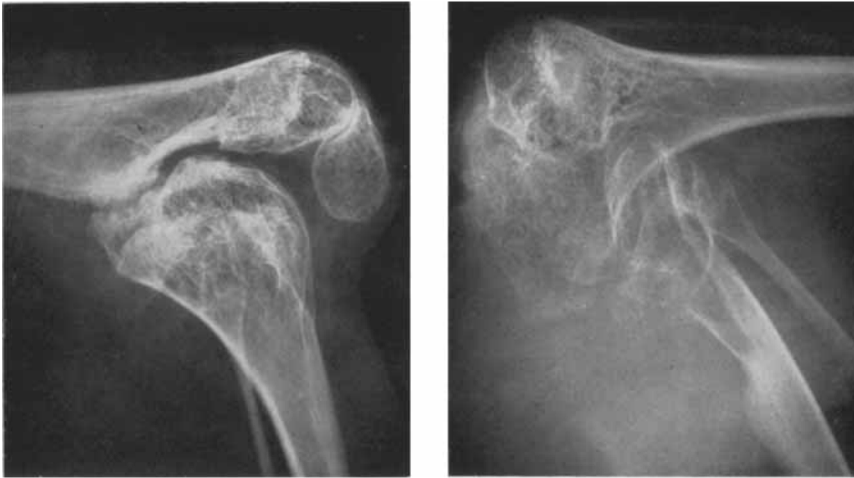


FIGURE 8 Severe destruction of knee joints, B.B., fam. 72, 15 years old.

that collapse of the lateral tibial condyle due to osteoporosis can cause valgus deformity. Jordan (1958) ascribed the outward rotation of the tibia, often seen in haemophilic arthropathy, to preponderance in growth of the medial femoral condyle. DePalma and Cotler (1956) felt that contracture of the joint capsule, shortening and contracture of the hamstring muscles and of the iliotibial band may cause angulation and rotation deformity and also subluxation backwards of the tibia. deAndrade *et al.* (1965) showed that irritation of the knee joint capsule results in weakening of the quadriceps and hyperactivity of the hamstrings. Such imbalance could readily produce flexion deformity and posterior subluxation of the tibia in haemophiliacs.

In this investigation flexion contracture was the commonest cause of disability. Valgus deformity and outward rotation of the leg were common but rarely severe enough to impair function. In one case, (B. M. fam. 95) a supracondylar osteotomy was performed in a knee with 30° valgus deformity and instability (Ahlberg *et al.* 1965). Varus deformity was uncommon. One patient (B. W. fam. 62) was operated upon with osteotomy of the tibia because of progressive varus deformity (p. 62). Complete derangement of the knee joint could occur early (Fig. 8). Bony ankylosis (Fig. 15) was present in 4 patients, all with severe haemophilia.

Ankle

Fifty-eight patients had changes in the talo-crural and/or subtalar joints. In 38 of them the lesions were bilateral. The joint changes were found in

one half of the patients with severe haemophilia, in one third of those with moderate haemophilia, and in only 1 of 24 with mild haemophilia. Grade 4 arthropathy was seen only in patients above 15 and then always in association with severe haemophilia.

In most of the cases the talo-crural as well as the subtalar joints were involved. Involvement of the talo-crural joints alone was more common than affection of the subtalar joints alone. In agreement with DePalma and Cotler (1956) flattening of the superior articular surface of the talus was a common observation here. Complete collapse of the body of the talus as described by Crock (1962) was seen in one case bilaterally (Fig. 9). Bony ankylosis of the ankle joints has been described by several authors (Fonio and Bühler 1952, DePalma and Cotler 1956, Jordan 1958). It was observed in one of the present cases (Fig. 16).

Foot

In only 1 patient, a man with severe haemophilia (B. S. fam. 46), were the small joints of the foot involved probably secondary to haemorrhage. In both feet the tarsal, tarso-metatarsal, and metatarso-phalangeal joints were severely affected and the toes were clawed. The first metatarso-phalangeal joint of one foot showed bony ankylosis.

Affection of the small joints of the feet and toes thus seems to be rare in haemophilia. No such changes are described in the compilations referred to previously (Table 1). Deformities caused by extraarticular haemorrhage are, however, known. Thomas (1936) has described a case of peripheral gangrene with loss of toes following extensive haemorrhage of the leg. Jordan (1958) reported one case of micromelia of the foot after haemorrhage in the central nervous system.

Shoulder

Twenty-one patients had shoulder joint changes, which were bilateral in 7. One fifth of the patients with severe haemophilia had shoulder affections, usually grades 3 or 4 (Figs. 10 and 11). Of 38 patients with moderate haemophilia, 2 had affection of the shoulder joints. In none of the 24 with mild haemophilia was the shoulder affected. Involvement of the shoulder was rare in children and became progressively severe with advancing age; of 53 patients with severe haemophilia and below 20 years the shoulder joints were affected in only 4 against 20 of 42 above 20. In 6 of the latter group the lesions were of grade 4.

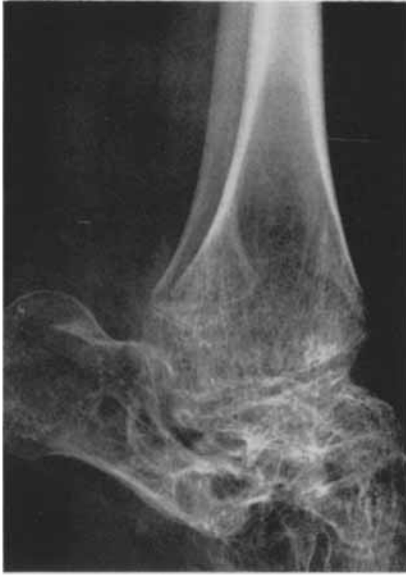
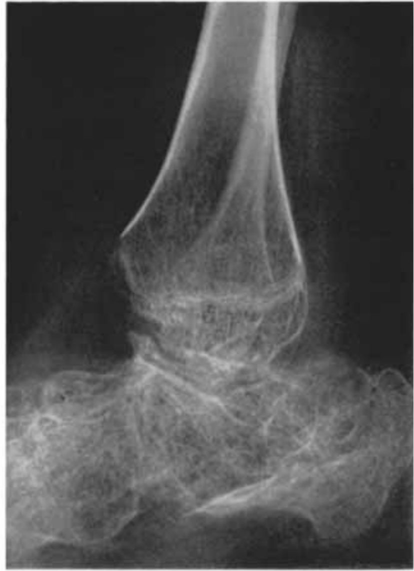



FIGURE 9 Collapse of the thalus, B.B., fam. 72, 15 years old.

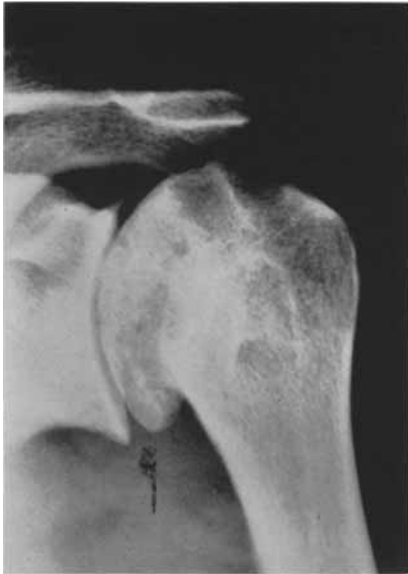


FIGURE 10 Shoulder joint, grade 3, Y.A., fam. 10, 29 years old.

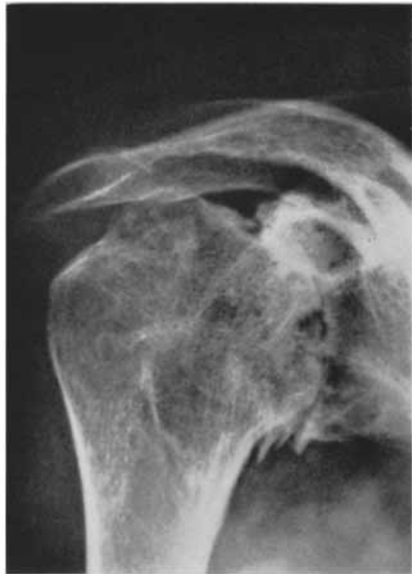


FIGURE 11 Shoulder joint, grade 4, L.O.W., fam. 48, 37 years old.

The literature contains little information on the incidence of shoulder arthropathy in haemophilia. Thomas (1936) reported the presence of the condition in only 1 out of 98 haemophiliacs, Ghormley and Clegg (1948) in none of 76, Webb and Dixon (1960) in 4 of 42. Jordan (1958), however, found 16 cases of shoulder arthropathy among 56 haemophiliacs, an incidence agreeing with that found in the present material.

Fonio and Bühler (1952) have described atrophy of the head of the humerus in 2 cases. The youngest patient with shoulder arthropathy in the present investigation, a boy of 7 (R. B. fam. 59), had restricted range of motion, muscular atrophy and roentgenologic evidence of atrophy of the head of humerus (Fig. 12). There was no evidence of any neurogenic cause of this condition.

Elbow

The elbow was affected in 86 patients, including 59 in whom the changes were bilateral. Two thirds of the patients with severe haemophilia were affected, half of them bilaterally. Of those with moderate haemophilia, half were affected, a quarter of them bilaterally. None of the patients with mild haemophilia were affected. Grade 4 arthropathy was seen in severe haemophilia in patients as young as 10—14 years and became progressively more common with advancing age. Grade 4 arthropathy was never observed before age of 40 in patients with moderate haemophilia.

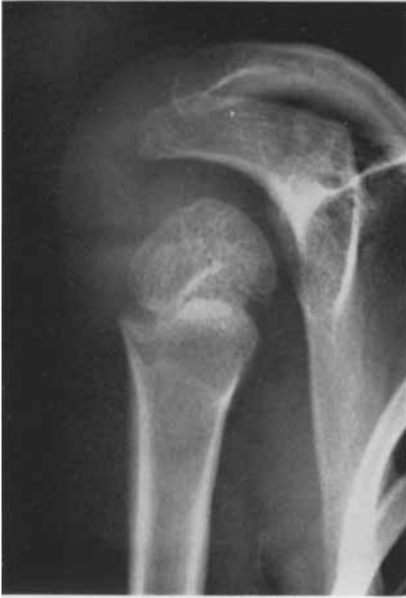
In patients with grade 3 or 4 extension-flexion as well as pronation-supination was as a rule impaired.

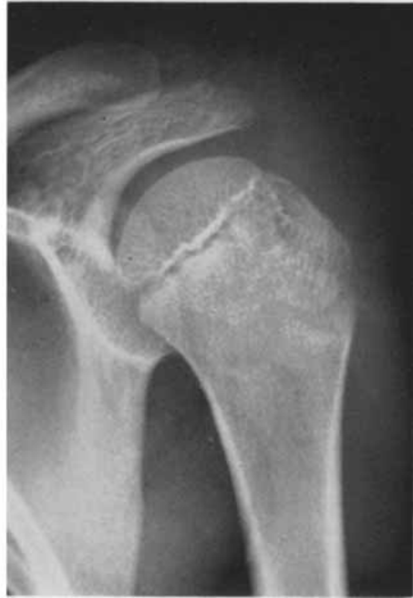
Enlargement of the head of the radius was observed as early as 1897 by Shaw, *i.e.*, 2 years after Roentgen's discovery of the x-ray. It was often seen in this investigation (Fig. 13). Knobbiness of the distal epiphysis of humerus, sometimes with valgus deformity (Klason 1921, Caffey and Schlesinger 1940) and deepening of the ulnar and radial incisuras and fossa olecrani (Fonio and Bühler 1952), are other typical changes. Bony ankylosis was not seen.

Wrist

Thirteen patients had wrist joint arthropathy, which was bilateral in 7. The condition was equally common in moderate and severe haemophilia, and was seen in about one tenth of these patients. Only 2 patients were below 20 years. It was not seen in patients with mild haemophilia.

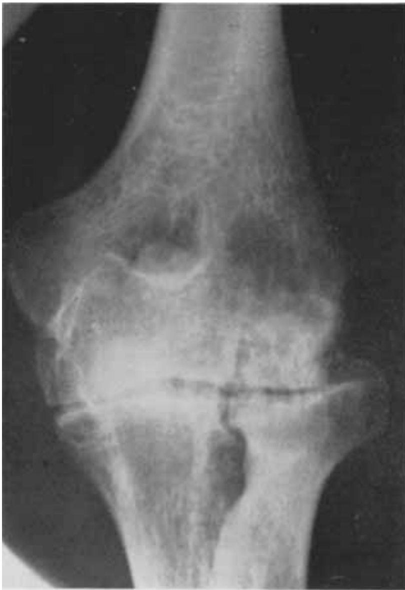
Newcomber (1939) described one case and Webb and Dixon (1960) two with deformity of the distal end of the ulna which they felt was due to





a. Right shoulder, atrophy b. Left shoulder, normal

FIGURE 12 Atrophy of head of humerus, R.B., fam. 59, 8 years old.



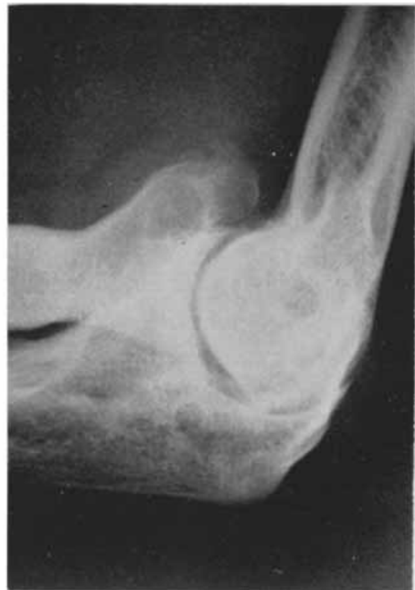


FIGURE 13 Elbow joint, grade 4, G.F., fam. 68, 34 years old.

haemorrhage. The only 2 cases of grade 4 observed here had a rather similar radiographic appearance: the distal end of the ulna had bent dorsally causing complete luxation of the carpo-ulnar joint (Figs. 14 a and b).

Hand

Of 157 patients, only 4, all with severe haemophilia, had lesions of the small joints of the hands or fingers. In all 4 the range of motion of at least one joint was impaired, probably from articular haemorrhage. None of these lesions caused any significant restriction of hand function.

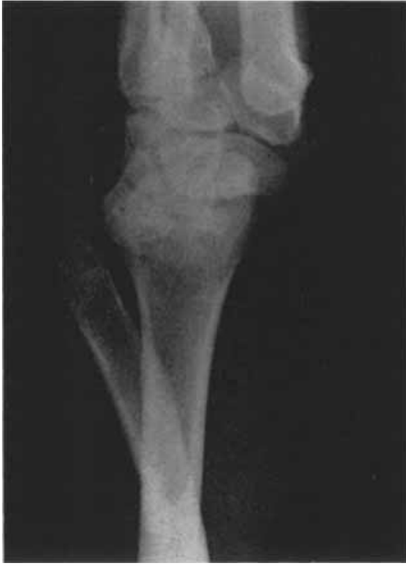
In haemophilia restriction of hand and finger function caused by haemorrhage into joints of the hand and fingers seems to be rare. Thomas (1936) states that finger-bleeding occurred in 15 of his 98 cases but with permanent joint changes in only 2. Fonio and Bühler (1952) described deformity of the metacarpals. However, impairment of hand or finger function following haemorrhage in the arm is important (p. 37).

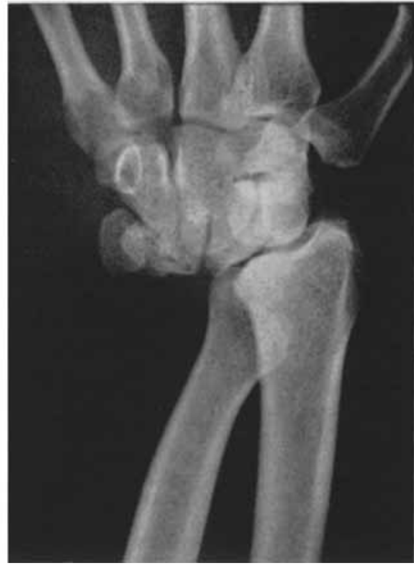
Bony Ankylosis

Bony ankylosis is rare in haemophilic arthropathy. Key (1932) stated that bony ankylosis "apparently does not occur" and DePalma and Cotler (1956), Jordan (1958), Stiris (1958), Holstein (1960) and Tengberg *et al.* (1960) have described ankylosis in all together 5 knee joints and 4 ankle or subtalar joints.

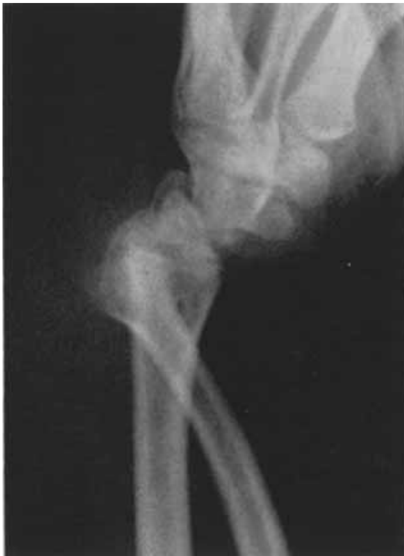
Astrup and Sjølin (1958) feel that protracted joint bleedings in haemophiliacs can give rise to increased formation of clots which are difficult to be dissolved completely by the available amount of fibrinolytic agents. Lack (1959) demonstrated a decreased fibrinolytic activity in tuberculous arthritis, so that fibrin accumulates on joint surfaces, which may result in pannus formation and fibrous ankylosis. In septic arthritis, however, there is increased fibrinolytic activity and frequently rapid destruction of the cartilage with consequent bony ankylosis. The deficiency of fibrinolytic activity in the joints in haemophiliacs may thus help to explain why bony ankylosis is rare in such patients.

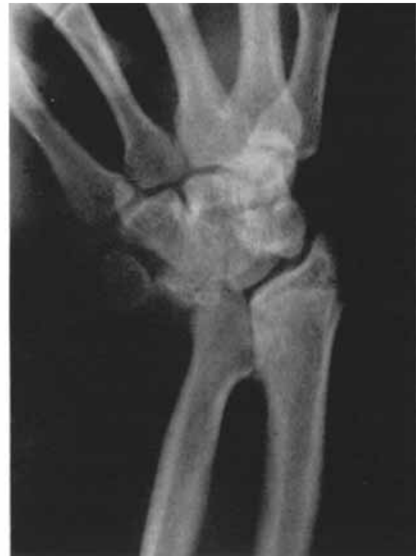
In the present investigation 6 joints with bony ankylosis were observed in 5 patients (Table 13), all of whom had severe haemophilia. Those 4 who had ankylotic knee or ankle joints (Figs. 15 and 16) believed that the joint had stiffened after treatment with traction, immobilization in plaster, joint puncture or other therapeutic measures. In one case (B. M., fam. 95) bony ankylosis of the knee developed after surgical correction of a valgus deformity.





a. O.P., fam. 27, 22 years old





b. G.E., fam. 61, 18 years old

FIGURE 14 Luxation of carpo-ulnar joint.

TABLE 13 Bony ankylosis in haemophilic arthropathy

	Family No.	Haemophilia	Initials	Year of Birth	Joint	Comments
1.	18	A Severe	N.G.W.	1930	Knee	Stiff after manipulation of flexion contracture under anaesthesia at 18 years
2.	18	A Severe	N.G.W.	1930	Ankle	Stiff after aspiration of haemarthrosis at 18 years
3.	31	B Severe	K.P.	1932	Knee	Stiff after repeated aspiration of haemarthrosis at 20 years
4.	46	A Severe	B.S.	1921	Metatarso-phalangeal joint first toe	
5.	56	B Severe	A.J.	1925	Knee	Stiff after treatment in cast for 6 months at 8 years
6.	95	A Severe	B.M.	1946	Knee	Stiff after wedge osteotomy of valgus deformity at 16 years

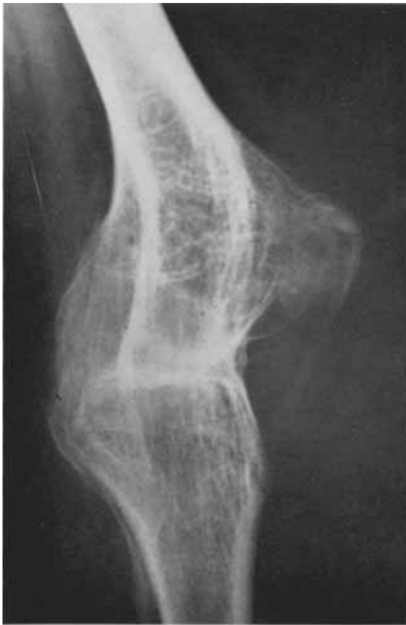


FIGURE 15 Ankylosis of knee joint, N.G.W., fam. 18, 33 years old.

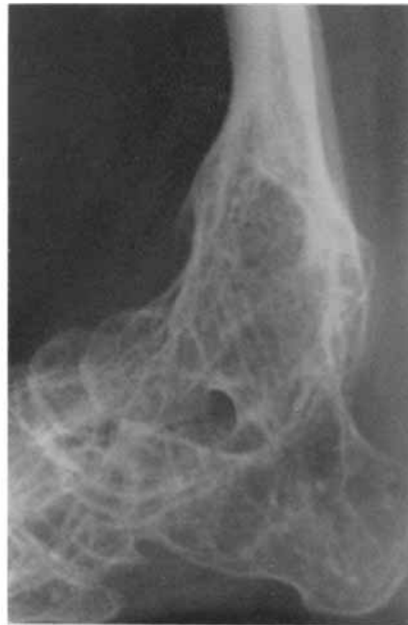


FIGURE 16 Ankylosis of ankle joint, N.G.W., fam. 18, 33 years old.

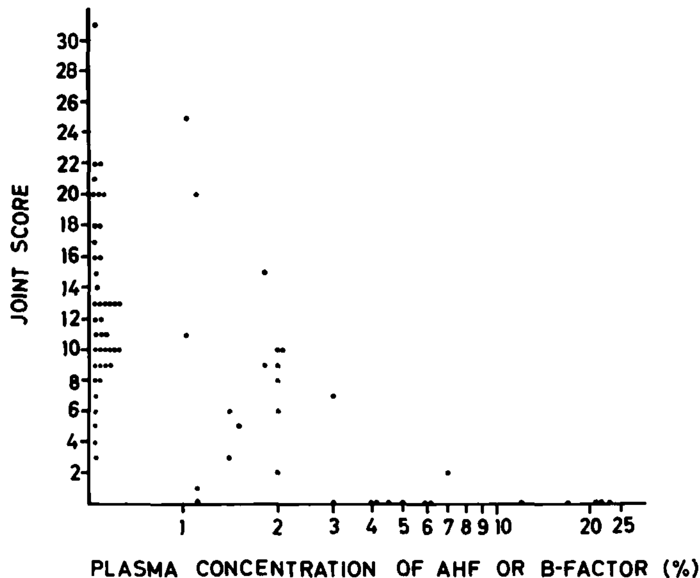


FIGURE 17 Arthropathy as a function of AHF and B-factor levels.

Incidence of Arthropathy of Various Joints

In both severe and moderate haemophilia arthropathy was most frequent and severe in knee, elbow and ankle joints in the order given (Table 11 and 12). Shoulder, wrist and hip joints were considerably less frequently involved. Involvement of the joints of hands and feet was rare in severe haemophilia, and was not observed in moderate haemophilia.

Arthropathy as a Function of Degree of Haemophilia

The frequency of arthropathy increased with the severity of the haemophilia (Table 11 and 12). In patients with mild haemophilia only 4 joints were involved (two grade 2 and two grade 3). In patients with severe haemophilia arthropathy of grade 4 was more than twice as common as in those with moderate haemophilia, and grade 3 was twice as common, while the difference in frequency of lesions of grade 2 was negligible. The age distribution is not taken into account here. Since the proportion of patients in the higher age classes in the group with moderate haemophilia was larger than in severe haemophilia, the true differences were more marked than those suggested by these numbers.

The relation between the levels of AHF and of B-factor in the plasma and the grade of arthropathy in adult haemophiliacs is shown in Fig. 17, where each point represents a haemophiliac of 20 years or more. The total

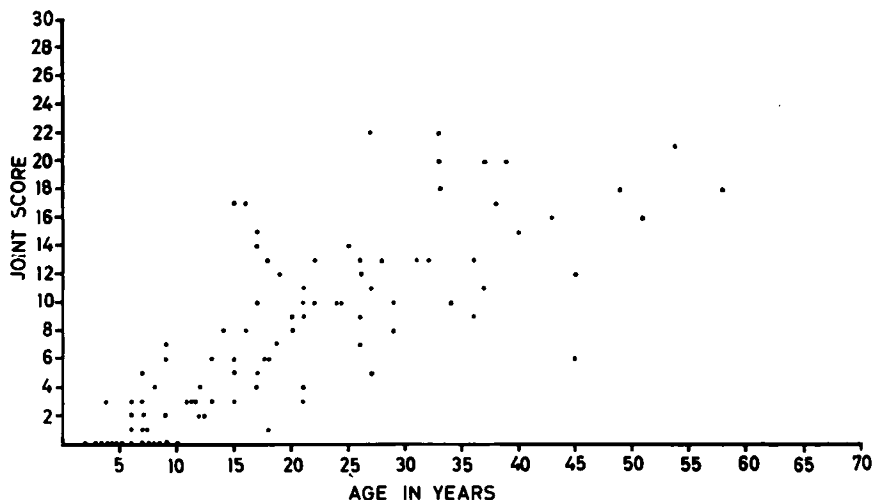


FIGURE 18 Arthropathy as a function of age. Severe haemophilia.

degree of arthropathy in each of the patients was calculated by giving the various degrees of arthropathy 1 to 3 points and then adding the points allotted to the joints affected. This value reflects the severity of the joint disease from a pathological-anatomical point of view rather than from a functional standpoint. The value obtained was called the joint score. These values were plotted against the plasma levels of the AHF and of the B-factor. Owing to the error of the method in the evaluation of these factors (page 11) values below 1 % could not be determined with exactitude and were therefore plotted as 0.5 %.

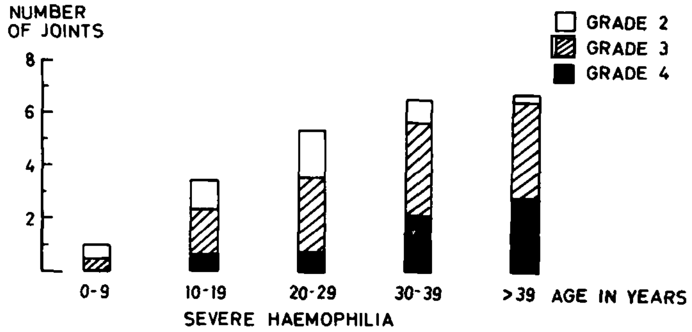
The joint score decreased with increasing values of the respective coagulation factors. Of the patients with a coagulation factor content above 2 %, only 2 had joint symptoms: a 49 years old man with an AHF content of 3 % (A. M., fam. 132) had a joint score of 7 and a 26 years old man with 7 % (L. T., fam. 135) had a joint score of 2.

Chronic joint changes in patients with a coagulation factor content above 2—3 % thus prove rare.

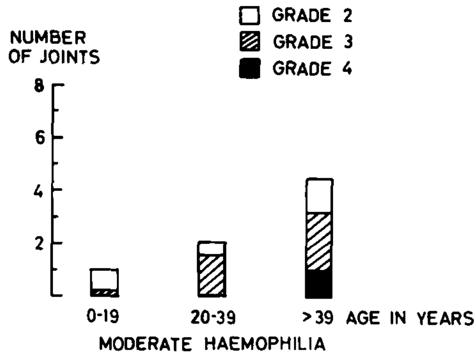
Arthropathy as a Function of Age

The joint scores of the patients with severe haemophilia were plotted against age (Fig. 18). Statistical treatment of the data[1] showed that in

[1] Data treated statistically under supervision of Professor C.-E. Quensel, Institute of Statistics, University of Lund.



a. Severe haemophilia



b. Moderate haemophilia

FIGURE 19 Mean number of affected joints per patient in various age-classes.

patients above 10 years the score increased with age at a fairly constant rate of 0.4 units per year.

For patients with a content of 1—3 % the rate of increase was about half of that for patients with a coagulation factor content of less than 1 %.

The patients with severe haemophilia were distributed among 10-year age classes and the mean number of joints affected (grades 2—4) per patient in each of the age classes was calculated (Fig. 19 a).

The total number of joints affected was found to increase with patients' ages up to 20 years, after which the increase in the number of joints involved was small (5.4 joints in the 20—29 year class, 6.6 in the 30—39 year class, and 6.8 in patients above 39 years), but the severity of the lesions continued to increase.

Table 14 Neurogenic lesions in haemophilia

	Family No.	Haemophilia	Initials	Year of Birth	Site of Haemorrhage	Functional Defect
1.	8	B Severe	K.E.C.	1909	Elbow Region	Paresis of ulnar and radial nerves
2.	68	A Severe	G.F.	1930	Gluteal Region	Paresis of sciatic nerve
3.	112	B Severe	S.J.	1943	Thigh	Drop foot
4.	184	A Moderate	T.B.	1958	Spinal Cord	Paraplegia

The number of patients with moderate haemophilia was small and therefore the patients were distributed only among 20-year age classes (Fig. 19 b). Here, too, the lesions tended to advance with age. The changes did not appear so early as in the group with severe haemophilia.

The haemophilic joint changes thus increase with age. The rate of increase after 10 years of age is largely constant in each grade of haemophilia, but it is higher in severe than in milder degrees of haemophilia.

EXTRA-ARTICULAR LESIONS

Neurogenic

Four patients were found to have permanent neurogenic joint dysfunction (Table 14); one had developed paraplegia following haematomyelia; one had paresis of the ulnar and radial nerves after haemorrhage in the elbow region; two had paresis of the foot following haemorrhage in the gluteal region or fracture of the femur. The lesions were 4—7 years old, so that they could be regarded as constant.

Aggeler and Lucia (1944) and Silverstein (1964) described neurogenic complications in haemophilia following haemorrhage affecting the ulnar, medial, peroneal, sciatic, femoral and facial nerves. Tallroth (1939) described a case of paralysis of the quadriceps musculature following haemorrhage in the iliopsoas muscle with injury to the femoral nerve. Haemorrhage in the central nervous system may, though rarely, cause temporary paresis (Aggeler and Lucia 1944). Jordan (1958) described a case of micromelia of the foot after bleeding in the central nervous system. The observations reported here confirm earlier impressions that neurogenic causes of chronic musculo-skeletal dysfunction are rare in haemophilia.

TABLE 15 Myogenic lesions in haemophilia

	Family No.	Haemo-philia	Initials	Year of Birth	Site of Haemorrhage	Functional Defect
1.	14	B Moderate	B.G.	1922	Iliopsoas Muscle	Flexion contracture of the hip
2.	34	A Severe	O.L.	1938	Calf Muscle	Equinus deformity of the ankle
3.	42	A Severe	B.R.	1924	Volar Muscles of Lower Arm	Contracture of fingers
4.	46	A Severe	B.S.	1921	Calf Muscle	Equinus deformity of the ankle
5.	61	B Severe	G.E.	1944	Wrist and Hand	Contracture of fingers
6.	72	A Severe	L.B.	1948	Calf Muscle	Equinus deformity of the ankle
7.	123	A Mild	K.A.	1949	Tigh Muscles	Contracture of the knee
8.	161	A Moderate	B.M.	1938	Calf Muscle	Equinus deformity of the ankle
9.	183	B Severe	B.A.	1947	Calf Muscle	Equinus deformity of the ankle

Myogenic

Nine patients were found to have myogenic joint dysfunction (Table 15); five had equinus deformity of the ankle joint following haemorrhage in the calf, one had flexion contracture of the hip following haemorrhage in the iliopsoas muscle, one a contracture of the knee after a femoral fracture, and two had flexion contracture of the fingers following haemorrhage in the musculature of the lower arm.

Intramuscular haemorrhage may cause fibrosis and muscle contracture. Field (1963) described 3 cases of equinus deformity of the ankle joint in whom achillotenotomy and capsulotomy were performed under protection of human fibrinogen, rich in AHF. Hip joint deformity following haemorrhage in the iliopsoas muscle has been described by Birch (1932), Tallroth (1939), Davidson *et al.* (1949).

Several authors have reported dysfunction following haemorrhage in the lower arm causing Volkmann's contracture (Lord 1926, Thomas 1936, Hill and Brooks 1936, Newcomber 1939). This complication might have occurred in one case here (B. R., fam. 42) but the lesion may also have been caused merely by organization of an intramuscular haematoma and need not have been related to ischaemic necrosis.

TABLE 16 Pseudotumours in haemophilia

	Family No.	Haemophilia	Initials	Year of Birth	Site	Comments
1.	14	B Moderate	B.G.	1922	Ilium	Fracture of femur at 36 years
2.	14	B Moderate	S.G.	1928	Ilium	
3.	34	A Severe	O.L.	1938	Femur	Traumatic haemorrhage at 10 years in knee region involving calf muscles
4.	83	A Severe	P.O.	1946	Humerus	
5.	169	A Moderate	B.S.	1909	Ilium	
6.	190	A Severe	M.E.	1926	Ilium	Traumatic haemorrhage hip region while skiing at 16 years

Pseudotumour

Six cases of haemophilic pseudotumour were seen (Table 16), 4 in the ilium (Fig. 20) and, 1 in the humerus (Fig. 21), and 1 in the femur (Fig. 22). Three of the patients with lesions in the ilium had a history of rather severe accidents with haemorrhage in the affected region. However, as the interval between the accident and diagnosis of the lesion was 6—15 years, a causal relationship cannot be proven. Two of the patients had associated contracture of the iliopsoas muscle (S. G., fam. 14) and of the calf (O. L., fam. 34).

Skeletal lesions of tumour-like appearance were first described in haemophilia by Starker (1918); a 14 year old patient died from haemorrhage and infection following needle biopsy of a lesion in the femur. Pathologic anatomic examination failed to reveal any evidence of neoplasm. Silber and Christensen (1959) traced 18 cases in the literature and described 3 cases of their own. In a survey of the literature on haemophilic pseudotumours Abell and Bailey (1960) found 23 cases and added 2 of their own. Eleven of those patients died, 5 probably because of surgery.

Since then operations for pseudotumours have been successfully performed under cover of coagulation preparations of bovine and human type (Hall *et al.* 1962, de Valderrama and Methews 1965, and others).

Eight of the patients in Abell and Baileys review had a history of violence directed against the affected area. As in our cases, there was usually an interval of several years between the accident and the diagnosis of the bony

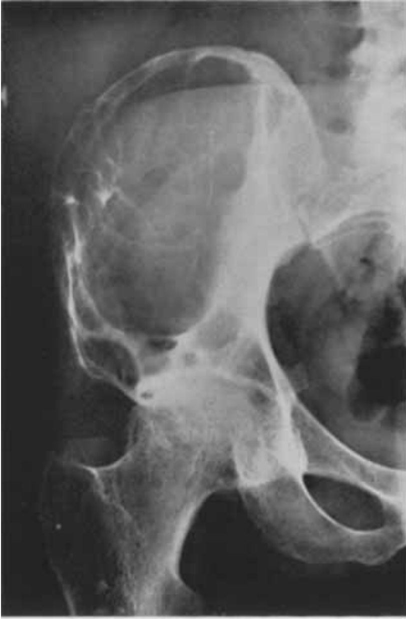


FIGURE 20 Pseudotumour of ilium, M.E., fam. 190, 38 years old.

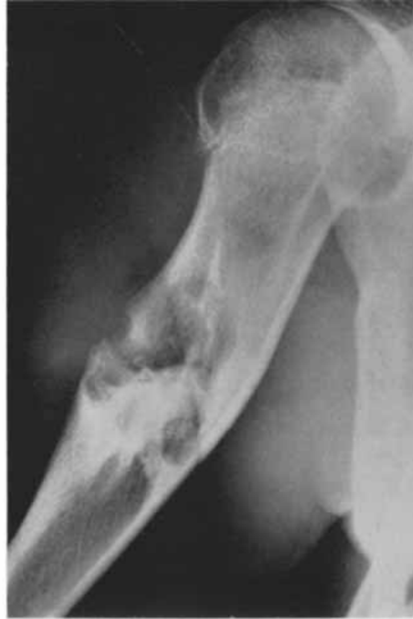
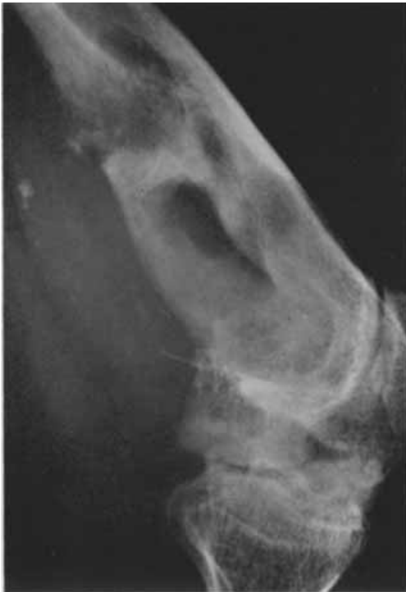


FIGURE 21 Pseudotumour of humerus, P.O., fam. 83, 18 years old.



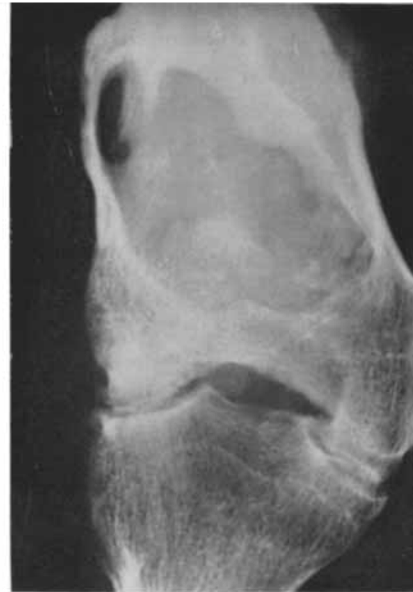


FIGURE 22 Pseudotumour of femur, O.L., fam. 34, 26 years old.

TABLE 17 Sites of pseudotumours in haemophilia

Site	No. of Cases
Femur	20
Ilium	13
Thumb	2
Tibia	2
Pubis	1
Olecranon	1
Humerus	1
Metatarsal	1
Total	41

This table is based on: Abell and Bailey (1960), Nelson and Mitchell (1962), Hall *et al.* (1962), Caen *et al.* (1964), Lewis *et al.* (1965), Jones (1965) and Table 16 reported here

lesion. A review of cases described to date is given according to localization in Table 17 from which it is clear that the commonest sites were the femur and ilium.

The roentgenologic appearance of haemophilic pseudotumours shows evidence of mingled areas of bone destruction and new bone formation. It has been described by Becker (1942) and Echtenacht (1943) and others. The appearance is sometimes difficult to distinguish from that of osteogenic sarcoma (Becker 1942, Nelson and Mitchell 1962, and others).

Histologic examination of material obtained at biopsy or autopsy has shown that the lesions consist of organizing haematoma in which new bone is being formed (Ghormley and Clegg 1948, Silber and Christensen 1959, Nelson and Mitchell 1962).

It is clear from the literature that the mortality from diagnostic and therapeutic surgery of pseudotumours has been high. Only when there is strong reason to suspect that the changes are malignant or if the tumour continues to grow despite conservative treatment, including infusion of concentrated AHF or B-factor preparations, should operation be considered and if decided upon, it should always be done under cover of adequate replacement therapy.

IV. Disability due to Musculo-skeletal Manifestations in Haemophilia

In a medicosocial study of haemophiliacs in Sweden in 1962 Ramgren reported *inter alia* the school attendance, occupation and working capacity of the patients. The present investigation is concerned with the general condition of haemophiliacs in Sweden from an orthopaedic point of view.

The degree of disability was assessed on the basis of the clinical findings and/or the questionnaires (p. 15). Two hundred and forty-two patients were classified in this respect (Table 18). It is clear from Table 4 that most of those studied only by questionnaire had haemophilia of mild type. The age distribution of the patients according to the severity of haemophilia was the same in the group studied by questionnaires as in the group studied clinically. The two groups were therefore pooled. The data refer to periods without acute bleeding.

DISABILITY RELATED TO AGE AND DEGREE OF HAEMOPHILIA

In patients with *severe haemophilia* (Table 19) the degree of disability increased markedly with age up to 15 years. About half of the patients below 15 years were free from any disability, against only 3 patients above this age (all in age-class 15—19 years). The variation of the degree of disability with age is clear from Fig. 23, where the various degrees are allotted points (0—3) and the mean scores of the various age classes are given. The mean scores increased markedly up to the 15 years after which no further increase could be demonstrated with certainty.

Ramgren (1962 b) found the life expectancy of severe haemophiliacs to be one third of that of the normal male population. The ratio between the observed and the expected number of deaths among severe haemophiliacs during the years 1958—1962 was 1 : 10. If the mortality varies with the degree of disability, *i.e.*, if those with a higher degree of disability die earlier, it would help to explain why no increase in the degree of disability could be demonstrated in patients above 15—20 years.

TABLE 18 Degree of disability as a function of severity of haemophilia

Degree of haemophilia	Severe	Moderate	Mild	Total
Number of patients	102	59	81	242
Degree of disability				
None	20	32	78	130
Mild	24	15	2	41
Marked	40	8	1	49
Severe	18	4		22

TABLE 19 General disability in severe haemophilia as a function of age

Age	Total	Examined	Degree of Disability			
			0	1	2	3
0— 4	13	6	5	1		
5— 9	22	20	10	5	3	2
10—14	11	11	2	2	3	4
15—19	21	20	3	4	7	6
20—24	13	12		7	3	2
25—29	13	12		2	9	1
30—34	5	5		1	3	1
35—39	6	6		1	5	
40—44	3	2			2	
45—49	3	3		1	2	
50—54	2	2			1	1
> 54	4	3			2	1
Total	116	102	20	24	40	18

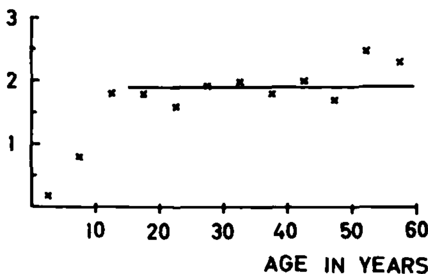


FIGURE 23 Mean degree of disability in different age classes in severe haemophilia

TABLE 20 General disability in moderate haemophilia as a function af age

Age	Total	Examined	Degree of Disability			
			0	1	2	3
0— 4	3	1	1			
5— 9	6	6	3	2	1	
10—14	5	5	2	2		1
15—19	7	6	3	3		
20—24	9	9	4	2	3	
25—29	4	3	3			
30—34	4	4	3	1		
35—39	5	5	2	2	1	
40—44	5	4	1		2	1
45—49	5	5	3	1		1
50—54	4	4	2		1	1
> 54	8	7	5	2		
Total	65	59	32	15	8	4

Of the 59 patients with *moderate haemophilia* (Table 20) 32 were free from any disability, while 12 were markedly or severely disabled. Observations made in the patients with moderate haemophilia suggested that the degree of disability tended to increase with advancing age; only 2 of 18 patients below 20 being markedly or severely disabled, against 6 of 20 above 40. The overmortality among the patients with moderate haemophilia was not high enough to have any substantial effect on the results. (The ratio between the expected and observed number of deaths was 1 : 2.) The series was, however, too small and too heterogenous from a point of view of coagulation defect to warrant any conclusion about the variation of the degree of disability with age.

Of 81 patients with *mild haemophilia* (Table 21), only 3 were disabled; 1 markedly and 2 mildly. In the markedly disabled patient (K. S., fam. 203) the disability was due to impaired function of the knee after a severe blow. In one of the mildly disabled patients (K. A., fam. 123) the disability was due to fracture of the femur. In the other patient (L. T., fam. 135) function of one of the ankles was impaired without any known preceding trauma.

In mild haemophilia then disability is rare and when it does occur, it may be due to trauma.

Table 21 General disability in mild haemophilia as a function of age

Age	Total	Examined	Degree of Disability			
			0	1	2	3
0— 4	2	2	2			
5— 9	9	8	8			
10—14	14	11	10	1		
15—19	9	7	7			
20—24	11	7	7			
25—29	13	7	6	1		
30—34	13	6	6			
35—39	11	8	8			
40—44	12	7	7			
45—49	10	5	4		1	
50—54	4	3	3			
> 54	19	10	10			
Total	127	81	78	2	1	

Table 22 Locomotor disability

Degree of Haemophilia	Severe	Moderate	Total
Bedridden	1	0	1
Wheelchair ambulatory	8	0	8
Crutch ambulatory	3	1	4
Using stick	7	5	12
Using other orthopaedic services (braces, shoes etc.)	9	4	13
Using no orthopaedic services			
Walking range less than one kilometer	22	6	28

Disability related to AHF and B-factor level. Of 66 patients, aged 20 years or more, with an AHF or B-factor level of 3 % or more, one (K. S., fam. 203) was markedly disabled after a trauma (see above) and 2 mildly (A. M., fam. 132, L. T., fam. 135). No disability was noted in any of the remaining patients.

USE OF ORTHOPAEDIC APPLIANCES

Only 1 of the 242 patients was bedridden and 8 had to use a wheelchair. All 9 had severe haemophilia. Four patients used crutches and 12 used one or two sticks. Thirteen patients wore orthopaedic braces, splints or shoes. (Table 22.)

ACTIVITY OF DAILY LIFE

Only 5 patients (1 bedridden and 3 bound to wheelchair) could not manage their daily life (dressing, eating, toilet) without help, because of disability due to the musculo-skeletal system.

V. Correction of Muskulo-skeletal Deformities in Haemophilia

INTRODUCTION

As shown in Chapters III and IV, joint contractures and deformities are common in haemophiliacs and are often disabling. Formerly the risk of haemorrhage severely limited the possibilities of active treatment in haemophilia. It is generally accepted that replacement therapy is necessary in association with surgical intervention on haemophiliacs. Even continuous traction and physiotherapy to correct the joint deformities carry a risk of haemorrhagic complications liable to prolong treatment and jeopardize the results. Blood and plasma were the preparations formerly used in the treatment of haemophilia A and B. But it is now known that these are not sufficient to control the bleeding in certain situations. Experience has shown that if haemostasis in association with surgical intervention is to be satisfactory, the plasma AHF or B-factor must be at least 30—70 % of normal during the first 24 hours after the operation and 20—40 % during the rest of the healing period (Brinkhous *et al.* 1956, Biggs and Macfarlane 1962, Nilsson *et al.* 1962 and others). Elevation of the AHF level from 0 to 35 % in an adult requires infusion of at least 3 litres of fresh blood or 1 1/2 litres of fresh plasma. AHF is rapidly consumed; Biggs (1963) found a half-time of about 14 hours, for which reason the infusion must be repeated often. This requires the use of concentrated preparations.

During the second world war Cohn *et al.* (1946) devised a method for fractionation of plasma (method 6). The various fractions were tested for antihaemophilic activity. Such activity was demonstrated mainly in fraction I. But it was found to vary, probably because of contamination with thromboplastin, prothrombin and plasmin. The fraction was therefore not widely used clinically.

Of greater practical importance was a fibrinogen fraction prepared by Kekwick *et al.* (1946, 1957). They used a fractionation technique with ether. The preparation had an AHF activity of 20—25 times that of human plasma per mg protein. It was used clinically, but side effects were reported.

Concentrated AHF has been prepared from bovine and pig blood (Bid-

well 1955 a, 1955 b). Treatment of patients with haemophilia A with this fraction has been reported by the Oxford group (Biggs 1960). Good results have been achieved, though the side effects and the antigenic properties considerably limit the range of indications for the preparation. Macfarlane *et al.* (1957) claim that the preparation should only be used in life-threatening situations.

In 1956 Blombäck and Blombäck described a method for purifying fibrinogen from Cohn's fraction I by treatment with a glycine solution containing ethanol and citrate. With this method they obtained a fraction, I—0, in which 85—90 % of the protein consisted of fibrinogen. Fraction I—0 proved practically free from plasmin and prothrombin and was therefore stable. It has been used in Sweden since 1956 in the treatment of haemophilia A (Blombäck and Blombäck 1956, Blombäck and Nilsson 1958, Blombäck *et al.* 1960, Nilsson *et al.* 1962, Nilsson 1965). This fraction proved successfully to control bleeding even in association with major operations and not to cause any serious side-effects. Preparations largely analogous to fraction I—0 have since been used by other authors in the treatment of haemophilia A (McMillan *et al.* 1961, Newcomb and Watson 1963).

Later concentrated preparations of B-factor also became available. Thus, Soulier (1961) prepared a haemophilia B concentrate, fraction P. P. S. B., from human serum and Biggs *et al.* (1961) a similar concentrate from human plasma. The preparations have proved clinically useful.

METHODS

Human fraction I—0 (AHF-concentrate)

Human fraction I—0 containing AHF was prepared at the Chemistry Department II, Karolinska Institutet, Stockholm, by the glycine method of Blombäck and Blombäck (1956). One dose of this fraction is prepared from 1400 to 1600 ml of plasma and contains about 3 g of protein. As a rule, half a dose or a whole dose is given at a time. A half dose of fraction I—0 is dissolved in 100 ml of isotonic saline. The preparation has an activity of 5—8 times that of normal plasma.

Fraction P. P. S. B., a concentrate of human haemophilia B factor

Fraction P. P. S. B.—10 (lot 206) was obtained from Centre National de Transfusion Sanguine by courtesy of Professor J. P. Soulier, Dr F. Josso and Dr D. Ménaché. The fraction is prepared according to the method

reported by Soulier (1961). This method consists of adsorption of human plasma to $Ca_3(PO_4)_2$, after which this precipitate is eluted with 0.18 M sodium citrate solution and concentrated by precipitation with 25 % ethanol at $-5°$ C and pH 5.2. The fraction is sterilized by filtration through "Millipore" filter after stabilisation by addition of a small amount of heparin and then freeze-dried. The fraction contains prothrombin, factor VII, factor X and factor IX. Each bottle contained about 260 mg of freeze-dried protein, and an isotonic solution was prepared by dissolving the content of one bottle in 10 ml of distilled water. According to Dr D. Ménaché, the activity of factor IX *in vitro* in the lot obtained was 30 times more than the equivalent volume of plasma, *i.e.* a bottle of 10 ml was equivalent to 300 ml of plasma.

Coagulation tests. During treatment the AHF and B-factor, respectively, were determined according to the method described on page 11.

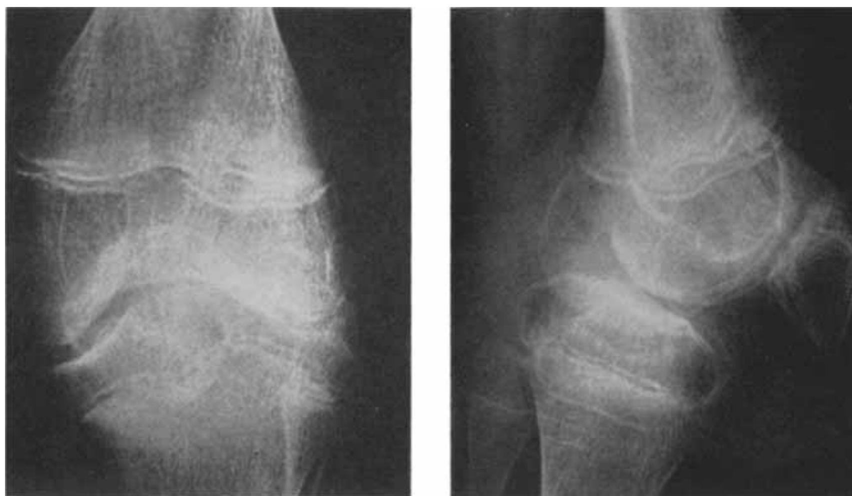


FIGURE 24 Case 4, L.-E.H., fam. 213, 10 years old. Left knee before treatment.

CASE REPORTS AND RESULTS

Eleven patients were treated on all together 13 occasions. All of them had severe haemophilia (type A in 9 and type B in 2). Nine were treated with continuous traction and 4 with surgical operations (Table 23). Three (L. W., L. R. C., and B. M.) have been reported previously (Ahlberg *et al.* 1965). The family histories, symptoms and coagulation data in all of the 11 cases have been described elsewhere (Nilsson *et al.* 1961, Ramgren 1962 a, and Addendum, p. 99).

Case 4. L. E. H., male, born in 1953, severe haemophilia A (family 213). Since the age of 2 years he had had repeated spells of bleeding into the joints of the knees, ankles, and elbows. A blow against the left knee in 1961 was followed by heavy bleeding into the joint. Since then he has had contracture of the knee joint and walking difficulties. Owing to an extension defect of the left knee he had to walk on his forefoot. In August 1963 he was admitted for treatment of the deformity of the left knee joint.

On admission the left knee was found to be increased in breadth, there was about 15° valgus deformity and slight outward rotation of the lower leg and an extension defect of 30°. Range of motion 50° (150°—100°). Atrophy of the thigh. The mobility of the left elbow was reduced (150°—60°). All the other joints examined appeared largely normal. Roentgen examination of the left knee revealed typical changes with increased breadth of the tibial and femoral condyles, deformation of the patella, coarse trabeculation and erosion of the articular surfaces (Fig. 24).

Treatment of the left knee joint

On August 9 continuous traction with a weight of 2 kg was started. After 10 days' extension the defect had diminished from 30° to 20° and treatment was continued

TABLE 23. Correction of deformities in severe haemophilia

Case No.	Family No.	Initials	Age in years at treatment	Type of haemophilia	Status before treatment	Orthopaedic treatment	Substitution therapy	Hospitalisation in weeks	Status on discharge	Complications
1	175	L.W.	6	A	Rt. knee 110—60° Uses crutches	Traction Extension brace	AHF 0.5 dose/wk. Total 8 doses	14	Rt. knee 170—150° Walks without crutches	—
2	74	L.R.C.	11	A	Lt. knee 110—100° Uses crutches	Traction Extension brace	AHF 0.5 dose/wk. Total 2.5 doses	10	Lt. knee 170—160° Walks without crutches	—
3	95	B.M.	16	A	Rt. knee 140—100° Valgus deformity. Uses wheelchair	1) Traction Extension brace	AHF 0.5 dose/wk. Total 4.5 doses	10	Rt. knee 180—75° Valgus 30°. Walks with knee brace	—
						2) Supracondylar Osteotomy	AHF total 30.5 doses	12	Rt. knee ankylotic at 175°, valgus 5°, walks without brace	Minor haemorrhage in the operation region on 18th postop. day
4	213	L.-E.H.	10	A	Lt. knee 150—100°, Valgus 15° Walks with severe limp	Traction Extension brace	AHF 0.5 dose/wk. Total 2 doses	4	Lt. knee 170—110° Valgus unchanged Walks well	—
5	106	S.-O.J.	8	A	Lt. knee 120—110° Uses crutches	Traction	AHF 0.5 dose×2	8	Lt. knee 180—180° Walks without crutches	Hemarthrosis lt. knee during treatment
6	28	S.W.	28	A	Lt. knee 160—135°, pain at motion, locking, repeated haemorrhage, unable to work	Arthrotomy with excision of osteophytes and extension	AHF total 16 doses	6	Lt. knee 180—90°, no pain at motion	—

7	100	B.A.	16	B	Lt. knee 90—60°, Uses crutches	Traction Extension brace	450 ml plasma × 14		Lt. knee 145—70° Walks without crutches. Uses stick occasionally	—
8	72	L.B.	16	A	Rt. knee 130—70°, Equinus 120° Uses wheelchair	Traction Extension brace	AHF 1 dose + 450 ml plasma × 5	6	Rt. knee 175—60°, Equinus unchanged Walks well	—
9	183	B. A.	18	B	Lt. knee 160—70° Equinus 140°, Walks with difficulty	1) Traction Extension brace	450 ml plasma × 6	4	Lt. knee 175—70° Equinus unchanged	—
						2) Lengthening of Achilles tendon and *posterior* capsulotomy	420 ml fraction PPSB + 4700 ml plasma	8	Foot in normal position. Walks well	—
10	159	R.H.	12	A	Lt. knee 145—90°, Walks with stick	Traction Extension brace	AHF 0.5 dose + 400—625 ml plasma × 5	9	Lt. knee 175—60° Walks better, but uses knee brace because of weak muscles	—
11	62	B.W.	23	A	Rt. knee 155—90° Varus deformity 25°. Walks with difficulty	Vedge osteotomi on the proximal tibia	AHF total 54 doses	18	Rt. knee in good position. 180—150°	Bleeding in the operation region 2 days and 8 weeks postop. Pneumonia on the 5th postop. day

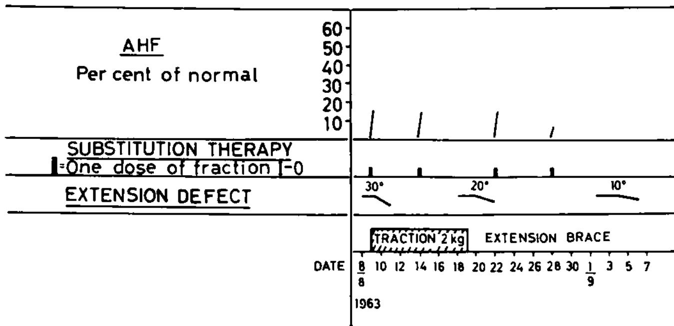


FIGURE 25 Case 4, L.-E.H., fam. 213. Treatment and course.

with an extension brace. Walking exercises were started. After a further 2 weeks the defect had decreased to 10°.

On September 6, when the patient left hospital, he could walk with less difficulty; he could step on the entire foot, and he limped only slightly. Range of mobility: 170°—110°. He was instructed to use the extension brace at night. Active movement exercises. At follow-up in February 1964 and July 1965 walking ability was still good. Mobility of the knee joint: 170°—80° and improved musculature of the thigh.

AHF dosage and plasma AHF levels (Fig. 25)

Before traction treatment was started the patient was given half a dose of fraction I—0, *i.e.* 100 ml. This dose was repeated three times at intervals of one week, *i.e.*, all together 4 half doses of fraction I—0. Before the first injection the patient had an AHF level of 0.1 % of normal. Immediately after administration of half a dose of fraction I—0 the AHF increased to between 14 and 18 %. After a week the AHF was 1 %. During his stay in hospital he had no bleeding into the left knee joint or other bleeding symptoms.

Case 5. S. O. J., male, born in 1955, severe haemophilia A (family 106). In 1959 he had bleeding into the left elbow joint, and in 1961, into the left knee joint. In the beginning of December, 1962, he again had bleeding into the left knee joint after wrenching of the knee. The symptoms persisted after 2 weeks' rest at home. Medical advice was then sought and the patient was admitted to hospital for AHF-therapy. Owing to persistence of the extension defect of the knee joint, on January 15, 1963, 6 weeks after the trauma, the patient was transferred to the Department of Orthopaedic surgery, Malmö general hospital.

On admission. Moderate exudate in the left knee joint. Extension defect of 60°. Range of motion 10° (120°—110°). Roentgen examination revealed broadening of the femoral condyles, coarse trabeculation of the bones and erosion of the articular surfaces (Fig. 26). The mobility of the elbow joint was somewhat reduced. Other joints examined appeared normal.

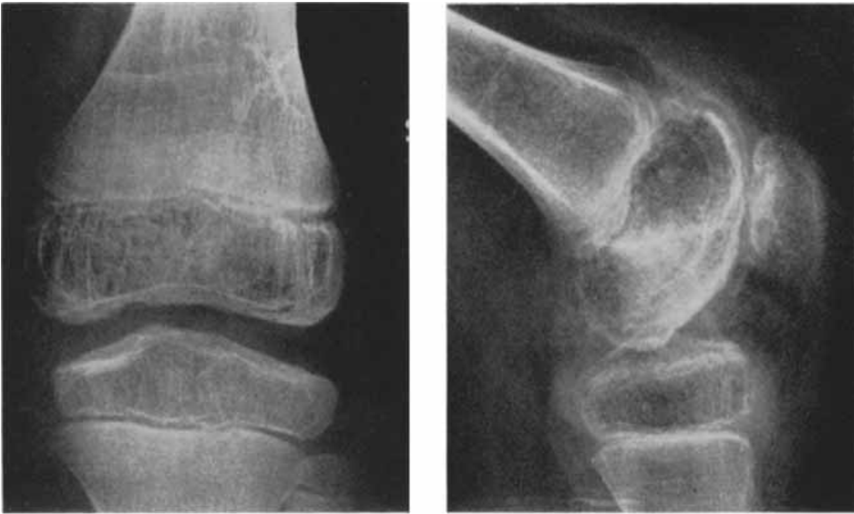


FIGURE 26 Case 5, S.-O.J., fam. 106, 8 years old. Left knee before treatment.

Treatment of the left knee joint. Continuous traction with a weight of 2 kg was started on January 15, 1963. After one week's treatment the extension defect was reduced to 20° (mobility 160°—135°). After a further week's treatment the weight was increased to 3 kg and used for one week. On February 8, 1963, the extension defect was 10°. Mobility 50° (170°--120°). Traction was discontinued and walking exercises were started. On February 18, 1963, the patient showed symptoms of fresh bleeding into the left knee joint with pain, swelling and extension defect. After 2 days' bedrest extension with a weight of 2 kg was re-assumed and continued for 5 days. The knee was fully extended but the range of flexion was only 10°. He left hospital on March 8, 1963. The range of movement of the knee joint was then 180°—170°.

At re-examination in January 1964 and March 1965 his condition was largely unchanged with the knee extended but with a range of flexion of only 10°.

AHF dosage and plasma AHF levels (Fig. 27)

During the period December 14 and January 15, the patient received 8 half doses of fraction I—0, because of an acute haemarthrosis in the left knee joint. In connection with the subsequent traction treatment he received only 2 half doses of fraction I—0 owing to shortness of the preparation. The preparations were given on January 22 and on March 3. AHF determinations were only performed before the administrations and the AHF level in these samples ranged between 0.1 and 1 % and was never higher than 1 %.

Case 6. S. W. male, born in 1936, severe haemophilia A (family 28). Ever since childhood he had had repeated bleeding into the knee joints, ankles, right elbow and wrists. Wrenching of the knee in 1962 was followed by severe haemarthrosis. Since then he has often had effusions and pseudolocking of the knee. The symptoms gradually progressed and from 1963 he was unable to work (draughtsman). In

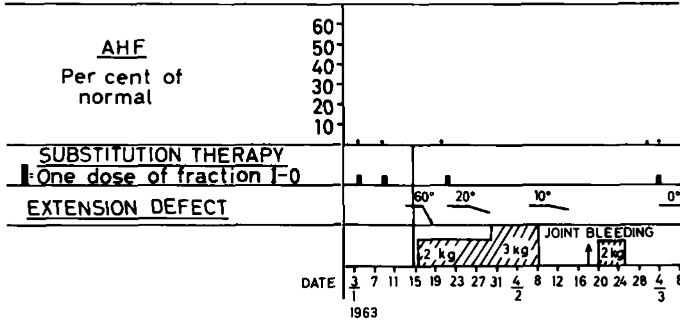


FIGURE 27 Case 5, S.-O.J., fam. 106. Treatment and course.

1964 he was admitted to hospital for investigation and treatment of increasing symptoms and disability.

On admission. No exudate in the knee. Range of mobility 160°—135°. Pain on movement. Tenderness to palpation over the medial aspect of the joint. Roentgen examination showed arthropathy of haemophilia with severe destruction of the joint cartilage, especially medially, and marginal spurring. Coarse trabeculation and subchondral cyst formation (Fig. 3).

Treatment of the left knee joint

Owing to the protracted and severe symptoms arthrotomy was considered indicated because of suspected medial meniscus rupture or loose body. The operation was performed on March 17, 1964, with a parapatellar incision medially. The synovia was thick, red-brown. The joint contained old liquid blood and some clots. The joint was markedly destroyed. Massive intraarticular adhesions made inspection difficult. No rupture of the medial meniscus. The medial femoral condyle showed abundant marginal osteophytes. These were chiseled off and the knee joint was fully extended. Partial synovectomy was done. Moderate bleeding during the operation. Bleeding vessels were ligated with fine silk. Pressure bandages were used. The postoperative course was smooth. No haemorrhage.

The patient left hospital one month after the operation. He then walked with a stick. No longer any tenderness or pain over the medial aspect of the joint. No symptoms of pseudolocking. The range of motion had improved to 180°—90°. At after-examination in September 1964 the patient walked without a stick. He had had no symptoms of pseudolocking. Mobility 180°—75°.

AHF dosage and plasma AHF levels (Fig. 28)

The patient received 2 doses of fraction I—0 immediately before the operation, one dose at the end of the operation and one dose 7 hours after the operation. During the night he received two transfusions of fresh blood. On the first postoperative day he received two and a half doses of fraction I—0, on the second postoperative day 2 doses of fraction I—0 and 600 ml of fresh plasma, on the third one and a half doses

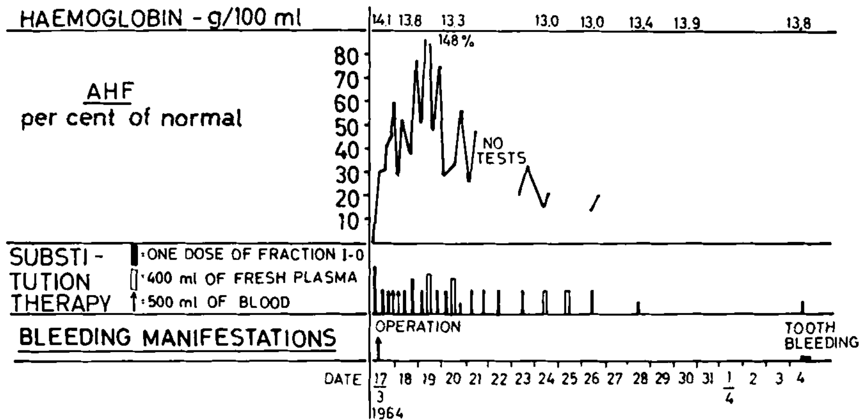


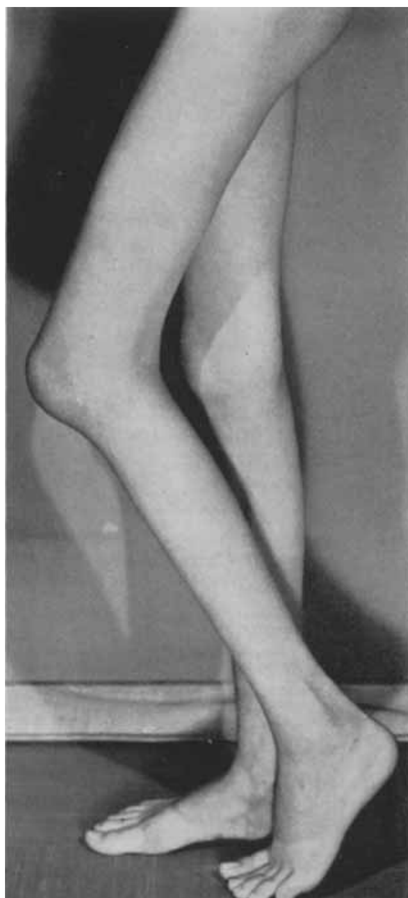
FIGURE 28 Case 6, S.W., fam. 28, Treatment and course.

of fraction I—0 and 600 ml of fresh plasma and on the fourth day 2 doses of fraction I—0. On each of the following 5 days he received one dose of fraction I—0 or 400 ml of fresh plasma. Two further half doses of fraction I—0 were given in the postoperative course. The AHF level was 30—60 % during and after the operation and between 30 and 148 % during the first four postoperative days and between 15 and 30 % during the following 5 days. The patient received all together 16 doses of fraction I—0, 2000 ml of fresh plasma and 2 blood transfusions.

Case 7. B. A., male, born 1948, severe haemophilia B (family 100). Ever since the age of 2 years he had had recurrent bleedings into the joints, usually the knees, less often the ankles and elbows. In the autumn of 1962 he had severe haemorrhage into the left knee joint with increasing reduction of the range of extension of the joint. He had to use a stick or crutches. In April 1964 he was referred to Malmö general hospital for treatment of the defective extension.

On admission. The left knee was increased in breadth and deformed. Ne exudate was demonstrable in the joint. The knee was flexed 90° and there was a subluxation backward of the tibia. Range of motion 90°—60°. The flexor tendons of the knee joint stood out like tense strings (Fig. 29 a). Roentgen examination revealed broadening of the femoral condyles, deformation of the patella and decalcification (Fig. 30). The right knee and the right elbow showed mild changes of the type seen in haemophilic arthropathy. Other joints examined were of normal appearance. The patient used crutches.

Treatment of the left knee joint. On April 23, 1964, treatment with traction was started with a weight of 3 kg. Traction was interrupted about an hour a day for leg exercises. After 2 weeks the extension defect had diminished from 90° to 50° with preservation of flexion. The weight was increased to 4 kg and treatment was continued for a further 4 weeks. The mobility of the leg was then 145°—70°. The



a. Left leg before treatment

b. Left leg after treatment

FIGURE 29 Case 7, B.A., fam. 100, 16 years old.

patient was then given an extension brace and cycling on an ergometer bicycle and walking exercises were started. After a further 4 weeks the patient was sent home. (Fig. 29 b.)

At re-examination on August 24, 1964, and April 22, 1965, extension had improved still more (Range of motion 155°—70°). He used a knee brace, but could walk short distances without it.

Plasma therapy (Fig. 31)

Before traction treatment was started the patient received 400 ml of stored plasma. The haemophilia B-factor level was less than 1 % of normal before treatment. From April 23 to June 30 he received all together 14 transfusions of stored plasma, *i.e.,* one or two transfusions a week. After transfusion of 400 ml of plasma the B-factor level increased from less than 1 % to 8—10 % of normal. During his stay in hospital he had no bleeding into the left knee joint or any other bleeding symptoms.

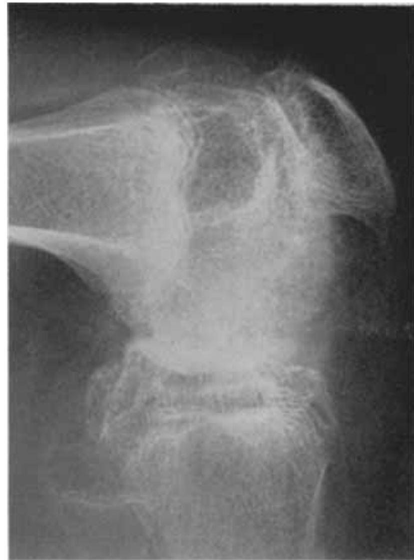


FIGURE 30 Case 7, B.A., fam. 100.
Left knee before treatment.

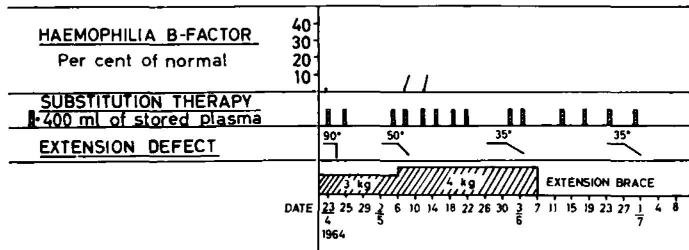


FIGURE 31 Case 7, B.A., fam. 100. Treatment and course.

Case 8. L. B., male, born 1948, severe haemophilia A (family 72). Since the age of 2 years he had had recurrent bleedings in most joints. For some years the mobility of the right knee, the elbows and ankles was reduced. He used a wheelchair because of the extension defect of the right knee for the last year. In July 1964 he was referred to Malmö general hospital for treatment of the right knee.

On admission extension of the right knee was found to be decreased by 50° (range of motion 130°—70°). The lower leg was rotated outwards. There was an equinus position of the right foot, which could not be deflected beyond 120°.

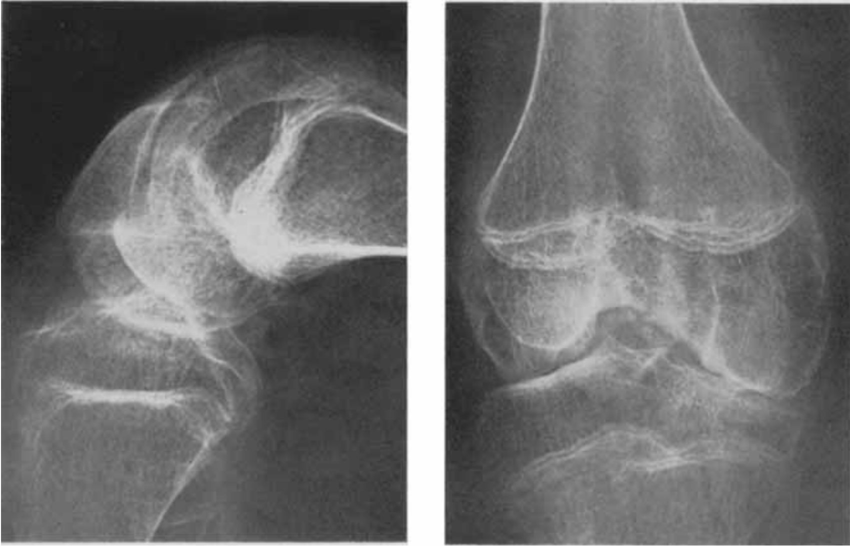


FIGURE 32 Case 8, L.B., fam. 72, 16 years old. Right knee before treatment.

Atrophy of the thigh and calf. Roentgen examination of the right knee (Fig. 32) and the right ankle showed changes of the type seen in haemophilic arthropathy. Extension of both elbows was slightly impaired.

Treatment of the right knee joint. Traction with 3 kg weight was started on July 20, 1964. After a week the range of extension had improved to 10°. Traction was replaced by an extension brace and active exercise (quadriceps gymnastics, exercise on an ergometer cycle) was started. Three weeks after the beginning of treatment the range of motion of the knee was 175°—60°. Despite attempted active and passive stretching the condition of the foot remained unchanged. The patient was now able to walk unaided. No bleeding complications occurred during treatment. When seen again on June 28, 1965, he was able to walk unaided. Range of motion of the knee was 175°—60°. The ankle could be deflected to 100°.

AHF dosage and plasma AHF levels (Fig. 33)

Before traction treatment was started the patient was given half a dose of fraction I—0, *i.e.* 100 ml. Before the infusion the patient had an AHF level of 0.1 % of normal. Immediately after administration of this dose the AHF level increased to 20 %. After 24 hours the AHF level was 10 % and after a week 4 %. In the further course he received 5 transfusions of fresh plasma (400—725 ml) at intervals of about one week. The AHF level was only determined before and after the first 2 plasma transfusions. The AHF level was 4 % and 5 %, respectively, before the infusions and 15 % immediately after. One week after the last plasma transfusion he received half a dose of fraction I—0. The AHF level then increased from 3 % to 13 % of normal. During the traction treatment this patient received all together 2 half doses of fraction I—0 and 5 plasma transfusions.

TRACTION OF RIGHT KNEE JOINT
L.B. (Fam. 72) 16 yrs (weight 44 kg)

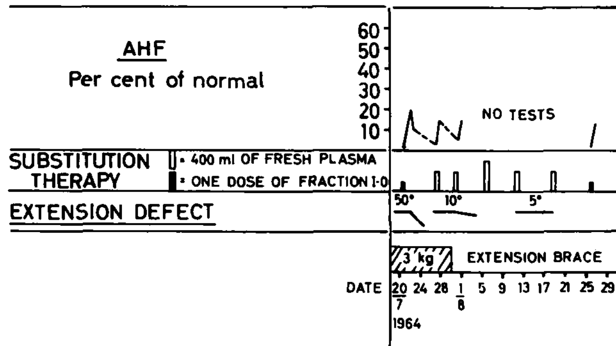


FIGURE 33 Case 8, L.B., fam. 72. Treatment and course.

Case 9. B. Å., male, born 1947, severe haemophilia B (family 183). Since the age of 5 years he had had recurrent haemorrhages into various joints, mostly into the knee and elbow joints. In 1961 he had been admitted to his local hospital because of heavy bleeding into the muscles of the left calf and simultaneous bleeding into the left knee joint. Since then the ankle had been stiff in almost full extension and extension of the left knee was slightly defective. In April 1964 he was admitted for treatment of this condition.

On admission. Extension of the left knee was reduced by about 20° (range of motion 160°—70°). Equinus deformity (140°) of the left foot (Fig. 34 a). With the knee bent the ankle could be flexed up to an angle of 115°. Severe atrophy of the thigh and calf. Roentgen examination showed moderate changes of haemophilia type in the knee and ankle.

Traction of the left knee joint

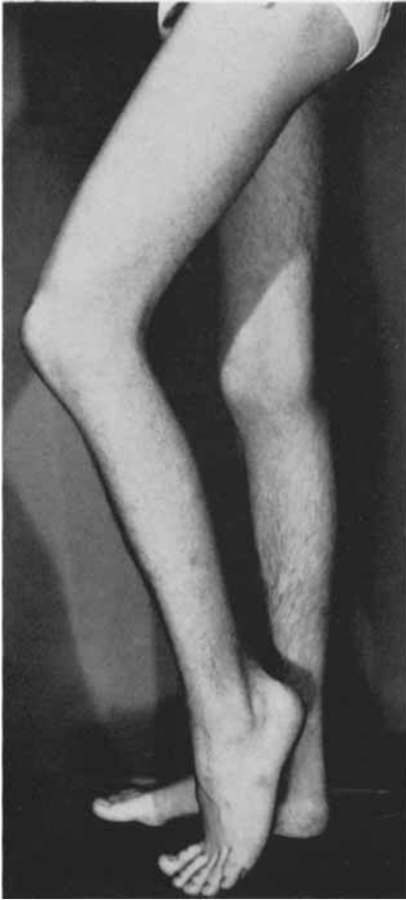
On April 23, 1964, traction was started with a weight of 4 kg. After 14 days' treatment extension was only slightly impaired. Range of flexion was good (175°—70°). The equinus deformity of the foot was unchanged. During the entire period of treatment the patient had received active physiotherapy (quadriceps exercise, cycling). No haemorrhages occurred during treatment.

Plasma therapy during treatment of knee with traction (Fig. 35 a)

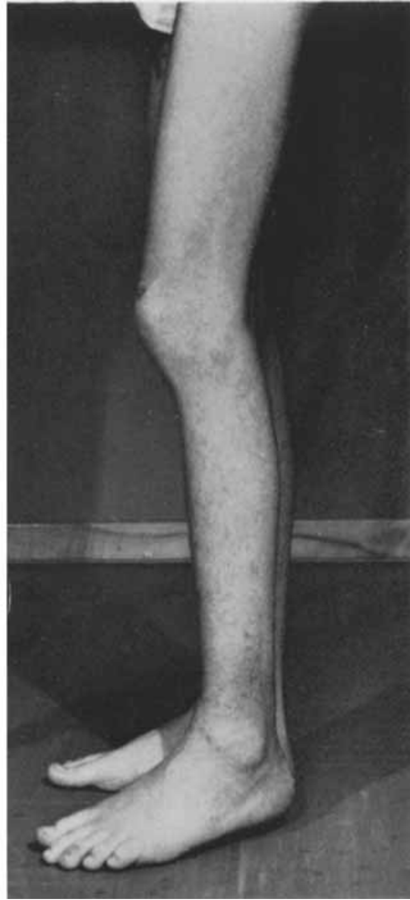
The haemophilia B-factor level was < 1 % of normal before treatment. During the time period April 23 and May 15 he received 6 transfusions of stored plasma. On each occasion 400 ml of plasma was given. After transfusion of this amount of plasma the B-factor level increased from < 1 % to about 10 % of normal.

Achillotenotomy

About 8 months after the end of traction treatment the patient was admitted for treatment of the contracture of the ankle. The mobility of the knee was then almost



a. Left leg before treatment



b. Left leg after treatment

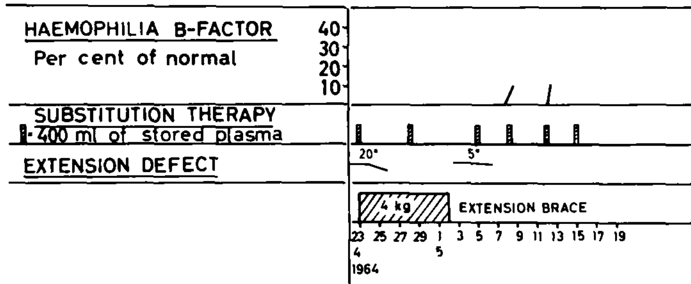
FIGURE 34 Case 9, B.Å., fam. 183, 17 years old.

normal (175°—30°). The condition of the ankle was the same as during previous treatment. On January 12, 1965, the patient was subjected to achillotenotomy and posterior capsulotomy. There was no abnormal loss of blood during the operation. The ankle could now be flexed to the 80° position. Pressure bandages were applied and the foot and lower leg were immobilised in plaster that was slit up in the front.

Fourteen days later the sutures were removed and the plaster exchanged. The wound had by then healed. No haemorrhage. After a further 14 days the plaster was removed and walking exercises were started (Fig. 34 b).

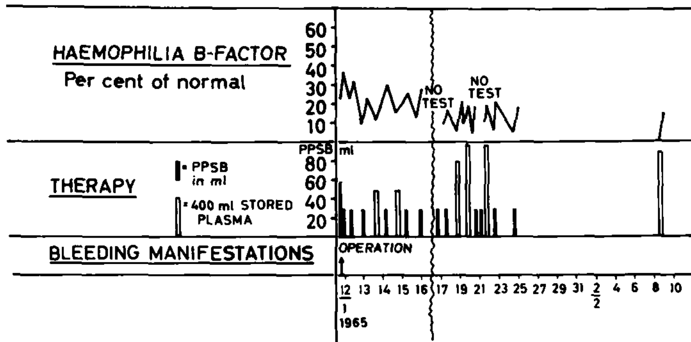
At after-examination in May 1965 the patient walked unaided. The ankle could be deflected to 80°.

TRACTION OF LEFT KNEE JOINT
B. Å. (Fam. 183) 17 yrs (weight 46 kg)



a. Traction of left knee joint

ACHILLOTENOTOMY
B.Å.(Fam. 183) 17 yrs (weight 50 kg)



b. Achillotenotomy

FIGURE 35 Case 9, B.Å., fam. 183. Treatment and course.

P. P. S. B. dosage and plasma haemophilia B-factor levels (Fig. 35 b)

The patient received 60 ml of fraction P. P. S. B. immediately before the operation, 30 ml during the operation and 30 ml 5 hours after the operation. The B factor level ranged between 24 and 37 % of normal. No haemorrhage occurred during the operation. On each of the 6 following days he received 30 ml of fraction P. P. S. B. and on the second and the third postoperative day also 500 ml of stored plasma. The B-factor level varied during these days between 10 and 30 % of normal. On the 7th and 8th postoperative days he received 800 and 1000 ml of stored plasma, respectively. The following day the patient complained of pain in the leg and as bleeding was suspected he was given 60 ml of fraction P. P. S. B. However, no signs of bleeding occurred. In the course of the following days he received a transfusion of 1000 ml of stored plasma on one occasion and of 30 ml of fraction P. P. S. B.

on two. During this latter course the B-factor level was maintained at 5—21 %. Two weeks later, when the plaster was removed, he received a transfusion of 900 ml of stored plasma. He had no bleedings in the postoperative course.

The patient received all together 420 ml of fraction P. P. S. B. and 4700 ml of stored plasma. No side reactions were seen.

Case 10. R. H., male, born 1952, severe haemophilia A (family 159). He had had recurrent bleeding into the ankle and knee joints. In 1962 he had a cycle accident with heavy bleeding into the left knee joint, which was also later the site of small recurrent haemorrhages. During the last year he had not been able to extend the knee. He used a stick when walking. In October 1964 he was admitted for treatment of the extension defect.

On admission. Capsular swelling and slight increase in the breadth of the left knee, but no exudate. Slight outward rotation and valgus position. Mobility 55° (145°—90°). Atrophy of the thigh and almost complete inability to innervate the extensors. Roentgen examination showed moderate haemophilic arthropathy.

Treatment of the left knee joint. On October 6, 1964, traction was started with a weight of 3 kg, which was increased to 4 kg after one week. Traction was interrupted every day for quadriceps exercise, ergometer cycling and walking exercises. Owing to the difficulty in innervating the extensors treatment included faradisation. After 3 weeks' treatment the range of motion was 75° (165°—80°). Traction was replaced by an extension brace and physiotherapy was continued. After a further 5 weeks' treatment the extension defect was 10° (range of motion 170°—80°). The patient could now innervate his extensors but he could not lift the leg when extended. He was also able to walk much better. Owing to the valgus deformity and the poor muscle function the patient was fitted with a jointless knee brace to be used when walking outdoors. Physical training was continued. In July 1965 the patient could walk without a stick or knee-brace. Range of motion as on discharge from hospital.

AHF dosage and plasma AHF levels (Fig. 36)

Before traction treatment was started the patient was given half a dose of fraction I—0, *i.e.* 100 ml. Before the infusion the patient had an AHF level of less than 1 % of normal. Immediately after administration of this dose the AHF level increased to 14 %. In the further course he received 5 transfusions of fresh plasma (400—625 ml) at intervals of about one week. After injection of the plasma transfusions the AHF level increased from 1 % to values between 12 and 19 %. At the end of the treatment he received half a dose of fraction I—0 because of bleeding in the left shoulder joint. During the traction treatment the patient received all together 2 half doses of fraction I—0 and 5 plasma transfusions. He had no bleeding into the left knee joint.

Case 11. B. W., male, born 1942, severe haemophilia A (family 62). He had had repeated bleeding of the nose, kidneys and joints. Severe symptoms of right leg because of varus deformity and extension defect of the knee. Pain and weakness of the right knee and ankle on exertion. He could only walk a few hundred metres at a time. Difficulties in stepping on to bus, train and the like. During the last few years the symptoms had progressed. Admitted for correction of the deformity.

On admission in March 1965 the right knee was deformed, there was an extension defect of 25° and varus of about 25° (Fig. 37 a). Range of motion 65° (155°—90°). Roentgen examination showed arthropathy of haemophilia type (Fig. 38).

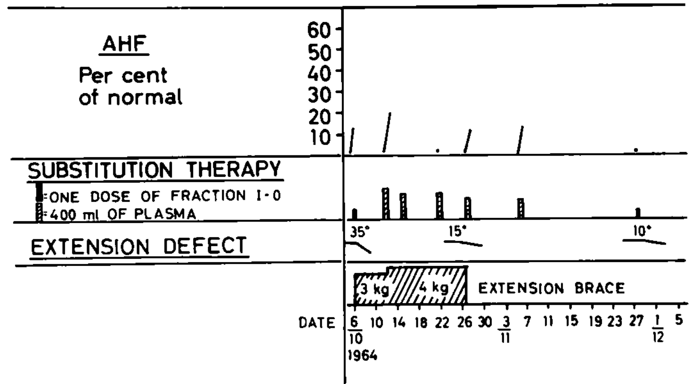
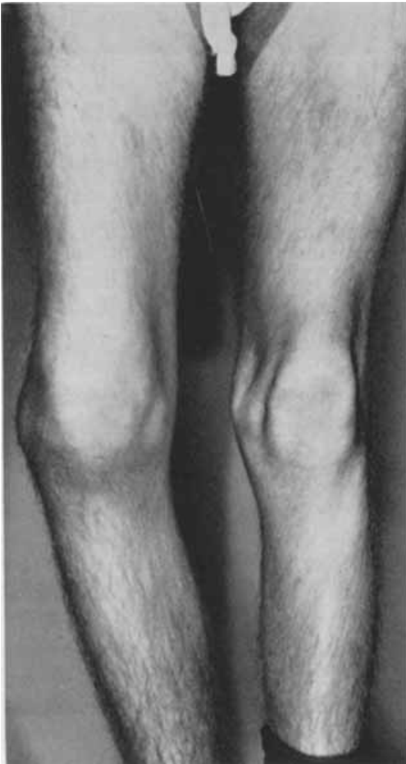
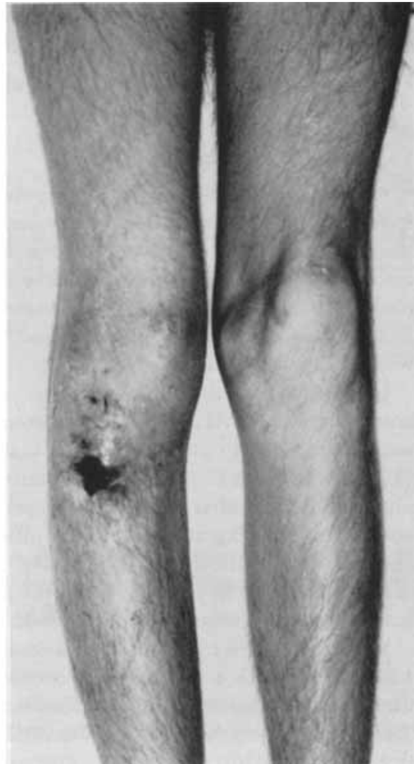


Figure 36 Case 10, R.H., fam. 159. Treatment and course.



a. Right leg before treatment



b. Right leg after treatment

Figure 37 Case 11, B.W., fam. 62, 23 years old.

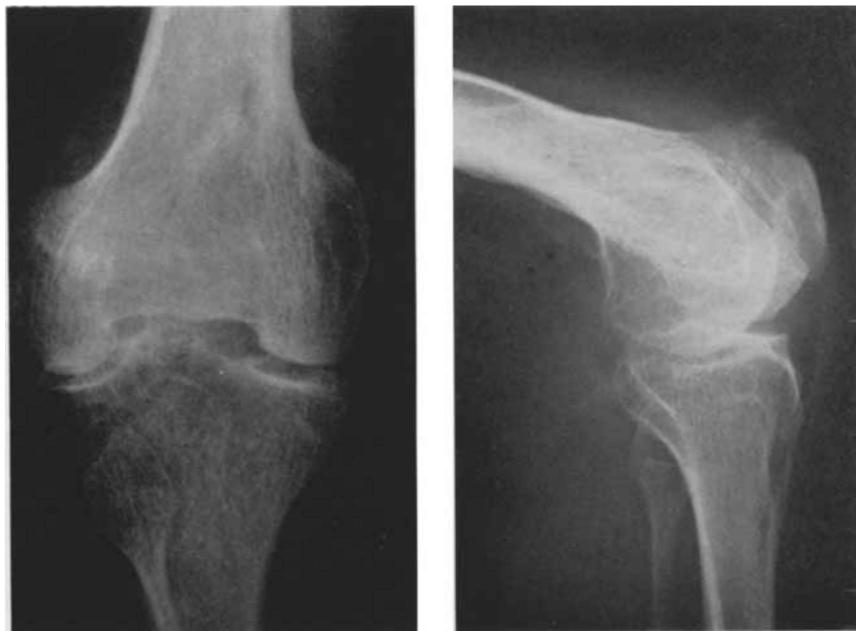


FIGURE 38 Case 11, B.W., fam. 62. Right knee before treatment.

Treatment of the right knee

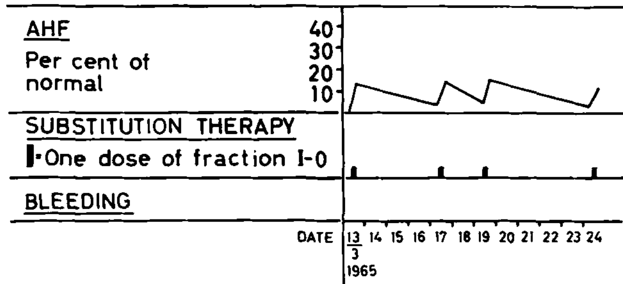
After a few weeks' *physiotherapy*, during which the extension defect diminshed from 25° to 10°, the patient was submitted to operation with wedge *osteotomy* of the right tibia and osteotomy of the fibula on March 30, 1965. Both the varus deformity and the extension defect were corrected. There was no undue loss of blood during the operation. The vessels were ligated with fine silk. No interior fixation was used. The joint was fixed in the corrected position in padded plaster, which was slit up anteriorly.

On the second day after the operation bleeding from the operative field was noted despite an AHF level of between 20 and 40 %. Since analysis of the bone wedge removed at operation showed high fibrinolytic activity, treatment with ε-ACA (Epsikapron® 5 g×5 orally) was started. The bleeding stopped within 24 hours. On the 5th day after operation pneumonia supervened with high grade fever and prostration. No explanation can be offered for this complication. The patient was treated with antibiotics and breathing exercises. The roentgenographic pulmonary changes disappeared rapidly. When the plaster was changed 4 weeks later the wound had healed. The sutures were removed.

When the plaster was again changed 8 weeks after the operation a haematoma (5 by 5 cm) with a small central necrosis was seen at the site of the operation, and there was still slight continuous bleeding. The haematoma had caused no symptoms. The patient was again treated with AHF and the bleeding stopped. The haematoma was soon absorbed.

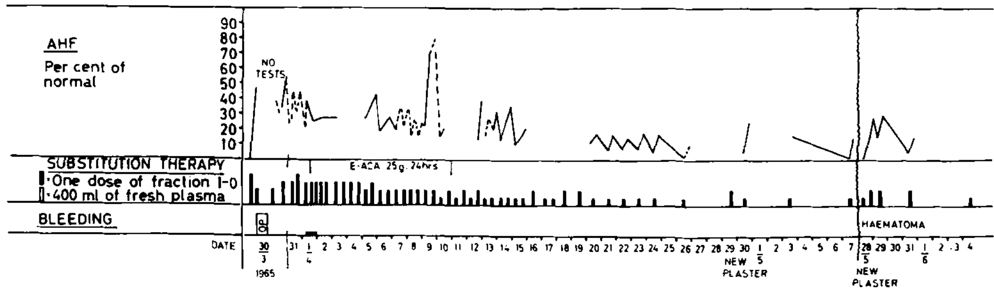
Three months after the operation the plaster was removed. The osteotomy then felt consolidated and the varus deformity was corrected. Walking and movement exercises were started (Fig. 37 b).

PHYSIOTHERAPY RIGHT KNEE JOINT
B.W. (Fam. 62) 22 yrs (weight 50 kg)



a. Physiotherapy

OSTEOTOMY OF RIGHT TIBIA
B.W. (Fam. 62) 22 yrs (weight 50 kg)



b. Osteotomy

FIGURE 39 Case 11, B.W., fam. 62. Treatment and course.

On Sept. 27, 1965, five months after operation, the patient could walk much longer distances than before the operation. No knee pain. Did not use a stick. Full range of extension, but flexion was still restricted (180°—135°).

AHF dosage and plasma AHF levels

Physiotherapy of right knee joint (Fig. 39 a). Before physiotherapy was started the patient was given half a dose of fraction I—0, *i.e.* 100 ml. Before the infusion the patient had an AHF level of < 1 % of normal. Immediately after administration of this dose the AHF level increased to 13 %. After 4 days the AHF level was 1 %, and he again received half a dose of fraction I—0. In the further course he received 2 half-doses of fraction I—0 at intervals of 2 days and 5 days, respectively. The AHF

level was 5 % and 8 %, respectively, before, and 15 % and 12 % immediately after these infusions. During the period of physiotherapy he thus received all together 4 half-doses of fraction I—0. He had no bleeding into the right knee joint or other bleeding symptoms.

Osteotomy of right tibia (Fig. 39 b). The patient received 3 doses of fraction I—0 immediately before the operation, one dose at the end of the operation and one and a half doses 6 hours after the operation. These doses were sufficient to keep his AHF level above 50 %. On the first postoperative day he was given one and a half doses in the morning and two doses in the evening. On each of the 4 following days he received one and a half doses in the morning and one and a half doses in the evening. During this period the AHF level was kept between 25 % and 45 %. Between the 6th and 10th postoperative days he received one dose in the morning and one or one and a half doses in the evening, which was sufficient to keep the AHF about 20 % or higher. Between the 11th and 20th postoperative days he received one to one and a half doses daily and the AHF was maintained at 10—35 %. During the following 3 weeks he received all together 5 and a half doses of AHF and the AHF level was kept between 4—20 %.

Owing to the fresh haematoma, which was discovered when the plaster was changed 8 weeks after operation, the patient was given 4 doses of AHF in the course of one week.

In connection with the operation the patient received 57 administrations (54 doses) of AHF.

DISCUSSION

Various methods with and without cover of transfusion of blood and/or plasma, have been tried in the *non-surgical treatment* of contractures in haemophiliacs. Thus in some cases of long-standing contracture of the knee joint Sköld 1944 successfully used gradual stretching with dressings in plaster under cover of blood transfusions. Jordan (1958) used a fairly complicated extension brace, and most of his patients were not given blood or plasma transfusions. According to him, the advantage of his brace is that the corrective forces are more effective than in traction, and the extension occurs about a more physiological axis so that posterior subluxation of the tibia should be prevented or corrected. Biggs and Macfarlane (1962) recommended gentle traction under cover of transfusion of fresh plasma, but they did not give any detailed case reports.

In the present material 9 patients with severe haemophilia, 7 of type A and 2 of type B, were treated with traction and an extension brace. They had an extension defect of 20 to 90° of the knee, and in all patients except one the contracture was more than half a year old. The defect was corrected or reduced to 10° in 8 of the 9 patients within 4 weeks. In the remaining case (case 7) the contracture, which was initially 90°, diminished to 35°.

Immediately before orthopaedic treatment was started all patients with haemophilia A, except one (case 5), were given 0.5—1 doses of AHF and afterwards 0.5—1 doses of AHF or 400—750 ml plasma about once a week throughout treatment. At the time of treatment of case 5 AHF was in short supply. AHF was therefore not given before orthopaedic treatment, and only half a dose some days after treatment had been started. Haemorrhage into the treated knee occurred in this case during physical exercises 3 weeks after the infusion. The AHF in the plasma at that time was below 1 % of normal. In the remaining cases, where substitution therapy was given throughout the orthopaedic treatment, the AHF was as a rule above 1 %. In other words, treatment had temporarily changed the haemophilia from a severe to a moderate form. In none of these cases did any haemorrhage into the knee joint occur during treatment.

The 2 patients with haemophilia B received about 400 ml of plasma a week during orthopaedic treatment. After every plasma transfusion the B-factor rose to a level of 10—15 %. In neither case was treatment complicated by haemorrhage.

Surgical treatment of contractures and deformities of bones and joints in haemophiliacs has been described in only a few cases. Pieper *et al.* (1959) gave a survey of the cases of major surgery published up to 1958. Their compilation included only 2 operations on the limbs: both amputations, including one with a fatal issue. Guilleminet (1964) reported a case of femoral osteotomy performed in 1950 under cover of plasma and blood infusions. The latter course was complicated by bleeding from the operative field, but the patient survived. DePalma (1956) reported 7 cases including 2 rotational osteotomies of the femur, one arthrodesis of the knee joint and one of the hip joint. None of the patients had severe haemophilia. Blood transfusions were given repeatedly in association with the operations. He stressed the risk of such operations and claimed that surgery is contraindicated in severe haemophilia. Substitution therapy with fresh blood and/or plasma — if it is to be effective in association with major operations in severe haemophilia — requires the infusion of volumes of fluid larger than what can be tolerated by the circulatory system. In such cases concentrated preparations must be used. Smaller doses of concentrated AHF in combination with large amounts of fresh blood and plasma have been used by Stefanini *et al.* (1959) in the correction of a deformity of the foot in a haemophiliac with AHF 2 %. The postoperative course was complicated by repeated bleedings in the region of the operation.

Bovine AHF alone or combined with fresh blood and plasma has been

used in various quarters in association with operations on the limbs (Egeberg *et al.* 1960, Biggs and Macfarlane 1962, deValderrama *et al.* 1965). Egeberg's case—exarticulation of the hip joint—was complicated by copious bleeding in the region of the operation. The coagulation-correcting effect in the other cases was good, but the antigenic properties of the animal preparations make their use unsuitable except in life-threatening situations. France and Wolf (1965) reported 3 operations for contractures of the lower limbs and one arthrodesis in 3 haemophiliacs, at least one of whom had severe haemophilia. The operations were performed under cover of plasma, bovine and human AHF. The haemostatic effect was good, but after 3 of the operations the patients developed symptoms of nephrosis with hyperproteinaemia and arterial hypertension owing to the infusion of such large volumes of plasma. Also respiratory distress occurred in these cases.

In recent years surgical operations have been carried out under cover of human preparations. The fraction prepared by the method of Blombäck and Blombäck has been used since 1956 not only in the aforementioned cases, but also in association with some 10 or more major operations (*e.g.* nephrectomy, cholecystectomy) on severe haemophiliacs. The course was largely uneventful in all of the cases. Other authors have since used fractions prepared in accordance with similar methods. Buchner and Sailer (1960) did 2 operations on knee joints, one with severe and one with moderate haemophilia, under cover of blood and antihaemophilic plasma. In the patient with severe haemophilia the postoperative course was complicated by repeated bleeding in the region of the operation.

Field *et al.* (1963) described 3 haemophiliacs in whom achillotenotomy was done under cover of human fibrinogen rich in AHF. In all 3 cases the patients had bleeding from the region of the operation or the nose and/or teeth. Albright *et al.* (1964) reported exarticulation of the hip of a haemophiliac under cover of fresh blood and plasma and human fibrinogen rich in factor VIII. Postoperatively the patient had numerous episodes of major bleeding. Because of the excessive volumes of fluid given he had 2 episodes of congestive heart failure, both of which required treatment. Lewis *et al.* (1965) used plasma fraction I in association with femoral amputation in a severe haemophiliac. Mild intermittent bleeding occurred from the 14th to 28th postoperative day.

Concentrated preparations of B-factor from human plasma have only recently become available (Soulier 1961). Biggs *et al.* (1961) reported exarticulation in the elbow of a boy with severe haemophilia B under cover

of such a preparation. The postoperative course was smooth. Biggs (1963) recommends that attempts should be made to achieve the same plasma level of B-factor as of AHF in haemophilia A.

Four patients in the present material were operated upon, 3 with severe haemophila A and 1 with severe haemophilia B.

As to the operative technique used in our cases, it might be mentioned that a plastic catheter for infusion was inserted percutaneously into a suitable vein before the operation. This makes repeated puncture unnecessary and sparse the veins. Surgical exposure of a vein should be avoided in haemophiliacs.

Tourniquet was not applied to the limb, bleeding being controlled as it occurred during the operation. Bleeding vessels were ligated with fine silk. Catgut and diathermy were not used.

The 3 patients (cases 3, 6 and 11) with severe haemophilia A have been subjected to 2 osteotomies and 1 arthrotomy with excision of osteophytes and partial synovectomy under cover of human fraction I—0. The AHF was maintained at a level of 20—90 % of normal during the operation and for the first postoperative week. The dose of fraction I—0 was then gradually reduced. On the 18th day after the operation, by which time the AHF had fallen to 2 %, a moderate haematoma developed in the region of the operation in case 3. The same complication occurred in case 11 eight weeks after operation, when the AHF level was below 1 %. The administration of fraction I—0 was increased and the further course was uncomplicated. In case 6 the postoperative course was smooth. In cases 3 and 11 the postoperative haemorrhages, though small, show the necessity of long careful observations and treatment with substitution therapy in association with bone surgery.

In case 11 the operative field began to bleed on the second day after the operation in spite of the fact that the AHF level was about 25 %. Since analysis of the piece of bone removed at operation showed high fibrinolytic activity as measured on fibrin plates it was thought that the bleeding might be due to local fibrinolysis. Treatment with ε-ACA was given. The bleeding ceased within 24 hours.

Astrup (1956, 1958) suggested that local liberation of tissue activators may be responsible for local haemorrhage. It is now known that the local fibrinolytic activity in the tissues can sustain bleeding at operations on the prostate and urinary bladder (Andersson and Nilsson 1961, Andersson 1962, McNicol *et al.* 1961, Andersson 1964, Nilsson *et al.* 1965). The findings of Nilsson *et al.* indicate that diffuse bleeding from an operative

wound may, at least in part, be due to the effect of local fibrinolytic activators. They found namely a favourable response to ε-ACA in 20 cases with diffuse bleeding from the operative field in connection with various surgical procedures. In these cases the fibrinolytic activity in the circulating blood was not increased. In this connection it should also be pointed out that Björkman and Nilsson (1961) have shown that red bone marrow has a high content of a labile fibrinolytic activator. Kwaan and Astrup (1964) have recently shown that granulation tissue is especially rich in fibrinolytic activator. In view of this the high fibrinolytic activity in the bone fragment of this patient and the cessation of bleeding following treatment with ε-ACA suggest that this complication may have been due to local fibrinolysis. Lord *et al.* (1960) have also reported fibrinolytic bleeding in association with an operation on the skeleton. We therefore think that it is advisable to extend the usual substitution therapy of haemophiliacs after skeletal operations to include ε-ACA.

In case 9, a patient with severe haemophilia B, the achilles tendon was elongated under cover of human B-factor concentrate. The plasma level was maintained at 24—37 % during the operation and at 10—30 % during the first week after the operation. The postoperative course was smooth and no side effects of the preparation were observed.

Conclusion

The few cases treated with traction and extension brace do not of course warrant any definite conclusions concerning the value of different forms of substitution therapy during non-operative orthopaedic treatment. They do, however, show that effective traction is possible without complicating haemorrhage into the joint undergoing treatment. The better the coagulation defect is controlled the smaller the risk of complications. It would appear that plasma transfusions are sufficient to suppress or prevent haemorrhages during traction treatment. In the one case in which bleeding into the joint occurred during orthopaedic treatment the patient had not received substitution therapy the last 3 weeks before the bleeding occurred, which strengthens the view that substitution therapy is desirable during this form of orthopaedic treatment. The orthopaedic treatment regularly produced considerable improvement of walking ability. Boys obliged to use a wheelchair or crutches could manage without them after the treatment. Treatment is facilitated if it is done at an early stage before contractures and muscular atrophy have become severe (see case 7).

In those cases where the contracture or deformity cannot be satisfactorily

corrected by conservative methods surgical treatment must be considered.

Previous experience has shown that substitution with blood and plasma is not sufficient for major operations on patients with severe haemophilia. The volumes of fluid necessary for haemostasis carries a great risk of complications in the form of heart failure, respiratory distress and nephrosis. Concentrated animal preparations produce good haemostasis, but they have antigenic properties and should therefore be used only in life-threatening situations. The only suitable substitution therapy is that using concentrated human preparations. Experience with such preparations in Sweden have shown that this preparation has good haemostatic properties and has no side effects.

The 4 operated cases in this material show that surgical correction of contractures and deformities in patients with severe haemophilia A or B can be performed without undue risk under cover of human fraction I—0 respectively B-factor preparations. The preparation must be given for a long time after the operation, probably longer after operations on the skeleton than on soft tissue. In one of the cases minor bleeding occurred in the region of the operation about 8 weeks after the intervention. ε-ACA may also help to reduce the risk of postoperative bleeding. The operations should only be done in intimate cooperation with a coagulation laboratory, where the AHF respectively B-factor levels can be measured at short intervals. In view of the risk of complications such operations should only be done on strictly orthopaedic grounds. In the 4 patients operated upon the severely impaired walking ability was considerably improved after the operations.

VI. Prophylaxis of Musculo-skeletal Manifestations in Haemophilia

INTRODUCTION

Joint haemorrhages and subcutaneous haemorrhages are the commonest symptoms of haemophilia (Sköld 1944, Ramgren 1962 a, and others). Sköld found joint haemorrhages in 90.3 % of his cases, and Ramgren in 87 of 90 patients with severe haemophilia, in 27 of 32 with moderate haemophilia and in 10 of 20 with mild haemophilia. Haemarthroses also occur in v. Willebrand's disease (Nilsson *et al.* 1957, Nilsson *et al.* 1959, Nilsson and Blombäck 1962) in which there is AHF deficiency as in haemophilia A. In 4 patients with v. Willebrand's disease the author has seen changes of the same type as those seen in haemophilia. On the other hand, almost no joint bleedings have been reported in certain other severe coagulopathies and bleeding disorders, such as factor V deficieny, factor VII deficiency, circulating anticoagulants, afibrinogenaemia and thrombasthenia (Biggs and Macfarlane 1962).

The cause of joint haemorrhages and the source of such bleedings in haemophiliacs are still obscure. Astrup and Sjölin (1958) showed that tissue thromboplastin activity in synovial and fibrous capsular tissue is low in normal individuals and the local haemostasis must therefore be effected by the plasma thromboplastin activity. As this activity is decreased or absent in haemophilia the local haemostasis is insufficient with the result that in the event of injury of these tissues, the lesion continues to bleed.

Rodnan *et al.* (1957) and others claim that subchondral and intraosseous haemorrhage accompanies haemarthrosis. Such bleeding may explain the dysgenesis of the epiphyses seen in haemophilic arthropathy (Caffey and Schlesinger, 1940, and others). During the period of growth the epiphyses are richly vascularised. This vascularity decreases considerably after the end of this period. This might help to explain the observation made by DePalma and Cotler (1956) and others in haemophiliacs, namely that haemarthrosis is more common during childhood and puberty than later.

Haemarthrosis often leads to permanent joint changes. Attempts should be made to counteract the joint lesions by the use of a general regimen during and between bleeding episodes and by correction of the coagulation defect.

The following principles in the *general prophylactic treatment* have been used in our patients.

We prescribe rest for all bleeding joints until the local symptoms of bleeding, *i.e.*, swelling and pain, have begun to subside. This usually requires only a few days. If the symptoms persist longer or are very severe, substitution therapy is given. Active exercise of the unloaded joint is then started. In patients with bleeding into the knee it is important to train the quadriceps function. When the muscles are strong enough, weight bearing is allowed.

Joint puncture is performed only if the pain is severe or if pressure necrosis is imminent. Puncture is otherwise avoided because of the risk of subsequent bleeding and, secondly, by the fact that puncture often gives only a meagre yield because the blood in the joint has coagulated, or the haemorrhage is mainly periarticular. When puncture is decided upon, the patient is always given substitution therapy.

After the acute stage of a joint haemorrhage the patient is instructed to exercise the joint until it has, if possible, recovered the same degree of function as it had before the haemorrhage. In some cases this exercise is performed under the supervision of a physiotherapeutist. During remissions the patient should do appropriate gymnastics. We recommend swimming, *i.e.*, all-round training with only a minimum risk of traumatic haemorrhage.

Prophylactic treatment with AHF. In Sweden 15 patients, aged 2—20 years, with severe haemophilia A have been treated prophylactically with AHF. (Nilsson *et al.* 1962, Nilsson 1965). These patients have been treated for 1—7 years. The purpose of the prophylaxis was to reduce the frequency and severity of bleeding from various organs including the joints. Treatment has been given according to two principles.

One series of patients consisting of 8 boys, aged 3 to 20 years, have been given half a dose of AHF (100 ml) every 2nd to 4th week for 1—7 years (Table 24). It is, of course, not possible to assess the value of prophylactic treatment of severe haemophilia A from these cases. However, during the prophylactic period the patients have been in a good general condition. They have had bleeding episodes, but these have been less severe and less frequent than formerly, as shown by the annual number of days in hospital beeing lower (Nilsson *et al.* 1962). After administration of half a dose of fraction I—0 the AHF rose to levels between 15 % and 40 %. The AHF content then fell fairly rapidly, but the last few per cent only very slowly, so that during the course of the major part of the month the AHF level was 1—3 % instead of about 0.1 %, *i.e.*, the level before prophylactic treat-

Table 24 Prophylactic treatment, series A. Treatment with 100 ml fraction I—0 every 2nd—4th week

Family	Case	Year of birth	Year when treatment started	No. of adm. (June 1965)
10	R.A.	1953	1961	59
37	C.S.	1951	1962	48
37	L.C.S.	1958	1961	40
62	B.W.	1942	1960	74
70	S.M.	1950	1964	17
72	B.B.	1946	1960	70
72	L.B.	1948	1958	75
140	T.B.	1956	1960	83

Table 25 Prophylactic treatment, series B. Treatment with fraction I—0 on incipient symptoms of joint bleeding

Family	Case	Year of birth	Year when treatment started	No. of adm. (June 1965)	No. of doses
4	C.H.-N.	1957	1963	18	9
32	U.T.	1957	1959	39	21.5
75	L.T.	1952	1959	36	18.5
76	L.S.	1942	1960	38	22
105	U.B.	1956	1961	57	28.5
108	P.V.	1945	1958	116	65.5
181	H.W.	1958	1961	12	6.5

ment was started. According to Nilsson *et al.* (1962), haemophilia appeared to change from severe to moderate form.

The other series of patients consisting of 7 boys, aged 2—18 years (Table 25), have not received AHF regularly but immediately on appearance of incipient symptoms of joint bleeding. The purpose of this series was to find out whether such prophylaxis could prevent the development of disabiling joint defects. These boys who lived in the neighbourhood of Malmö and Gothenburg (1 patient) had been instructed to contact the hospital as soon as they noticed any signs of joint bleeding. They usually received 0.5—1 dose of AHF on each occasion. The affected joint was immobilised immediately, but 2 or 3 days later physiotherapy was started. The patients have so far received from 12 to 116 administrations of AHF in the course

of 2 to 6 years. Three of these boys (L. T., U. B., H. W.) have not developed disabling joint deformities. Four of the remaining boys had joint changes already before treatment but no further defects have appeared. The number of cases and the duration of treatment are, however, not sufficient to expect any demonstrable difference between treated and untreated age-matched patients.

PRESENT STUDY

On the basis of the data presented in Chapters III and IV principles of prophylactic treatment with AHF were devised.

Dosage

It has been shown (Fig. 17) that the joint score rapidly decreases with rising plasma levels of AHF or B-factor. At plasma levels above 3 % chronic arthropathy is rare and even when it does occur, it is only mild. This also holds for the degree of disability (p. 44). These findings suggest that chronic arthropathy could be prevented if the plasma concentration of pertinent coagulation factors could be kept above a critical level. From a practical point of view it seems that a level of about 3 % of normal would be enough in most cases.

Two boys with severe haemophilia A received half a dose (100 ml) AHF at about 2 weeks interval. The AHF level in the plasma, which was checked before each infusion, varied between 0.5 and 4 % (Figs. 40 and 41). Maintenance of the value above the desirable 3 % level thus seems to require infusions at shorter intervals or a larger dose. But even with the dose given the AHF level was above 3 % during a major part of the time between consecutive infusions.

Age-range for Prophylaxis

Chronic joint changes were not common in the 0—9 year age class (p. 22). In 6 patients with severe haemophilia and below 5 years of age only one patient showed joint changes (L. C. S., fam. 37). After this age the frequency and degree of joint lesions increased successively with age. In severe haemophilia joints were rarely involved for the first time after the age of 20 (Fig. 19 a). This may be due to the fact that the usually engaged joints (knee, ankle, elbow) then were affected. Another reason may be that joint bleedings are less common in adult patients than in young children and

PROPHYLACTIC TREATMENT

H. W. (Fam. 181) 7 yrs (weight 27 kg)

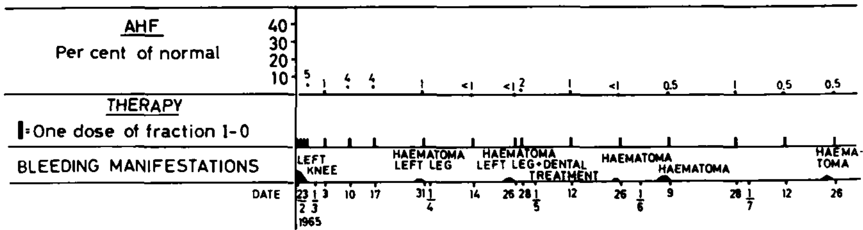


FIGURE 40 Prophylactic AHF-treatment, H.W., fam. 181.

PROPHYLACTIC TREATMENT

L.T. (Fam. 75) 13 yrs (weight 31 kg)

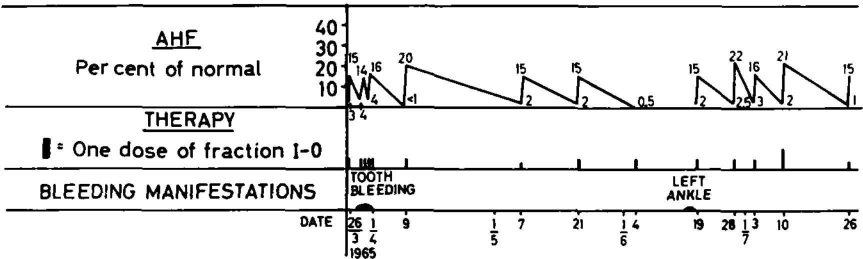


FIGURE 41 Prophylactic AHF-treatment, L.T., fam. 75.

adolescents (DePalma 1956, Eyring *et al.* 1965). Lesions in already affected joints tended to progress. This may be due to progressive arthrosis deformans on the basis of joint lesions, that occurred already before this age and that were largely due to dysgenesis of the epiphyses. In severe haemophilia the degree of disability did not increase with certainty after the age of 15—20 years in this material (Fig. 23). It would therefore appear sufficient to begin prophylaxis with AHF at the age of about 5 and to continue it until the end of the period of growth, *i.e.*, 15—20 years.

Practicability of Prophylaxis with AHF and B-factor

In Sweden there are at present about 50 persons aged 5—20 years, with severe haemophilia A. Prophylaxis according to the principles set forth above would require about 1000 doses of AHF a year. Such treatment would presumably reduce the number of doses otherwise necessary in the treatment of bleeding episodes and the correction and surgical treatment of joint deformities as well as the need for hospital care. It would therefore appear warranted to give such prophylaxis as far as circumstances allow.

The same principles hold also for haemophilia B. It may be possible to use a smaller dose because the half-time of B-factor is longer than that of AHF. According to Biggs (1963), the half-time of AHF is 14 hours; that of B-factor, 16—30 hours.

VII. Summary

MATERIAL AND METHODS

The clinical material consisted of 242 of the 308 known haemophiliacs (A and B) in Sweden. The investigation included *clinical examination* of all major joints in 95 of 116 patients with severe haemophilia, in 38 of 65 patients with moderate haemophilia, and in 24 of 127 patients with mild haemophilia, and roentgen examination of practically all joints found to be abnormal at the clinical examination. In addition information about 7 patients with severe haemophilia, 21 with moderate haemophilia, and 57 with mild haemophilia was obtained by *questionnaire* only.

The degree of arthropathy (Grades 2, 3 and 4) was classified largely according to DePalma and Cotler (1956). Evaluation of general disability was made with regard to ability to manage (walk, dress, eat, toilet) without help. This latter evaluation comprised also extra-articular manifestations of haemophilia.

INCIDENCE OF MUSCULO-SKELETAL MANIFESTATIONS IN HAEMOPHILIA

No difference was found between haemophilia A and haemophilia B regarding incidence, type and degree of associated arthropathy. The incidence and degree of arthropathy increased with the severity of haemophilia. In patients with a plasma concentration of AHF or B-factor above 3 % of normal arthropathy was rare. Arthropathy involving the knee, elbow and ankle joints was common; the hips, shoulders, and wrists were less often affected, and the hands and feet were rarely involved. Knee joint affection occurred in 4 out of every 5 patients with severe haemophilia, in every other one with moderate haemophilia, and only occasionally in patients with mild haemophilia. Both in moderate and severe haemophilia knee affection, when present, was often of Grade 3 or 4, and it was bilateral in two-thirds of those with severe and one-third of those with moderate haemophilia. Six joints were found to have bony ankylosis. Joint changes

were rare in patients below 5 years. Above this age they became increasingly common, and then quicker in severe than in moderate haemophilia.

Extra-articular involvement of the musculo-skeletal system was less common than arthropathy. Four neurogenic and 8 myogenic lesions were found to cause deformity, and 6 cases of haemophilic pseudo-tumour were demonstrated.

DISABILITY DUE TO MUSCULO-SKELETAL MANIFESTATIONS IN HAEMOPHILIA

Disability due to musculo-skeletal deformities was common in severe haemophilia and sometimes occurred in moderate haemophilia. Half of the patients with severe haemophilia and one-fourth of those with moderate haemophilia had difficulties in walking, but only 1 individual in the entire material was permanently confined to bed. The degree of disability increased markedly with age up to 20 years.

CORRECTION OF MUSCULO-SKELETAL DEFORMITIES IN HAEMOPHILIA

In 9 patients with severe haemophilia A or B knee joint flexion deformity was corrected under cover of AHF (human fraction I—0) or plasma. The methods employed were continuous traction for 2—3 weeks, extension braces and intense physiotherapy. The importance of adequate correction of the coagulation defect during treatment was discussed. An improvement of walking capacity was noted in all of the cases. Six patients who had formerly used crutches or a wheel chair no longer required such aids. After the end of treatment several of the boys could cycle or go skiing.

In 3 cases of severe haemophilia A and 1 case of severe haemophilia B were orthopaedic operations done under cover of human fraction I—0 or human B-factor concentrate; one supracondylar wedge osteotomy to correct valgus deformity of the knee, one tibia-osteotomy to correct varus deformity, one arthrotomy of the knee with removal of osteophytes and partial synovectomy, and one correction of equinus deformity of the foot with lengthening of the Achilles tendon and posterior capsulotomy. The post-operative course was favourable in all. The operations have considerably improved walking in all of the patients. The necessity of keeping the AHF or B-factor plasma levels sufficiently high during the postoperative period was stressed.

PROPHYLAXIS OF MUSCULO-SKELETAL MANIFESTATIONS IN HAEMOPHILIA

Chronic arthropathy hardly ever occurred at plasma levels of AHF or B-factor higher than 3 % of normal. Experience with AHF indicates that administration once every other week in severe haemophilia will maintain plasma levels at about 3 % of normal during most of the period. It would thus seem possible largely to prevent the occurrence of disability in haemophilia. Prophylactic treatment should be started when the child is about 5 years old and should be continued throughout adolescence.

VIII. Acknowledgements

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IX. Coded Data

SYMBOLS

Se = severe
Mo = moderate
Mi = mild

Arthropathy

0 = No arthropathy, clinically and roentgenologically examined
2 = Grade 2, „ „ „ „
3 = „ 3, „ „ „ „
4 = „ 4, „ „ „ „

0 = No arthropathy, clinically examined
2 = Grade 2, „ „
3 = „ 3, „ „
4 = „ 4, „ „

Extra-articular lesions

a = neurogenic lesions
b = myogenic „
c = pseudotumor

Degree of disability

0 = none
1 = mild
2 = marked
3 = severe

Treatment

a = nonsurgical correction
b = surgical „
c = prophylaxis

Fam. No	Case	Year of birth	Type of haemoph.	AHF- or B-factor % of normal	Hip R	Hip L	Knee R	Knee L	Ankle R	Ankle L	Foot R	Foot L	Shoulder R	Shoulder L	Elbow R	Elbow L	Wrist R	Wrist L	Hand R	Hand L	Extra-art. lesions	Degree of dis-ability	Treat-ment
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
4	C.H.N.	1957	A Se	< 1	0	0	0	0	0	3	0	0	0	0	0	3	0	0	0	0		1	c
4	H.N.	1962	A Se																				
6	R.L.	1903	A Mi	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
6	H.A.	1899	A Mi	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
8	K.E.C.	1909	B Se	< 1	3	0	4	4	3	3	0	0	0	3	3	4	0		0		a	3	
9	E.F.	1911	A Mo		0	0	4	4	0	3	0	0	0	0	3	3	0	0	0	0		2	
9	S.M.	1943	A Mo	1—2	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0		1	
10	Y.A.	1935	A Se	< 1	0	0	4	4	4	4	0	0	3	3	3	3	2	2	0	0		2	
10	R.A.	1953	A Se	< 1	0	0	0	3	3	0	0	0	0	0	2	3	0	0	0	0		2	c
11	B.L.	1937	A Se	< 1	0	0	4	4	2	0	0	0	0	0	0	0	0	0	0	0		2	
11	K.L.	1944	A Se	< 1	0	0	2	3	4	2	0	0	0	0	3	0	0	0	0	0		3	
12	T.B.	1934	A Se	0	0	0	3	3	2	2	0	0	0	0	3	3	0	0	0	0		3	
13	L.E.H.	1919	A Mi																				
13	N.O.H.	1924	A Mi	8																			
13	T.L.	1910	A Mi																			0	
13	K.E.T.	1923	A Mi	7																		0	
13	G.J.	1931	A Mi	10																			
13	B.F.	1944	A Mi																				
14	B.G.	1922	B Mo	1.8	0	0	4	4	3	2	0	0	0	0	4	4	0	0	0	0	b, c	3	
14	S.G.	1928	B Mo	2	0	0	3	3	0	0	0	0	0	0	3	3	0	0	0	0	c	2	
14	K.D.	1962	B Mo	3																			
18	G.B.	1912	A Se	< 1																			
18	N.G.W.	1930	A Se	< 1	4	0	4	4	4	2	0	0	3	3	3	4	0	0	0	0		3	
22	B.E.	1948	A Se		0	0	3	4	0	0	0	0	0	0	3	0	0	0	0	0		3	
22	R.K.	1940	A Se	0.5	0	0	3	2	2	2	0	0	0	0	2	4	0	0	0	0		2	
22	E.K.	1951	A Se	0.5	0	0	3	2	0	0	0	0	0	0	0	0	0	0	0	0		1	
27	A.P.	1907	A Mo	2	0	0	2	2	3	3	0	0	0	0	0	3	0	3	0	0		1	
27	M.H.	1921	A Mo	2	0	0	3	3	2	2	0	0	0	0	3	2	0	0	0	0		2	

27	G.H.	1923	A Mo	1	0 0	3 3	3 2	0 0	0 0	3 3	0 0	0 0		2	
27	G.A.	1919	A Mo	1	0 0	4 4	3 3	0 0	4 4	4 4	2 3	0 0		3	
27	O.P.	1941	A Mo	1.8	0 0	3 2	0 3	0 0	0 0	2 0	4 0	0 0		1	
27	A.A.	1941	A Mo	1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
27	L.J.	1946	A Mo	1	0 0	2 0	0 0	0 0	0 0	0 2	0 0	0 0		0	
27	B.J.	1947	A Mo	1	0 0	0 0	0 0	0 0	0 0	0 3	0 0	0 0		1	
27	B.K.	1952	A Mo	1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
28	G.S.	1920	A Se												
28	S.W.	1936	A Se	< 1	0 0	3 3	2 3	0 0	2 0	3 2	0 0	0 0		2	b
31	K.O.K.	1913	B Se	0.9	0 0	4 4	3 3	0 0	0 0	3 3	0 0	0 0		2	
31	K.P.	1932	B Se	0.3	3 0	4 0	0 3	0 0	0 0	4 4	0 0	0 0		2	
31	L.G.P.	1954	B Se	< 1	0 0	0 3	0 0	0 0	0 0	0 0	0 0	0 0		3	
31	N.S.N.	1961	B Se	0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
32	U.T.	1957	A Se	0.1	0 0	0 0	2 0	0 0	0 0	0 0	0 0	0 0		0	c
32	T.S.	1953	A Se	0.1	0 0	0 3	0 0	0 0	0 0	2 0	0 0	0 0		1	
34	O.L.	1938	A Se	< 1	0 0	4 2	4 0	0 0	0 0	2 4	0 0	0 0	b, c	2	
35	R.L.	1917	A Se	< 0.5	0 0	3 3	0 0	0 0	3 0	4 4	0 0	0 0		2	
35	H.L.	1926	A Se	< 0.5	0 0	2 3	0 2	0 0	4 0	3 3	0 0	0 0		1	
36	L.L.	1929	A Se	< 0.1	0 0	4 4	3 3	0 0	3 0	3 3	3 3	0 0		2	
37	C.S.	1951	A Se	0.5	0 0	3 2	0 0	0 0	0 0	0 0	0 0	0 0		2	c
37	L.C.S	1958	A Se	< 1	0 0	3 0	2 0	0 0	0 0	0 0	0 0	0 0		1	c
40	S.H.	1952	A Se	0.6	0 0	0 2	0 0	0 0	0 0	2 0	0 0	0 0		0	
41	K.R.O.	1904	B Mi	6											
41	K.G.O.	1916	B Mi	10											
41	K.L.	1925	B Mi												
42	B.R.	1924	A Se	0.1	3 0	3 3	4 3	0 0	0 0	3 4	0 3	0 0	b	2	
43	S.P.	1901	A Mo	3.3										0	
43	B.P.	1904	A Mo	6										0	
43	O.P.	1906	A Mo	2.6										0	
44	J.Ö.	1955	B Se	0.1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
45	G.S.	1898	A Mo												
46	B.S.	1921	A Se	0.1	0 0	4 2	4 3	3 4	0 2	3 3	3 2	0 0	b	2	
48	L.W.	1926	A Se	0	0 0	3 3	2 2	0 0	4 4	4 4	0 3	0 0		2	
49	S.Ö.	1921	B Mo	1—2	0 0	0 0	3 0	0 0	0 0	2 3	0 0	0 0		0	
54	E.K.	1919	A Mi	9											

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
54	R.N.	1923	A Mi																			0	
54	K.E.K.	1937	A Mi	5																			
54	L.G.N.	1949	A Mi	9																			
56	A.J.	1925	B Se	< 1	0	3	4	3	3	3	0	0	0	3	3	3	0	0	0	0		2	
56	G.J.	1931	B Se	< 1	0	0	3	3	2	3	0	0	0	0	3	3	0	0	0	0		1	
57	J.S.	1906	A Se	< 1	0	0	4	4	3	3	0	0	3	3	3	3	0	0	0	0		2	
57	H.B.	1947	A Se																			0	
58	U.H.	1932	A Mo	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
59	R.B.	1954	B Se	< 1	0	0	3	0	0	2	0	0	3	0	0	0	0	0	0	0		2	
60	E.R.	1892	B Se	< 1	0	0	4	4	4	4	0	0	4	3	4	4	3	3	3	3		2	
61	P.O.C.	1941	B Se	< 0.5	0	0	3	2	2	3	0	0	0	0	3	3	0	0	0	0		1	
61	S.L.	1940	B Se	< 0.5	0	0	3	0	3	3	0	0	0	4	3	3	0	0	0	0		3	
61	G.E.	1944	B Se	< 0.5	0	0	3	3	0	0	0	0	0	0	3	3	0	4	0	0	b	2	
62	B.W.	1942	A Se	0.3	0	0	3	2	2	2	0	0	0	0	3	3	0	0	0	2		2	b, c
64	J.E.F.	1951	B Mi	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
64	P.F.	1953	B Mi	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
64	N.F.	1953	B Mi	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
65	B.J.	1948	A Mi	9—14																		0	
67	J.A.J.	1947	A Se	< 1																		2	
68	G.F.	1930	A Se	< 1	0	0	4	3	0		0	0	0	0	4	3	0	0	0	0	a	2	
68	O.F.	1936	A Se	< 1	2	0	3	3	0	0	0	0	0	0	4	4	0	0	0	0		2	
69	E.G.	1910	B Mi	8																		0	
70	S.M.	1950	A Se	< 1	0	0	3	3	0	0	0	0	0	0	0	0	0	0	0	0		2	c
71	J.A.	1884	B Mi	8—10																		0	
71	B.A.	1941	B Mi	9																		0	
72	B.B.	1946	A Se	0.1	0	0	4	4	4	4	0	0	0	0	3	2	0	0	0	0		3	c
72	L.B.	1948	A Se	0.1	0	0	3	0	3	3	0	0	0	0	3	3	0	0	0	0	b	3	a, c
73	A.J.	1945	A Se	< 1	0	4	0	0	0	0	0	0	0	0	2	3	0	0	0	0		1	
74	L.R.C.	1951	A Se	< 1	0	0	2	3	0	0	0	0	0	0	0	0	0	0	0	0		3	a
75	L.T.	1952	A Se	< 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	c
76	L.S.	1942	A Se	< 1	0	0	3	3	0	0	0	0	0	0	3	3	0	0	0	0		1	c
77	T.S.	1949	A Se	< 1	0	0	3	2	0	0	0	0	0	0	4	0	0	0	0	0		2	

77	S.S.	1955	A Se	< 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
78	B.E.	1955	A Se	< 1										3	
79	A.M.	1922	A Mi												
79	S.J.	1933	A Mi												
79	B.J.	1938	A Mi												
80	L.N.	1936	A Se	< 1	0 0	3 3	0 0	0 0	0 0	2 0	0 0	0 0		1	
80	R.P.	1958	A Se	< 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
81	U.J.	1951	A Mo	2	0 4	0 0	0 0	0 0	0 0	0 0	0 0	0 0		1	
82	E.W.	1933	A Se	< 1										1	
82	R.H.	1950	A Se	< 1										2	
83	P.O.	1946	A Se	< 1	0 0	4 4	3 2	0 0	2 0	3 3	0 0	0 0	c	2	
84	R.H.	1938	A Se	< 1	0 0	3 3	3 3	0 0	2 0	3 3	0 0	0 0		2	
85	B.C.	1948	A Se	< 1	0 0	3 2	0 0	0 0	0 0	2 3	0 0	0 3		2	
86	G.S.	1945	A Se	< 1	0 0	3 2	0 0	0 0	0 0	2 0	0 0	0 0		1	
87	R.F.	1949	A Mo	1.1	0 0	2 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
89	K.A.	1943	A Se	0	0 0	0 3	0 0	0 0	0 0	2 2	0 0	0 0		1	
90	P.B.	1956	A Se	< 1	0 0	0 2	0 2	0 0	0 0	0 3	0 0	0 0		1	
91	M.G.	1960	A Se												
92	B.F.	1942	A Se												
93	G.R.	1938	A Mi	11										0	
93	I.G.	1935	A Mi	8										0	
94	A.K.	1895	A Mi	12										0	
94	K.K.	1904	A Mi	10										0	
95	B.M.	1946	A Se	< 1	0 0	4 2	0 0	0 0	0 0	3 3	0 0	0 0		3	a, b
95	I.M.	1954	A Se	< 1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
96	R.A.	1943	A Mi	15	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
97	R.F.	1926	A Mo	2	0 0	3 3	0 0	0 0	0 0	3 0	0 0	0 0		1	
99	G.G.	1947	B Se	0.1	0 0	3 2	3 3	0 0	0 0	3 3	0 0	0 0		1	
100	B.W.	1914	B Se	< 1	0 0	3 4	3 3	0 0	0 4	4 4	0 0	0 0		2	
100	B.A.	1948	B Se	< 1	0 0	2 4	0 0	0 0	0 0	2 0	0 0	0 0		3	a
101	K.G.J.	1944	B Mo	2										0	
102	H.I.H.	1946	A Mi	7—8										0	
103	L.G.J.	1947	A Se	< 1	0 4	4 4	2 2	0 0	0 0	4 4	0 0	0 0		3	
104	N.V.	1926	A Mi	16	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
104	J.V.	1937	A Mi	5										0	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
105	U.B.	1956	A Se	< 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	c
106	S.O.J.	1955	A Se	< 1	0	0	0	2	0	0	0	0	0	0	0	3	0	0	0	0		1	a
107	S.O.	1925	A Mi	11																		0	
108	P.V.	1945	A Se	0.1	0	0	2	2	0	0	0	0	0	0	3	3	0	0	0	0		1	c
109	U.P.	1913	B Mo																				
109	G.A.	1943	B Mo	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
110	J.H.	1942	B Se	0	0	0	4	2	3	2	0	0	0	0	2	2	0	0	0	0		2	
111	E.N.	1929	A Mo	2—3																		1	
112	S.J.	1943	B Se	0	0	0	0	2	0	0	0	0	0	0	3	0	0	0	0	0	a	2	
113	R.A.	1939	A Mo	2																		0	
114	T.J.	1937	A Se																				
114	B.J.	1957	A Se	0.7																			
115	B.P.	1904	A Mi		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
115	A.P.	1922	A Mi	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
116	U.O.	1956	B Se	< 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
118	C.P.	1955	B Se	0.9	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0		1	
119	J.M.	1956	A Se	0.8	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
120	L.E.A.	1957	A Se	< 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
121	I.H.	1935	A Se	< 1	0	0	2	3	0	0	0	0	0	0	4	2	0	0	0	0		2	
122	R.B.	1915	A Mi	16																		0	
122	K.B.	1918	A Mi																			0	
122	E.B.	1920	A Mi	5—7																		0	
123	P.A.	1883	A Mi																				
123	K.A.	1949	A Mi	5—6	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	b	1	
124	F.H.	1930	B Mo	1.4	0	0	3	3	0	0	0	0	0	0	3	0	0	0	0	0		1	
125	S.A.L.	1939	B Mi																			0	
126	L.J.	1957	A Mi	5—6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
127	A.P.	1888	A Mi	4																		0	
127	C.F.	1945	A Mi	10																			
129	R.J.	1949	A Se		0	0	2	0	0	2	0	0	0	0	2	0	0	0	0	0		0	
131	H.S.	1955	A Mo																			0	
132	A.M.	1915	A Mo	3	0	0	0	0	2	2	0	0	0	0	3	4	0	0	0	0		1	

133	S.B.	1915	A Mo	4—5	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
133	S.G.K.	1928	A Mo	2.5—3.9									0	
133	A.K.	1934	A Mo	3.3									0	
134	S.N.	1919	B Mo	2.6										
135	L.T.	1937	A Mi	7	0 0	0 0	3 0	0 0	0 0	0 0	0 0	0 0	1	
136	G.P.	1908	A Mo		0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
137	Å.F.	1935	A Mi	5									0	
138	T.H.	1942	A Mo	1.5									2	
139	T.E.	1947	B Mi	8									0	
140	T.B.	1956	A Se	0.4	0 0	3 0	0 0	0 0	0 0	0 0	0 0	0 0	1	c
141	O.F.	1918	A Mi	24									0	
141	L.F.	1926	A Mi	20									0	
142	H.E.K.	1946	A Se	< 1	2 3	3 3	3 3	0 0	0 0	3 3	0 0	0 0	2	
143	K.J.	1923	A Se	< 1	0 0	4 4	3 0	0 0	0 0	4 4	0 0	0 0	2	
144	J.E.K.	1941	A Mo	1.7									2	
144	B.N.	1939	A Mo	1.3	0 0	0 3	0 0	0 0	0 0	0 2	0 0	0 0	2	
144	O.L.	1946	A Mo										1	
145	A.H.	1927	A Mi	21	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
145	H.H.	1942	A Mi	23	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
145	K.H.	1953	A Mi	21	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
145	R.H.	1956	A Mi	20	0 0	2 2	0 0	0 0	0 0	0 0	0 0	0 0	0	
146	S.P.	1928	A Mi	21									0	
148	P.W.	1956	A Mo	1.5	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
149	A.S.	1930	A Mi	5										
150	K.R.C.	1907	B Mo	4	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
150	R.E.	1955	B Mo	4	0 0	2 2	0 0	0 0	0 0	0 0	0 0	0 0	1	
151	T.K.	1959	B Se	0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
152	S.B.	1918	A Mo	4									0	
153	B.E.	1945	B Mo	1	0 0	2 0	0 0	0 0	0 0	3 0	0 0	0 0	1	
154	B.E.	1947	A Mi	8	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
154	R.E.	1950	A Mi	5	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0	
155	Å.F.	1954	A Mo	3									3	
156	K.F.	1953	A Mi										0	
157	O.B.	1899	A Mi											
157	E.J.	1909	A Mi											

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
157	T.T.	1919	A Mi																			0	
157	S.E.A.	1949	A Mi																			0	
157	K.R.	1948	A Mi																			0	
157	J.E.R.	1957	A Mi																			0	
158	S.K.	1939	A Se	0.1																		1	
159	R.H.	1952	A Se	< 1	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0		3	a
160	S.E.	1927	A Mo		*0*	*0*	0	0	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*		0	
160	L.E.	1931	A Mo	2.5																		0	
160	P.E.	1935	A Mo	2.7																		0	
161	B.M.	1938	A Mo	2	0	0	3	3	3	3	*0*	*0*	0	0	2	3	2	0	*0*	*0*	b	1	
162	K.N.	1918	A Se	0.1	0	0	3	3	*0*	*0*	*0*	*0*	0	0	2	2	*0*	*0*	*0*	*0*		1	
163	O.O.	1895	B Mi		*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*		0	
163	H.H.	1928	B Mi		*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*		0	
163	B.O.	1943	B Mi	20																			
163	T.O.	1947	B Mi	18																		0	
164	B.E.O.	1945	A Se	< 1	0	0	3	3	2	2	*0*	*0*	3	0	0	3	0	0	*0*	*0*		1	
165	E.O.	1947	A Mo																			0	
166	E.R.O.	1892	A Mo	3																		1	
167	O.Ö.	1903	B Mi	9																			
167	H.K.	1956	B Mi	10																		0	
168	E.S.	1927	A Se	< 1	0	0	4	4	0	0	*0*	*0*	0	0	3	2	0	0	*0*	*0*		2	
169	B.S.	1909	A Mo	1.2	0	0	4	4	3	2	*0*	*0*	3	3	3	2	3	3	*0*	*0*	c	3	
170	L.W.	1913	A Mo	1																		0	
171	T.Y.	1941	B Mo	3	*0*	*0*	0	0	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*		0	
172	J.B.	1908	A Se	0.1																		2	
173	L.B.	1954	B Mo	3	0	0	0	2	0	0	*0*	*0*	0	0	0	0	0	0	*0*	*0*		0	
174	B.S.	1928	A Mi	9.5																		0	
174	D.S.	1935	A Mi	12																			
175	L.W.	1956	A Se	< 1	0	0	3	0	0	0	*0*	*0*	0	0	0	0	0	2	*0*	*0*		3	a
176	L.G.L.	1959	B Se	< 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
177	B.H.	1930	B Mi	10																		0	
177	A.H.	1938	B Mi	12																		0	

177	T.R.S.	1951	B Mi	9	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
178	M.L.	1938	A Mo	2										0	
179	G.L.	1945	A Se	< 1	0 0	0 0	2 0	0 0	0 0	0 0	0 0	0 0		0	
180	L.O.K.	1939	B Se	1.4	0 0	3 3	2 2	0 0	0 0	3 3	0 0	0 0		1	
180	G.K.	1943	B Se	1.4	0 0	3 2	0 2	0 0	0 0	4 3	0 0	0 0		1	
181	H.W.	1958	A Se	0.1	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	c
182	I.E.	1938	A Se	< 1	0 0	3 3	2 2	0 0	0 0	4 4	2 2	0 0		2	
183	B.A.	1947	B Se	< 1	0 0	2 3	0 2	0 0	0 0	3 2	0 0	0 0	b	2	a, b
184	P.B.	1955	A Mo	2.6	0 0	0 2	0 2	0 0	0 0	2 0	0 0	0 0		1	
184	T.B.	1958	A Mo	3—4	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	a	2	
185	A.E.	1954	B Mi												
186	A.M.	1960	A Se	0.4											
187	J.L.	1890	A Mi	16											
188	L.P.	1949	A Mi	8	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0		0	
189	I.O.	1958	A Se	0.7											
189	S.O.	1960	A Se												
190	M.E.	1926	A Se	< 1	3 0	4 4	2 2	0 0	2 0	3 0	0 0	0 0	c	2	
191	J.E.C.	1953	A Mi	6										0	
192	M.L.	1918	A Mo	2	0 0	2 0	2 0	0 0	0 0	0 0	0 0	0 0		0	
193	P.G.	1943	A Mi	22										0	
193	S.T.	1936	A Mi	24											
194	A.A.	1922	A Mi	25										0	
195	R.B.	1940	A Mi	23										0	
195	R.B.	1946	A Mi	25										0	
195	K.P.	1945	A Mi	30										0	
196	K.A.	1961	A Se	0.2											
197	E.M.	1891	A Mi	13										0	
197	O.M.	1896	A Mi												
198	K.W.	1943	A Mi	11											
199	D.S.	1912	A Mo	4										0	
200	B.J.	1959	A Mo	2											
201	B.J.	1933	A Mo	1.1	0 0	0 2	0 0	0 0	0 0	0 0	0 0	0 0		0	
201	S.S.	1935	A Mo												
202	E.S.	1919	B Mi	15										0	
203	K.S.	1919	A Mi	6										2	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
204	R.D.	1929	A Mi																			0	
204	E.G.	1918	A Mi	12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
204	H.G.B.	1938	A Mi																			0	
204	Å.G.	1925	A Mi	11																		0	
205	A.G.S.	1925	A Mi	21																			
206	L.E.	1938	A Mi	20																			
206	K.E.	1944	A Mi	20																			
207	L.G.K.	1959	A Se	0.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
208	P.S.	1960	A Mo	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
209	B.Å.A.	1961	A Se	0.8																			
210	L.G.L.	1936	A Se	< 1	3	0	3	3	3	0	0	0	0	0	4	3	0	0	0	0		2	
212	B.L.	1910	A Mi	8																			
212	L.L.	1901	A Mi	8																		0	
212	B.A.L.	1910	A Mi	9																		0	
212	E.L.	1920	A Mi	6																			
213	L.E.H.	1953	A Se	0.5	0	0	2	4	0	0	0	0	0	0	0	3	0	0	0	0		2	a
214	J.J.	1942	B Mi	5																		0	
215	S.P.	1957	B Se	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0		0	
216	I.E.	1953	A Mi	13																			
216	G.M.	1955	A Mi	8																			
217	E.K.	1911	A Mi	23																			
217	S.K.	1926	A Mi	32																			
217	L.C.	1950	A Mi	35																		0	
218	K.R.	1917	A Mi	21																		0	
218	R.R.	1919	A Mi																				
219	F.P.	1933	A Mi	36																			
220	S.Å.A.	1937	A Mi	11																		0	
220	A.H.	1928	A Mi	11																		0	
221	T.H.	1957	B Mi	14																			
222	Y.N.	1931	A Mi	6																			
222	M.N.	1930	A Mi	5																			
223	H.N.	1933	A Mi	12																		0	

223	G.N.	1935	A	Mi	9									
223	R.N.	1937	A	Mi	10									
223	C.N.	1946	A	Mi	14									
224	T.O.	1959	A	Mi	14									0
224	L.T.	1960	A	Mi	5									0
225	J.O.L.	1952	A	Mi	18									
226	K.S.	1949	A	Mi	25									0
226	R.W.	1950	A	Mi	23									
227	M.L.	1961	A	Se	0.5									
228	J.K.	1938	B	Mi	21	*0 0*	*0 0*	*0 0*	*0 0*	*0 0*	*0 0*	*0 0*	*0 0*	0
229	J.H.	1934	B	Mi	16									
230	V.N.	1913	A	Mi	10									

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Addendum

TO THE REVIEW OF HAEMOPHILIA IN SWEDEN IN 1962

By

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MARGARETA BLOMBÄCK and ÅKE AHLBERG

A review of haemophilia in Sweden was published by Sköld in 1944. He investigated 60 families with 101 living haemophiliacs. Sköld studied the hereditary pattern in the Swedish families, the symptomatology of the haemophiliacs, the coagulation time of whole blood in the haemophiliacs and the carriers, and evaluated the effect of blood transfusion therapy in haemophilia. In 1955 Nilsson, Blombäck and Ramgren started a follow-up study of Sköld's investigation, and in 1961 and 1962 they published a new review of haemophilia in Sweden. All together 179 haemophilic families in Sweden with 253 living haemophiliacs were investigated. This review included the coagulation status of the haemophiliacs (Nilsson *et al.* 1961) and the carriers (Nilsson *et al.* 1962), the symptomatology of haemophilia A and B, (Ramgren 1962 a), hereditary investigation (Ramgren *et al.* 1962), medico-social aspects (Ramgren 1962 b), and the treatment of haemophilia A with human AHF preparations (Nilsson *et al.* 1962). A short case history was compiled for each haemophiliac, as well as a pedigree of the family.

Since 1961 a further 50 families with haemophilia have been discovered in Sweden. In addition 4 affected members have been born in the 180 previously known families. Coagulation studies have been carried out on 42 haemophiliacs belonging to families 1—180 and not tested in the previous investigation. In addition, 18 patients have been re-examined either because check analysis had shown that the previous tests had been incomplete or that the results of the tests deviated from those obtained in

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the remaining affected family members or appeared incompatible with the clinical course.

The information obtained on the hereditary pattern, symptomatology and coagulation status in these cases is given in this addendum. All together 230 haemophilic families were known in Sweden in January 1964.

The methods used for collection and preparation of the blood samples and for determination of the various coagulation factors have been described elsewhere (Nilsson *et al.* 1961).

Histories of additional cases in fam. 1—180

THE SYMBOLS USED IN THE PEDIGREES

NORMAL WOMAN

NORMAL WOMAN, CHILDLESS

FEMALE GENETIC CARRIER

FEMALE GENETIC CARRIER, EXAMINED BY COAGULATION TESTS

FEMALE CARRIER ACCORDING TO COAGULATION TESTS

FEMALE HAEMOPHILIAC

NORMAL MAN

HAEMOPHILIAC

HAEMOPHILIAC, EXAMINED BY COAGULATION TESTS

PROBABLE HAEMOPHILIAC

DESCENDANTS, NUMBER AND SEX UNKNOWN OR OF NO INTEREST

V:9 GENERATION V, MEMBER NO. 9 AS COUNTED FROM THE LEFT
DESCENDANTS DESIGNED AS ◇ ARE NOT COUNTED

Family 4. Haemophilia A, severe form.

VI: 4 (H.N.) Born 1962. First symptom of haemophilia at 1 year. Has had haemarthrosis in ankle joints which have not impaired the joint function.

Family 14. Haemophilia B, moderate form.

Son of IV: 6 (K.D.) Born 1962. First symptom of haemophilia at 1 year (large haematoma in the forehead). He has had several large subcutaneous and intramuscular haematoma. No haemarthroses.

Family 31. Haemophilia B, severe form.

VI: 4 (S.N.) Born 1961. First symptoms of haemophilia at 1 year (subcutaneous bleedings). He has had several large subcutaneous bleedings. Recurrent haemarthroses in knee, ankle and elbow joints. Hospitalized on several occasions. Has received blood and plasma transfusions.

VI: 5 (H.N.) Born 1962. First symptom of haemophilia at 3—4 months (subcutaneous bleedings). He has always been covered with haematomas. At 2 years he bit his tongue and bled heavily. Then given one blood transfusion, and 2 plasma transfusions. Haemarthroses in knee and elbow joints. Often hospitalized and blood transfusions on several occasions.

Family 105. Haemophilia A, severe form.

III: 5 (Å.N.) Born 1934. This patient was included as a haemophiliac in the foregoing review. Recent clinical examination and coagulation studies revealed no symptoms of haemophilia and a normal AHF content.

Family 130. Haemophilia A, mild form.

(K.E.P.) Born 1936. In the preceding paper (Ramgren, 1962) this patient was described as having mild haemophilia A. Repeated recent examinations, however, showed a normal AHF and B-factor content, which thus excludes haemophilia.

Family 134. Haemophila B, moderate form.

II: 3 (S.N.) Born 1919. This patient is the same as case III: 5 (S.P.) in family 109. The family has been registered twice because on two occasions the patient had used different surnames.

Family 177. Haemophilia B, mild form.

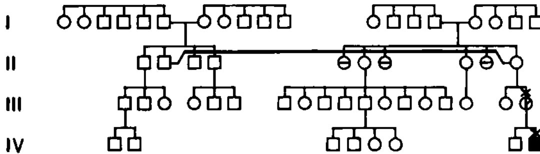
V: 3 (T.R.S.) Born 1951. First symptom of haemophilia at 4 years (profuse wound bleeding). He has had several large intramuscular and subcutaneous haematomas. No haemarthrosis. No operations have been performed. No transfusions. He attends school.

Histories of cases in fam. 181—230

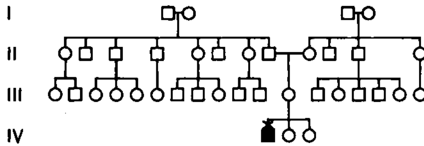
Family 181. Haemophilia A, severe form.

IV: 8 (H.W.) Born 1958. First symptom of haemophilia at 6 weeks (subcutaneous haemorrhage). Repeated hospitalization for haemarthroses and intramuscular bleedings. No disabling joint changes. He has received fraction I—O on about 40 occasions. Since March 1965 he has been receiving half a dose every other week prophylactically.

FAMILY 181



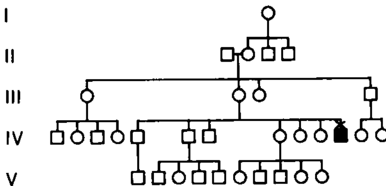
FAMILY 182



Family 182. Haemophilia A, severe form.

IV: 1 (I.E.) Born 1938. First symptom of haemophilia at 9 months (postoperative bleeding). Repeated haemarthroses in all main joints. Impaired function of knee joints. Hospitalized several times for haemarthroses, gastrointestinal bleedings and bleedings after tooth extractions. He has received about 40 blood and plasma transfusions. He attended a school for vocational training. Present occupation: typographer.

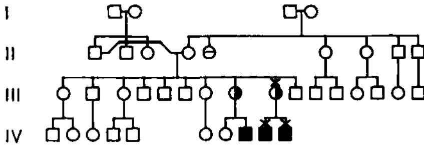
FAMILY 183



Family 183. Haemophilia B, severe form.

IV: 11 (B.Å.) Born 1947. First symptom of haemophilia at 18 months (intramuscular bleeding). Repeated bleedings in all main joints. Impaired function of the left knee joint. Hospitalized several times for haemarthroses and renal bleeding. He has received about 40 blood or plasma transfusions. Attends school. In January 1965 achillotenotomy was performed under cover of a preparation of human haemophilia B factor.

FAMILY 184

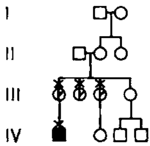


Family 184. Haemophilia A, moderate form.

IV: 9 (P.B.) Born 1955. First symptoms of haemophilia at 5 years (tooth extraction). Occasional bleeding in the ankle, knee and shoulder joints, which have not impaired the joint function. Hospitalized a few times for haemarthroses and bleeding after tooth extraction. He has received 5 blood transfusions. He attends school.

IV: 10 (T.B.) Born 1958. First symptom of haemophilia at 1 year (intracranial bleeding). Since then paraplegia. Recurrent haemarthroses, most often in the knee joints. Hospitalized several times for correction of paralytic pes equino-varus. Right-sided achillotenotomy in 1965 (Malmö) under cover of human fraction I—O.

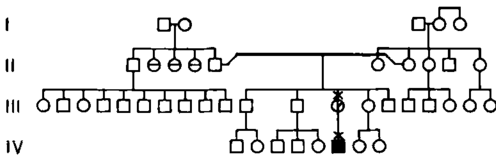
FAMILY 185



Family 185. Haemophilia B, severe form.

IV: 1 (A.E.) Born 1954. First symptom of haemophilia at 1 year (bleeding at dentition). Repeated haemarthroses in the ankle, knee and elbow joints, which have not caused impaired function of the joints. Hospitalized for bleeding from a wound, bleeding after tooth extractions and nose bleeding. He has received about 15 blood transfusions. He attends school.

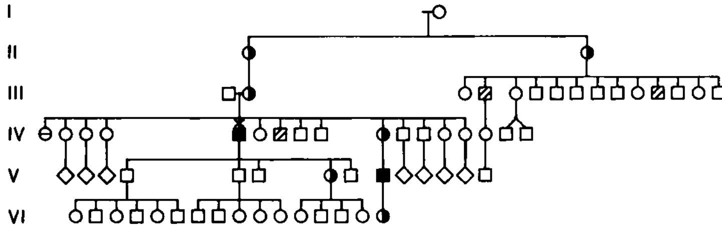
FAMILY 186



Family 186. Haemophilia A, severe form.

IV: 6 (A.M.) Born 1960. First symptom of haemophilia at 9 months (postoperative bleeding). A few haemarthroses in the main joints. Hospitalized for bleeding in connection with operation for hernia. Treated with fraction I—O for operation of hernia and haemarthroses.

FAMILY 187



Family 187. Haemophilia A, mild form.

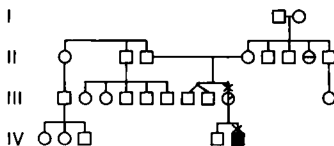
III: 4 and III: 12 are said to have bled easily after tooth extractions and from wounds. Both are dead.

IV: 5 (J.L.) Born 1890. First symptom of haemophilia at 3 years (wound haemorrhage). Occasional haemarthroses in the knee joints, which have not impaired joint function. Hospitalized several times for nose bleedings, bleedings after tooth extractions and surgery. He has received about 70 blood and plasma transfusions. Treated with fraction I—O for nose bleedings (1960) and for operation of hernia (1963). He attended school, he did his military service but was discharged because of recurrent nose bleeding. He worked as a farmlabourer and road-worker, but in 1948 he was granted a disability pension because of cardiosclerosis.

IV: 7 (J.E.L.) Is said to have a bleeding tendency, lives in Canada.

V: 9 (L.S.) Born 1915. First symptom of haemophilia at 25 years (bleeding after tooth extraction). No haemarthroses. Hospitalized once for postoperative bleeding. He attended school and did his military service. Present occupation: farmer.

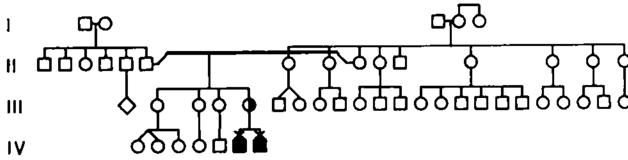
FAMILY 188



Family 188. Haemophilia A, mild form.

IV: 5 (L.P.) Born 1949. First symptom of haemophilia at 2 years (wound bleeding). No haemarthroses. Severe bleeding after tooth extractions and from wounds. Several large haematomas. No blood transfusions. He attends school.

FAMILY 189

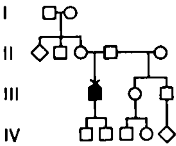


Family 189. Haemophilia A, severe form.

IV: 6 (I.O.) Born 1958. First symptom of haemophilia at 7 months (subcutaneous haemorrhages). Recurrent haemarthroses in the ankle, knee, elbow and wrist joints. No impairment of joint function. In 1961 a large haematoma in the back. The haemoglobin value decreased to 6.0 g/100 ml. Blood transfusions on several occasions.

IV: 7 (S.O.) Born 1960. First symptom of haemophilia at 1 year (subcutaneous hameorrhages).

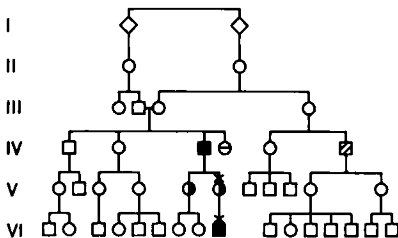
FAMILY 190



Family 190. Haemophilia A, severe form.

III: 1 (M.E.) Born 1926. First symptom of haemophilia at 1 year (subcutaneous haemorrhage). Recurrent haemarthroses in all main joints. Stiff right knee and impaired function of other joints. Hospitalized several times for haemarthroses, renal bleeding and bleeding after tooth extractions and trauma. He has had repeated episodes of severe melaena (haemoglobin values about 2.8 g/100 ml). Roentgenography of stomach revealed nothing remarkable. He has received about 150 blood transfusions. Treated with fraction I—O for gastrointestinal bleeding (1961), haematomas and bleedings from tonsils (1961). He attended school, he was exempted from military service and got ordinary vocational training at a school of commerce. Present occupation: businessman.

FAMILY 191

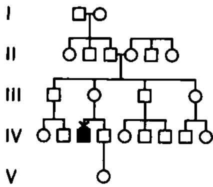


Family 191. Haemophilia A, mild form.

IV: 3 (J.Z.) Born 1895, died 1959 of myocardial infarction. He bled easily after tooth extractions and wounds.

VI: 9 (J.E.C.) Born 1953. First symptom of haemophilia at 2 years (bleeding from a wound in the tongue). No haemarthroses. Hospitalized occasionally for bleeding after tooth extractions and from wounds. He attends school.

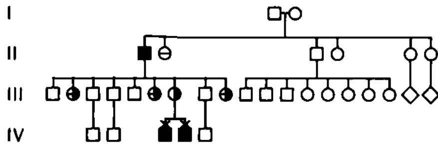
FAMILY 192



Family 192. Haemophilia A, moderate form.

IV: 3 (M.L.) Born 1918. First symptom of haemophilia at 7 years (bleeding after tooth extraction). Haemarthroses 4 times in the right knee joint. Hospitalized 7 times for bleeding after tooth extraction, haemarthroses and renal bleedings. He has received 8 blood and plasma transfusions. He attended school and has served in the army as an officer. Present occupation: staff manager.

FAMILY 193



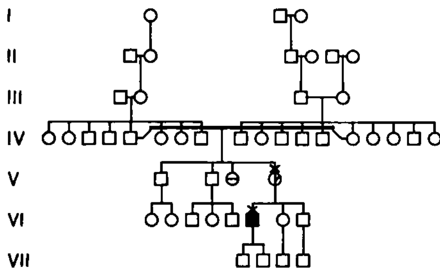
Family 193. Haemophilia A, mild form.

II: 1 (G.J.) Born 1873, died 1944 of intracranial bleeding. He always bled easily after tooth extractions and trauma.

IV: 3 (S.T.) Born 1936. First symptom of haemophilia at 4 years (bleeding from a wound). No haemarthroses. He has had excessive bleeding after tooth extractions and from wounds, but has not required hospitalization or blood therapy. He attended school and was exempted from military service. Present occupation: foreman.

IV: 4 (P.G.) Born 1943. First symptom of haemophilia at 7 years (bleeding after tooth extraction). Haemarthroses 2—3 times in the right knee joint in connection with cross-country runs. In 1961 he was hospitalized after a traffic accident. He had sustained a fracture of the right femoral neck and several flesh wounds, from which he bled profusely. This excessive bleeding led to the diagnosis of his disease. Healing of the fracture was retarded by complicating bleedings. He received 7 blood transfusions. He could attend school. He was exempted from military service. He is now at college.

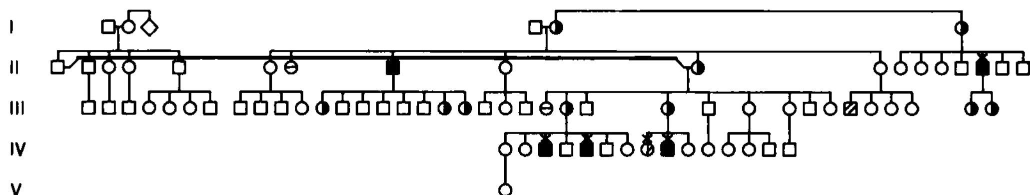
FAMILY 194



Family 194. Haemophilia A, mild form.

VI: 6 (A.A.) Born 1922. First symptom of haemophilia at 1 year (bleeding after a wound in the tongue). Occasional haemarthroses in the right knee joint. Slightly impaired function of both knee joints owing to rheumatoid arthritis. Recurrent bleedings in the muscles. Hospitalized several times because of gastrointestinal and renal bleedings and retroperitoneal haematoma and has received about 25 blood and plasma transfusions. Treated with fraction I—O for tooth extraction (1961). Attended school. Exempted from military service. Present occupation: engineer.

FAMILY 195



Family 195. Haemophilia A, mild form.

II: 8 (K.H.) Born 1877. Treated several times in hospital for gastrointestinal bleeding. He has always bled easily from wounds and after tooth extractions.

II: 16 (N.L.) Born 1876, died 1962 of post-operative bleeding. Treated several times in hospital for haematuria and postoperative bleeding after prostatectomy and collum femoris fracture.

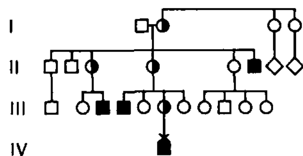
III: 32 (T.B.) He is said to bleed easily from wounds and after tooth extractions.

IV: 3 (E.R.B.) Born 1940. First symptom of haemophilia at 21 years (postoperative bleeding after tonsillectomy). No haemarthroses. He has had excessive nose bleedings. Hospitalized once for bleeding after tonsillectomy and received 11 blood transfusions. He attended school and did his military service. He is manual worker but is studying to get lighter work.

IV: 5 (R.B.) Born 1946. First symptom of haemophilia at 11 years (bleeding after tooth extraction). No haemarthroses or hospitalization. He attended school. Exempted from military service. He is receiving vocational training as a clerk.

IV: 9 (K.P.) Born 1945. First symptom of haemophilia at 16 years (postoperative bleeding after tonsillectomy). No haemarthroses. Hospitalized once for bleeding after tonsillectomy but did not require blood transfusions. He attended school. Exempted from military service. He is receiving vocational training as a clerk.

FAMILY 196



Family 196. Haemophilia A, severe form.

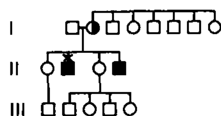
II: 6 (H.S.) Born 1924, died 1926 of internal bleeding. He had had subcutaneous bleedings and haemarthroses.

III: 3 (T.N.) Born 1939, died 1943 of unknown bleeding. He had repeatedly had haemarthroses and subcutaneous bleedings.

III: 4 (K.E.) Born 1934, died 1938 of internal bleeding. He had had haemarthroses several times.

IV: 1 (K.A.) Born 1961. First symptom of haemophilia at 2 weeks (subcutaneous haemorrhage). Repeated haemarthroses in knee joints. Occasionally hospitalized because of haemarthroses and gastrointestinal bleedings. He has received 5 blood transfusions. Treated with fraction I—O for bleedings from gingivae and tonsillae (1962, 1964).

FAMILY 197

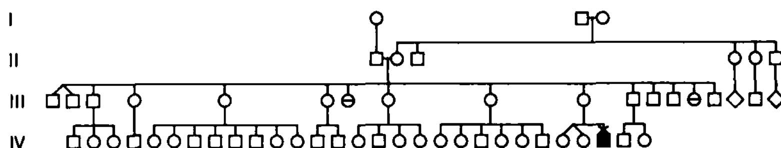


Family 197. Haemophilia A, mild form.

II: 2 (E.M.) Born 1891. First symptom of haemophilia at 30 years (bleeding after tooth extraction). No haemarthroses. Hospitalized several times for gastrointestinal bleedings and has received about 10 blood transfusions. He did his military service and worked as a forester. He is now an old-age pensioner.

II: 4 (O.M.) Born 1896. First symptom of haemophilia at 40 years (bleeding after tooth extraction). No haemarthroses or hospitalization. He did his military service and worked as a forester. He is now an old-age pensioner.

FAMILY 198

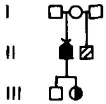


Family 198. Haemophilia A, mild form.

IV: 27 (K.W.) Born 1943. First symptom of haemophilia at 9 years (haemarthroses left ankle). Otherwise no haemarthroses. He has bled profusely after tooth extraction and several

times been troubled by prolonged and severe wound bleeding. Appendectomy in 1961. In the postoperative course he developed a large haematoma in the operative field. He attended school. Exempted from military service. Now studying at university.

FAMILY 199

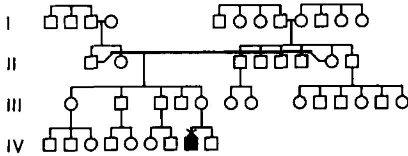


Family 199. Haemophilia A, moderate form.

II : 1 (D.S.) Born 1912. First symptom of haemophilia at 2 years (prolonged nose bleedings). No haemarthroses. Repeated subcutaneous and intramuscular bleedings. Hospitalized a few times for gastrointestinal bleedings and bleedings after tooth extractions. Has received about 20 blood transfusions. He attended school and did his military service. Present occupation: engine-driver.

II : 2 Is said to bleed easily after wounds and after tooth extractions.

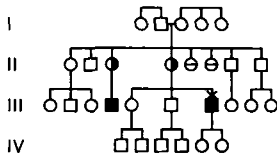
FAMILY 200



Family 200. Haemophilia A, moderate form.

IV : 8 (B.J.) Born 1959. First symptom of haemophilia at 2 days (subcutaneous haemorrhage). Occasional haemarthroses in the ankle and elbow joints. Hospitalized several times for subcutaneous, intramuscular and intraarticular bleedings, and bleeding from wounds and gingivae. He has received about 10 blood and plasma transfusions. Treated with fraction I—O for haemarthroses (1964).

FAMILY 201

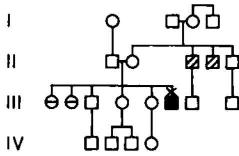


Family 201. Haemophilia A, moderate form.

III : 4 (S.S.) Born 1935. First symptom of haemophilia at 6 years (bleeding after tooth extraction). Repeated haemarthroses in the ankle and knee joints, which have not impaired function. Hospitalized a few times for bleeding after tooth extraction and haemarthroses.

III : 7 (B.J.) Born 1933. First symptom of haemophilia at 4 years (haemarthroses). Repeated haemarthroses in the knee joints which have not impaired function. Hospitalized several times for haemarthroses, renal bleeding and bleeding after tooth extractions. He has received about 50 blood and plasma transfusions. He attended school, did his military service. Present occupation: clerk.

FAMILY 202



Family 202. Haemophilia B, mild form.

II: 3 (A.J.) Born 1876. He has had profuse bleedings after tooth extractions.

II: 4 (J.S.) Born 1878. He has had profuse bleedings after tooth extractions.

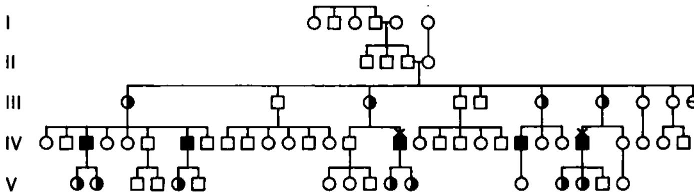
III: 6 (E.S.) Born 1919. First symptom of haemophilia at 6 years (bleeding after tooth extraction). No haemarthroses. Recurrent intramuscular bleedings after slight trauma. Hospitalized a few times for bleedings after tooth extractions and has received one blood transfusion. He attended school, he did his military service and took a university degree (Bachelor of Economics). Present occupation: managing director.

Family 203. Haemophilia A, mild form.

It is not possible to get any information about the family, because the patient was adopted and does not know his parents.

(K.S.) Born 1919. First symptom of haemophilia at 16 years (postoperative bleeding after tonsillectomy). Haemarthroses once in the right knee after trauma, which has caused impaired function of the joint. Prolonged bleeding after tooth extractions and after wounds. Hospitalized a few times for bleedings after trauma and gastrointestinal bleeding and given about 10 blood transfusions. He attended school. After 4 months military service he was discharged because of his bleeding tendency. Present occupation: unskilled labourer.

FAMILY 204



Family 204. Haemophilia A, mild form.

IV: 3 (S.D.) Born 1918, died 1957 of intracranial haemorrhage. He bled easily after tooth extraction and from wounds.

IV: 7 (R.D.) Born 1929. First symptom of haemophilia at 21 years (postoperative bleeding

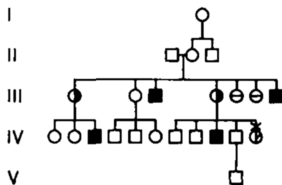
after tonsillectomy). No haemarthroses. Hospitalized a few times because of bleeding after tooth extractions and after tonsillectomy. Has received 2 blood transfusions. He attended school and did his military service. Present occupation: consultant.

IV: 16 (E.G.) Born 1918. First symptom of haemophilia at 18 years (postoperative bleeding). No haemarthroses. In connection with appendectomy and operation for hernia he bled heavily and required several blood transfusions. Hospitalized several times for gastrointestinal and renal bleeding and bleeding after tooth extractions. He has received about 25 blood and plasma transfusions. In 1964 tooth extractions in Malmö under cover of AHF. No bleeding complications. He attended school, he was exempted from military service because of asthma. Present occupation: mechanic.

IV: 22 (H.G.B.) Born 1938. First symptom of haemophilia at 25 years (bleeding after tooth extraction). No haemarthroses or hospitalizations. He attended school and did his military service. Present occupation: businessman.

IV: 25 (Å.G.) Born 1925. First symptom of haemophilia at 10 years (prolonged nose bleeding). No haemarthroses. Hospitalized several times for renal bleeding and bleedings after tooth extractions and minor surgery. He has received about 5 blood transfusions. He attended school and did his military service. Present occupation: radio operator.

FAMILY 205



Family 205. Haemophilia A, severe form.

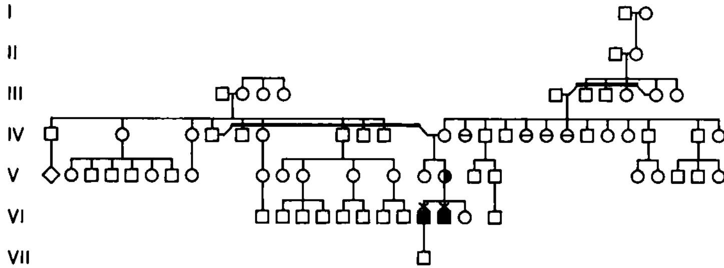
III: 3 (N.J.) Born 1890, died 1917 of internal bleeding. He had haemarthroses and had difficulty in walking.

III: 7 (J.I.) Born 1899, died 1923 of bleeding. He had haemarthroses.

IV: 3 (H.J.) Born 1918, died 1922 of internal bleeding.

IV: 9 (E.A.) Born 1919, died 1926 of tetanus. First symptom of haemophilia at 2 months (subcutaneous haemorrhages). Repeated haemarthroses, intramuscular and nose bleedings. Received one blood transfusion from his mother.

FAMILY 206

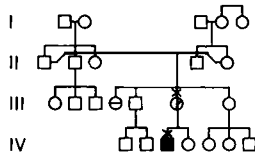


Family 206. Haemophilia A, mild form.

VI: 9 (L.E.) Born 1938. First symptom of haemophilia at 23 years (bleeding after tooth extraction). No haemarthroses or hospitalization. Prolonged bleeding after tooth extractions and abrasio. He attended school and did his military service. Present occupation: electrician.

VI: 10 (K.E.) Born 1944. First symptom of haemophilia at 5 years (bleeding after tooth extraction). Occasional haemarthroses in ankle, knee and hip joints after trauma. Hospitalized for bleeding after tooth extraction and haemarthroses. Has received 2 blood transfusions. He attended school but was exempted from military service. Present occupation: electrician.

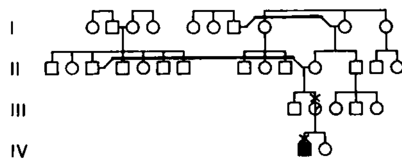
FAMILY 207



Family 207. Haemophilia A, severe form.

IV: 3 (L.G.K.) Born 1959. First symptom of haemophilia at 1 year (bleeding after puncture for blood test). Haemarthroses several times in different joints, mainly knee joints and ankle joints, but hitherto no impaired joint function. Several episodes of large subcutaneous and intramuscular haematomas. Repeated hospitalizations and has received about 10 blood transfusions. Treated with fraction I—O for haemarthroses.

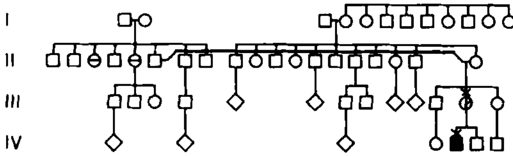
FAMILY 208



Family 208. Haemophilia A, moderate form.

IV: 1 (P.S.) Born 1960. First symptom of haemophilia at 14 months (prolonged bleeding from a wound in the tongue). Haemarthroses several times in the knee, hip and elbow joints, but hitherto no impaired joint function. Hospitalized for profuse bleeding after wounds in the tongue, episodes of haemarthroses and large intramuscular haematomas. He has received several blood transfusions and AHF on 3 occasions.

FAMILY 209



Family 209. Haemophilia A, severe form.

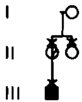
IV : 3 (B.Å.A.) Born 1961. First symptom of haemophilia at 3 months (bleeding after venipuncture). Hospitalized for intracranial bleeding and haemarthroses. Has received 5 blood transfusions. Treated with fraction I—O for bleeding after venipuncture in the groin (1961).

Family 210. Haemophilia A, severe form.

Information about the family unavailable. It is only known that the patient is the only child and has no relatives with a bleeding tendency.

(L.G.L.) Born 1936. First symptom of haemophilia at 1 year (subcutaneous bleedings). Recurrent haemarthroses in all main joints, which have impaired function of the ankle, knee and elbow joints. Hospitalized several times for haemarthroses, nose bleeding, bleeding after tooth extractions and fracture of tibia, gastrointestinal bleeding. Has received about 100 blood transfusions. Treated with fraction I—O for fractures after traffic accident (1962). He attended school. Exempted from military service. Present occupation : clerk.

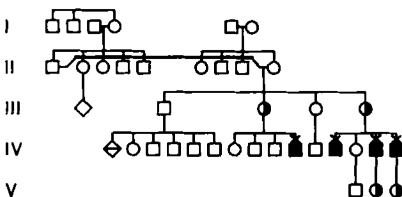
FAMILY 211



Family 211. Haemophilia A, severe form.

III : 1 (G.G.) Born 1954, died 1956 of internal bleeding. He had subcutaneous bleedings from early age.

FAMILY 212



Family 212. Haemophilia A, mild form.

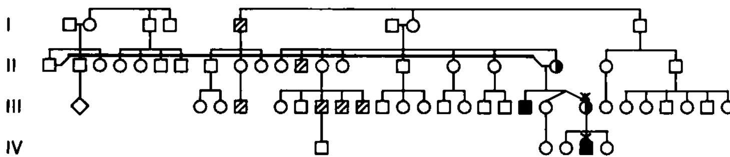
IV : 9 (B.L.) Born 1910. First symptom of haemophilia at 8 years (bleeding after tooth extraction). A few times haemarthroses after trauma in the ankle and knee joint, which have not impaired function of the joints. Hospitalized several times for bleeding after tooth extractions, profuse wound bleeding and haematuria. Has received 2 blood transfusions. He attended school. Exempted from military service. Present occupation : taxi driver.

IV: 11 (L.L.) Born 1901. First symptom of haemophilia at 30 years (bleeding after tooth extraction). No haemarthroses. Hospitalized once for postoperative bleeding after operation for hernia and received 4 blood transfusions. He attended school and he did his military service. Present occupation: furrier.

IV: 13 (B.L.) Born 1910. First symptom of haemophilia at 21 years (bleeding after tooth extraction). No haemarthroses. Hospitalized twice because of bleedings after tooth extractions and has been given 4 blood transfusions. He attended school and he did his military service. Present occupation: furrier.

IV: 14 (E.L.) Born 1920. First symptom of haemophilia at 13 years (bleeding after tooth extraction). Haemarthroses once in the knee joint after trauma. Hospitalized twice for haemarthroses and bleeding after tooth extraction. He attended school. Exempted from military service. Present occupation: workshop assistant.

FAMILY 213



Family 213. Haemophilia A, severe form.

I: 5 (I.R.) Born 1858, died 1912. Is said to have had bleeding tendency.

II: 12 (T.M.) Born 1883, died 1913. Is said to have bled easily.

III: 3 (J.M.) Born 1920. Is said to bleed easily.

III: 6, III: 7, III: 8 (O.J., A.J., E.J.) Born 1932, 1934 and 1939. Are said to bleed easily. All these probable haemophiliacs lived or live in Norway.

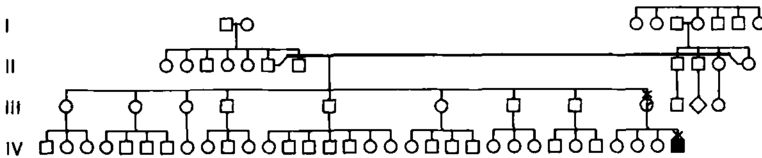
III: 16 (O.T.) Born 1928. He bleeds easily from wounds and has had repeated haemarthroses in main joints.

IV: 4 (L.E.H.) Born 1953. First symptom of haemophilia at 5 months (bleeding from a wound in the tongue). Repeated haemarthroses in all main joints. A marked deformity had developed in the left knee joint. Hospitalized several times because of haemarthroses. Often received blood and plasma transfusions. In August 1963 a flexion defect in the left knee joint was corrected in Malmö under cover of AHF. Treated with AHF for retroperitoneal bleedings and haematuria (1964). He attends school but is exempted from gymnastics.

Family 214. Haemophilia B, mild form.
Information about the family unavailable.

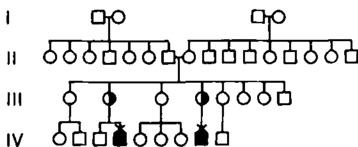
(J.J.) Born 1942. First symptom of haemophilia at 20 years (postoperative bleeding). No haemarthroses. Hospitalized once for bleeding after traumatic injury in the shoulder and received 5 blood transfusions. He attended school and did his military service. Present occupation: sheet-metal worker.

FAMILY 215



Family 215. Haemophilia B, severe form.
IV: 32 (S.P.) Born 1957. First symptom of haemophilia at 4 months (subcutaneous haemorrhage). Repeated haemarthroses in the ankle and knee joints, which have not impaired joint function. Hospitalized a few times because of haemarthroses, bleeding from wounds and subcutaneous and intramuscular bleedings. Has received about 20 blood transfusions.

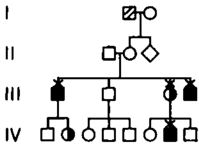
FAMILY 216



Family 216. Haemophilia A, mild form.
IV: 4 (I.E.) Born 1953. First symptom of haemophilia at 10 years (bleeding after tooth extraction). No haemarthroses or hospitalizations. He attends school.

IV: 8 (G.M.) Born 1955. First symptom of haemophilia at 2 years (prolonged bleeding from a wound). Haemarthroses once in right knee joint. Hospitalized a few times because of postoperative bleeding after abrasio and tooth extractions but has not received any blood transfusions. He attends school.

FAMILY 217



Family 217. Haemophilia A, mild form.

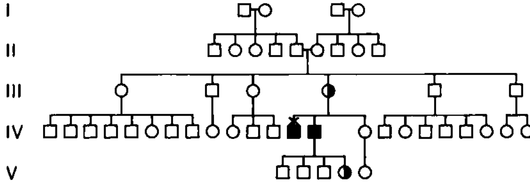
I: 1 (N.D.) Born about 1850. He is said to have bled profusely after wounds.

III: 1 (E.K.) Born 1911. He bleeds easily after tooth extractions and from wounds. Present occupation: farmer.

III: 4 (S.K.) Born 1926. He bleeds easily after tooth extractions and from wounds.

IV: 7 (L.C.) Born 1950. First symptom of haemophilia at 5 years (bleeding after tooth extraction). No haemarthroses and never hospitalized. He attends school.

FAMILY 218



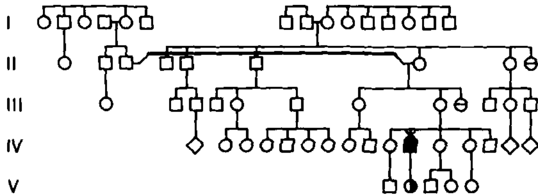
Family 218. Haemophilia A, mild form.

IV: 13 (K.R.) Born 1917. First symptom of haemophilia at 6 years (bleeding after tooth extraction). Haemarthroses in the ankle and knee joints after trauma, which have not impaired joint function. Hospitalized several times because of bleeding after tooth extractions and postoperative bleeding after minor surgery. He has received about 10 blood transfusions. Treated with fraction I—O for gastrointestinal bleedings (1963). He attended school and did his military service. Present occupation: stockroom worker.

IV: 14 (R.R.) Born 1919. First symptom of haemophilia at 5 years (bleeding after a wound

in the head). No haemarthroses. Hospitalized a few times because of bleeding after tooth extractions. He attended school. Exempted from military service. Present occupation: bricklayer.

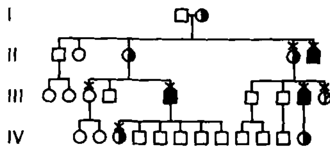
FAMILY 219



Family 219. Haemophilia A, mild form.

IV: 10 (F.P.) Born 1933. First symptom of haemophilia at 15 years (bleeding after tooth extraction). Haemarthroses a few times in knee and hip joints after slight trauma. Hospitalized for haematuria, nose bleeding and bleeding after tooth extractions. Has received 70 blood and plasma transfusions. He attended school and did his military service. Present occupation: commercial traveller.

FAMILY 220



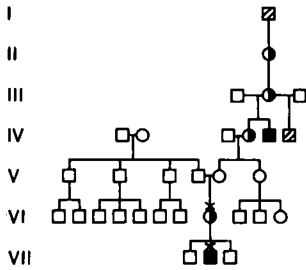
Family 220. Haemophilia A, mild form.

II: 5 (E.N.) Born 1908. Died 1963 of gastrointestinal bleeding. He bled easily after tooth extractions and from wounds. No haemarthroses. In 1959 he bled heavily after a fracture of the left femur and required several blood transfusions. In July 1963 he was admitted to the hospital in Malmö with profuse gastrointestinal bleeding. He received about 100 blood transfusions, 29 AHF administrations and ε-ACA. It was not possible to stop the bleeding, and he died after 10 days. Post mortem examination revealed necrotising erosive gastritis.

III: 5 (A.H.) Born 1928. First symptom of haemophilia at 9 years (bleeding after wound in the head). Hospitalized twice because of profuse bleeding after operation of abscesses of neck requiring 3 blood transfusions. No haemarthroses. Tooth extractions in Malmö in 1964 under cover of AHF and plasma transfusions. No bleeding complications. He attended school and did his military service. Present occupation: railway mechanic.

III: 8 (S.Å.A.) Born 1937. First symptom of haemophilia at 5 years (bleeding after tooth extraction). No haemarthroses. Often had nose bleeding, profuse wound bleeding and large haematomas. Hospitalized for postoperative bleeding after operation on knee joint and bleedings after tooth extractions. He has received one blood transfusion. He attended school and did his military service. Present occupation: iron worker.

FAMILY 221

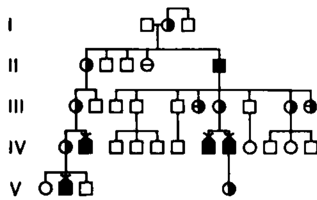


Family 221. Haemophilia B, mild form.

IV: 5 (G.F.) Born 1912, died 1935 of retroperitoneal bleeding. He always bled easily after wounds and tooth extractions.

VII: 2 (T.H.) Born 1957. First symptom of haemophilia at 4 years. He then bled profusely after abrasio and required blood transfusions. At 5 years he sustained a blow with a spade against the big toe of the left foot. The nail loosened and the toe bled continuously for 10 days. The haemoglobin decreased to 5.8 g/100 ml and blood transfusions had to be given. He also had had several large haematomas. No joint bleedings. In 1963 four teeth were extracted under cover of plasma transfusions. No bleeding complications. He attends school.

FAMILY 222



Family 222. Haemophilia A, mild form.

II: 5 (E.K.) Born 1867, died 1937 of intracranial bleeding.
He bled easily from wounds and after tooth extractions.

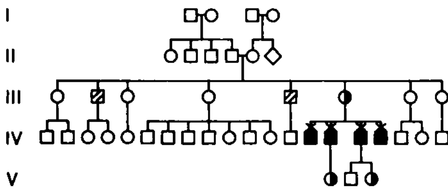
IV: 2 (B.J.) Born 1936. First symptom of haemophilia at 11 years (bleeding after tooth extraction). No haemarthroses. Hospitalized because of bleeding from a wound. He attended school, did his military service. Present occupation: farmer.

IV: 7 (M.N.) Born 1930. First symptom of haemophilia at 5 years (excessive bleeding from a wound). Haemarthrosis once in a knee joint after trauma. Hospitalized for postoperative bleeding after operation for hernia and bleeding after tooth extractions. He has received 12 blood transfusions. He attended school but was exempted from military service. Present occupation: farmer.

IV: 8 (Y.N.) Born 1931. First symptom of haemophilia at 24 years (bleeding after tooth extraction). Occasional haemarthroses in the left ankle and knee joint after light trauma. Hospitalized for bleedings after tooth extractions and haemarthroses. Has received about 30 blood and plasma transfusions. He attended school and did his military service. Present occupation: farmer.

V: 2 (J.R.) Born 1958. First symptom of haemophilia at 5 years (bleeding after tooth extraction). Once after slight trauma he had haemarthroses in the knee joint, which needed hospitalization. No blood transfusions. Treated with fraction I—O for tooth extraction.

FAMILY 223



Family 223. Haemophilia A, mild form.

III: 2 (N.W.) Born 1900, died 1947 of myocardial infarction. He had frequently had nose bleeding and bleeding after tooth extractions.

III: 5 (Å.W.) Born 1906. He has had prolonged bleedings after tooth extractions.

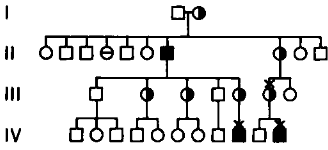
IV: 14 (H.N.) Born 1933. First symptom of haemophilia at 25 years (bleeding after tooth extraction). No haemarthroses. Hospitalized because of bleedings after tooth extraction and postoperative bleeding after a knee operation. He attended school and did his military service. Present occupation: pianotuner.

IV: 15 (G.N.) Born 1935. First symptom of haemophilia at 17 years (bleeding after tooth extraction). No haemarthroses or hospitalizations. He attended school and did his military service. Present occupation: clerk.

IV: 16 (R.N.) Born 1937. First symptom of haemophilia at 10 years (bleeding after tooth extraction). No haemarthroses or hospitalizations. He attended school and did his military service. Present occupation: supervisor.

IV: 17 (C.H.N.) Born 1946. First symptom of haemophilia at 7 years (prolonged nose bleedings). No haemarthroses or hospitalizations. He also has cerebral palsy. He attended school and is now receiving vocational training.

FAMILY 224



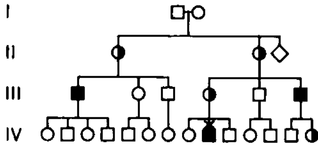
Family 224. Haemophilia A, mild form.

II: 7 (E.E.G.) Born 1900. He bleeds easily after wounds and tooth extractions.

IV: 9 (L.G.T.) Born 1960. First symptom of haemophilia at 2 years (subcutaneous haemorrhage). Hospitalized once for bleeding from a wound. Has received 2 blood transfusions.

IV: 11 (T.O.) Born 1959. First symptom of haemophilia at 4 years (bleeding after tooth extraction). No haemarthroses. Hospitalized once because of bleeding after tooth extraction. Has received one blood transfusion.

FAMILY 225



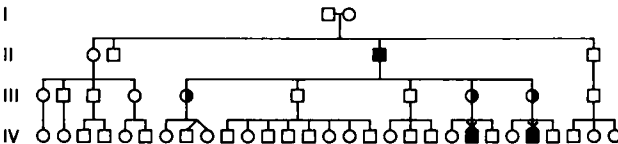
Family 225. Haemophilia A, mild form.

III: 1 (O.A.) Born 1910. He bleeds easily after tooth extractions and from wounds. No haemarthroses and never hospitalized.

III: 6 (K.L.) Born 1928. He bleeds easily after tooth extractions. No haemarthroses and never hospitalized.

IV: 9 (J.O.L.) Born 1952. First symptom of haemophilia at 10 years (postoperative bleeding after abrasio). No haemarthroses. Prolonged bleeding after tooth extraction. Hospitalized because of postoperative bleeding, no blood transfusions. He attends school.

FAMILY 226



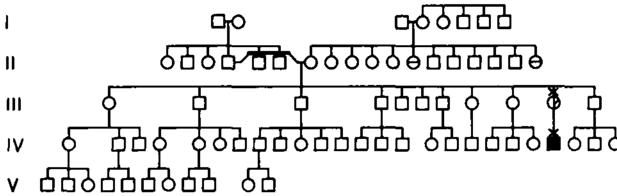
Family 226. Haemophilia A, mild form.

II: 3 (F.K.) Born 1893, died 1963 of postoperative bleeding after operation on prostate. He bled easily after tooth extractions.

IV: 22 (K.S.) Born 1949. First symptom of haemophilia at 10 years (prolonged bleeding from a wound). No haemarthroses and never hospitalized. He attends school.

IV: 25 (R.W.) Born 1950. First symptom of haemophilia at 11 years (bleeding after tooth extraction). No haemarthroses or hospitalizations. He attends school.

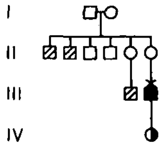
FAMILY 227



Family 227. Haemophilia A, severe form.

IV: 22 (M.L.) Born 1961. First symptom of haemophilia at 7 months (subcutaneous bleedings). Haemarthroses a few times in the ankle and knee joints. Hospitalized because of bleedings from wounds and intramuscular bleedings. Has received 5 blood transfusions. Treated with fraction I—O for bleeding after venipuncture.

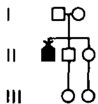
FAMILY 228



Family 228. Haemophilia B, mild form.

III: 2 (J.K.) Born 1938. First symptoms of haemophilia at 14 years in connection with appendectomy. The postoperative course was complicated by severe bleeding, and the required several blood transfusions. In 1961 and 1963 he was hospitalized for bleeding after tooth extractions and after gastrointestinal bleeding. After trauma he developed large haematomas. No joint bleedings. He attended school, but was exempted from military service. Present occupation: punch card operator. He plays football.

FAMILY 229



Family 229. Haemophilia B, mild form.

II: 1 (J.H.) Born 1934. First symptom of haemophilia at 25 years (postoperative bleeding after tonsillectomy). Haemarthroses in the ankle joint after trauma. Hospitalized because of postoperative bleeding and bleeding after tooth extractions. Has received about 20 blood and plasma transfusions. He attended school and did his military service. Present occupation: clerk.

Family 230. Haemophilia A, mild form.

No known bleeding tendency among relatives (the patient is from Russia).

(V.N.) Born 1913. First symptom of haemophilia at 5 years (bleeding after tooth extraction). Haemarthroses once in the ankle joint after trauma. Hospitalized because of haematuria, bleeding after tooth extractions. Has received about 10 blood transfusions. He attended school and did his military service. Present occupation: electrician.

Table

TABLE 1 Survey of the present case material

Fam. No.	Coordinate No.	Type of haemophilia	Case	Year of birth	Heredity None=0 Pos. =+	Mth/yr of invest.	Coagulation time min.	Bleeding time (Duke) min.	Platelets per mm³	AHF % of normal	B-factor % of normal	Circulating anticoagulant	Prothrombin consumption residual %	P&P (prothrombin+f. VII) %	Factor V % of normal	Fibrinogen g/100 ml
4	VI : 3	A (severe)	C.H.N.	1957	+	10/57	16 (capillary)	2	190,000	< *1*	—	0	—	95		
						4/63	> 60			*0.6*	123	0	—	160	92	0.48
6	III : 9	A (mild)	H.A.	1899	+	11/58	11	3	—	*4*	100	0	127	68	200	0.45
						2/62				*5*	73					
9	IV : 2	A (moderate)	S.M.	1943	+	8/58	73	11	290,000	*1—2*	110	0	136	66	120	0.32
						1/62	60			*1*						
						9/63	60			*1*						
						9/64	> 60			*1*						
14	Son of IV : 6	B (moderate)	K.D.	1962	+	6/63	15	2	504,000	190	*3*	0	26	101	107	0.32
22	VI : 2	A (severe)	B.E.	1948	+	6/59	—	4	—	*1.8*[1]	90	0	—	96	100	0.43
	VI : 6	A (severe)	R.K.	1940	+	6/59	115	5	220,000	*0.5*	98	0	88	83	100	0.42
	VI : 10	A (severe)	E.K.	1951	+	6/59	100	4	—	*0.5—2*	93	0	147	78	105	0.49
28	VI : 5	A (severe)	A.K.	1960	+	5/62	75	1		*2*[2]	55	0	—	77	105	0.34
	Son of VI : 2	A (severe)	M.J.	1963	+	9/64	46	10		*0.3*	78	0	—	89	143	0.17
31	VI : 4	B (severe)	S.N.	1961	+	2/62	30	7	472,000	125	*0*	0	—	99	107	0.29
	VI : 5	B (severe)	H.N.	1962	+	8/64	25	2	284,000	100	< *1*	0	100	71	99	0.22
41	III : 10	B (mild)	K.R.O.	1904	+	5/63	9	2	—	66	*6*	0	—	125	108	0.31
	IV : 13	B (mild)	K.G.O.	1916	+	5/63	11	2	—	110	*10*	0	—	108	113	0.40
42	Son of V : 2	A (severe)	L.O.G.	1964	+	10/64	50	—		< *1*	55					

57	V : 1	A (severe)	H.B.	1947	+	7/61	90	4		*1.3*[2]	94	0	77	74	123	0.21
71	III : 7	B (mild)	J.A.	1884	+	5/63	—	3		113	*10*	0	—	74	140	0.26
						6/63	10				*8*					
73	IV : 22	A (severe)	A.J.	1945 †1964	+	1/63	> 60	3	402,000	< *1*	100	0	110	84	132	0.51
77	IV : 4	A (severe)	S.S.	1955	+	1/61	> 60	1	500,000	< *1*	68	0	43	88	165	0.33
83	IV : 25	A (severe)	P.O.	1946	0	1/63	> 60	3	342,000	< *1*	78	0	147	74	98	0.31
93	III : 15	A (mild)	G.R.	1938	+	7/61	20	2	260,000	*11*	110	0	33	126	155	0.70
94	III : 10	A (mild)	K.K.	1904	+	12/63	11	6	—	*10*	88					
100	III : 3	B (severe)	B.W.	1914	+	11/61	60	2	n	107	< *1*	0	—	69	150	—
	IV : 4	B (severe)	B.A.	1948	+	10/61	60	8	352,000	73	< *1*	0	80	49	114	0.45
109	IV : 3	B (moderate)	G.A.	1943	+	8/62	19	2	242,000	80	*2*	0	43	106	130	0.49
	IV : 6	B (moderate)	J.A.	1953 †1963	+	5/63				50	*3*	0		70	56	—
114	II : 7	A (severe)	T.J.	1937	+	10/62	21			1.5[3]	133	0	—	74	71	0.44
122	IV : 4	A (mild)	R.B.	1915	+	11/63	12	2	—	*16*	61	0	—	89	163	0.33
124	III : 2	B (moderate)	F.H.	1930	0	6/58	12	3	161,000	86	*0.5—2*	0	100	67	113	
						1/64	12			98	*1.4*	0	—	87	115	0.39
126	IV : 1	A (mild)	L.J.	1957	+	1/59	12	3	—	*6*	145	0	66	85	60	0.25
						3/61				*5*						
133	III : 11	A (moderate)	S.B.	1915	+	11/58	17	5	—	*4—5*	58	0	31	65	98	0.30
						3/59				*4*						
	IV : 4	A (moderate)	S.G.K.	1928	+	8/62	17	2		*2.5*		0	91	108	110	0.28
						9/62	18			*3.9*	110	0				
	IV : 6	A (moderate)	A.K.	1934	+	1/64	17	6		*3.3*	109	0	—	132	123	0.31
	IV : 15	A (moderate)	N.K.	1948	+	6/64	9	4		*7*	258	0	—	100	98	0.26
						6/64	9			*7*	175					
144	IV : 1	A (moderate)	J.E.K.	1941	+	8/61	26	4	250,000	*1.7*	83	0	70	115	107	0.30
	IV : 4	A (moderate)	B.N.	1939	+	9/62	40	1	262,000	*1.3*	113	0	113	140	139	0.60

Fam. No.	Coordinate No.	Type of haemophilia	Case	Year of birth	Heredity None=0 Pos. =+	Mth/yr of invest.	Coagulation time min.	Bleeding time (Duke) min.	Platelets per mm³	AHF % of normal	B-factor % of normal	Circulating anticoagulant	Prothrombin consumption residual %	P&P (pro-thrombin+ f. VII) %	Factor V % of normal	Fibrinogen g/100 ml
145	II : 2	A (mild)	A.H.	1927	+	2/61	13	4	—	*28*	103	0	—	77	105	—
						11/63	13			*21*						
	II : 6	A (mild)	H.H.	1942	+	2/61	19	2	—	*19*	55	0	—	59	96	—
						4/64	16			*23*						
	III : 4	A (mild)	K.H.	1953	+	1/61	12	1	200,000	*18*	80	0	8	110	110	0.36
						11/62	13			*21*						
	III : 5	A (mild)	R.H.	1956	+	1/61	14	3	200,000	*15*	95	0	93	66	75	0.41
						3/62	17			*20*						
147	IV : 6	A (severe)	K.S.	1961 †1963	+	5/62	> 60	3	n	< *1*	185	0	> 100	93	147	—
148	IV : 1	A (moderate)	P.W.	1956	+	3/61	—	—		*1.5*	90	0	105	90	85	0.38
151	IV : 1	B (severe)	T.K.	1959	+	11/62	> 60	5	—	91	*0*	0	—	81	94	0.33
153	III : 6	B (moderate)	B.E.	1945	0	10/62	40	3	242,000	135	*1*	0	10	91	140	0.31
						10/62					*1*					
158	IV : 7	A (severe)	S.K.	1939	+	4/62	> 60	3	352,000	*0.1*	100	0	61	80	90	0.51
159	V : 9	A (severe)	R.H.	1952	+	3/63	> 60	5	n	*0*	69	0	—	114	69	0.28
						10/64	> 60			< *1*						
160	IV : 3	A (moderate)	L.E.	1931	+	1/61	14	3		*2.5*	103	0	71	105	110	0.22
	IV : 5	A (moderate)	P.E.	1935	+	1/61	17	3		*2.7*	78	0	86	105	120	0.29
166	IV : 10	A (moderate)	E.R.O.	1892	+	5/62	20	3	224,000	*3*	150	0	85	112	190	0.71
169	III : 2	A (moderate)	B.S.	1909	0	10/61	60	1	226,000	*1.2*	112	0	100	62	114	0.32
170	IV : 1	A (moderate)	L.W.	1913	0	9/63	11	—	—	*1*	115	0	—	128	103	0.13
171	IV : 1	B (moderate)	T.Y.	1941	0	10/60	—	2	—	115	*3*	0	53	132	—	0.30
172	III : 4	A (severe)	J.B.	1908	+	9/60	> 60	3	214,000	*0.1*	123	0	80	120	150	0.36

174	III : 27	A (mild)	B.S.	1928	+	2/61	15	2		*9.5*	—	0	11	76	85	0.34
	III : 28	A (mild)	D.S.	1935	+	7/64	—	—	—	*12*	82	0	—	128	87	0.43
175	IV : 10	A (severe)	L.W.	1956	+	9/62	> 60	5	410,000	< *1*	93	0	70	144	155	0.38
176	IV : 14	B (severe)	L.G.L.	1959	+	2/61	8			133	*6.4*[4]	0	107	110	153	0.45
177	IV : 7	B (mild)	B.H.	1930	+	12/60	15	4	192,000	90	*12*	0	41	61	130	0.37
						8/64					*10*					
	IV : 8	B (mild)	S.O.H.	1935	+	10/60	17	2	304,000	64	*6*	0	83	78	73	0.23
	IV : 9	B (mild)	A.H.	1938	+	11/60	17	3	180,000	60	*12*	0	61	83	152	0.30
	V : 3	B (mild)	T.R.S.	1951	+	3/63	23	3	296,000	95	*9*	0	19	108	124	0.33
178	IV : 8	A (moderate)	M.L.	1938	+	2/60	31	3	368,000	*2*	55	0	180	120	133	0.56
179	IV : 10	A (severe)	G.L.	1945	0	10/60	—	3	—	< *1*	93	0	105	—	—	—
180	IV : 1	B (moderate)	L.O.K.	1939	+	4/62	31	2	248,000	102	*1.4*	0	—	65	106	0.38
	IV : 2	B (moderate)	G.K.	1943	+	2/61	13	1	—	65	*1.4*	0	35	93	66	0.28
181	IV : 8	A (severe)	H.W.	1958	+	4/61	52	6	354,000	*0.1*	100	0	157	106	111	0.37
						8/63	60			*0.1*						
						4/65				*0.1*						
182	IV : 1	A (severe)	I.E.	1938	0	5/61	60	2	344,000	< *1*	95	0	100	59	139	0.28
183	IV : 11	B (severe)	B.A.	1947	0	5/61	28	2	322,000	119	< *1*	0	92	55	105	0.45
						1/64	60				< *1*	0		52	100	
184	IV : 9	A (moderate)	P.B.	1955	+	12/60	17	2		*2.6*	74	0	75	102	113	0.26
	IV : 10	A (moderate)	T.B.	1958	+	11/62	—	4	285,000	< *15*[3]	58	0	76	88	150	
						4/65	26			*4*						
						5/65				*3*						
185	IV : 1	B (severe)	A.E.	1954	+	6/64	15	4	—	74	*0.5*	0	patol.	105	107	0.30
186	IV : 6	A (severe)	A.M.	1960	+	6/61	—	5	···	*0.4*	89	0	73	133	160	0.53
187	IV : 5	A (mild)	J.L.	1890	+	8/60	8	2	185,000	*23*			80	92		
						1/63				*16*						
188	IV : 5	A (mild)	L.P.	1949	+	7/61	19	4	314,000	*8*	90	0	100	110	148	0.35

Fam. No.	Coordinate No.	Type of haemophilia	Case	Year of birth	Heredity None=0 Pos. = +	Mth/yr of invest.	Coagulation time min.	Bleeding time (Duke) min.	Platelets per mm³	AHF % of normal	B-factor % of normal	Circulating anticoagulant	Prothrombin consumption residual %	P&P (pro-thrombin + f. VII) %	Factor V % of normal	Fibrinogen g/100 ml
189	IV : 6	A (severe)	I.O.	1958	+	7/61	60	2	314,000	*0.7*	90	0	100	78	98	0.25
	IV : 7	A (severe)	S.O.	1960	+											
190	III : 1	A (severe)	M.E.	1926	?	3/59	43	4	206,000	*0.4*	55	0	108	85	60	0.35
						11/61	53			*0.1*						
191	VI : 9	A (mild)	J.E.C.	1953	+	10/61	17	4		*6*	68	0	—	77	61	0.29
192	IV : 3	A (moderate)	M.L.	1918	0	9/61	12	3		*2*	84	0	90	89	93	0.36
193	IV : 3	A (mild)	S.T.	1936	+	10/63	24	2	312,000	*24*	70	0	23	85	84	0.23
	IV : 4	A (mild)	P.G.	1943	+	5/62	12	1	260,000	*22*	148	0	71	124	89	0.31
194	VI : 6	A (mild)	A.A.	1922	+	10/58	10	6	n	*16*	134	0	—	102	81	0.69
						2/62	17	5		*23*	130	0	—	83	93	0.44
						3/63				*25*						
195	II : 16	A (mild)	N.L.	1876 †1962	+	10/62	—	—	—	*39*[3]	248	0	—	56	51	0.42
	IV : 3	A (mild)	R.B.	1940	+	9/61	12	3	288,000	*23*	105	0	33	69	88	0.27
	IV : 5	A (mild)	R.B.	1946	+	2/62	6	2	294,000	*25*	78	0	44	97	105	—
	IV : 9	A (mild)	K.P.	1945	+	11/61	12	2		*30*	66	0	—	—	—	0.24
						2/62	12	3		*34*	78	0	—	71	80	0.27
196	IV : 1	A (severe)	K.A.	1961	+	10/61	29	3		*0.2*	87	0	—	61	82	—
197	II : 2	A (mild)	E.M.	1891	+	11/61	14	3	155,000	*13*	130	0	—	115	93	0.31
198	IV : 27	A (mild)	K.W.	1943	0	1/62	20	4	172,000	*11*	89	0	52	82	99	0.27
199	II : 1	A (moderate)	D.S.	1912	+	2/62	7	2	233,000	*4*	73	0	15	66	60	0.32
200	IV : 8	A (moderate)	B.J.	1959	0	2/62	16	—	—	*2*	96	0	—	103	139	0.38
201	III : 7	A (moderate)	B.J.	1933	+	3/62				*2*	138	0	—	140	172	—
						2/63	15	5		*1.1*						0.29

202	III : 6	B (mild)	E.S.	1919	+	3/62	10	2	170,000	116	*15*	0	—	77	62	0.28
203	—	A (mild)	K.S.	1919	0	5/62	20	3	236,000	*6*	123	0	68	60	51	0.21
204	IV : 16	A (mild)	E.G.	1918	+	9/62	16	4	406,000	*12*	140	0	17	170	127	0.55
						1/64	18			*13*						
	IV : 25	A (mild)	Å.G.	1925	+	6/62	18	3	186,000	*11*	118	0	72	80	131	0.32
206	VI : 9	A (mild)	L.E.	1938	+	6/62	10	6	—	*20*	70	0	—	94	95	0.31
	VI : 10	A (mild)	K.E.	1944	+	6/62	11	6	—	*20*	107	0	—	96	82	0.26
207	IV : 3	A (severe)	L.G.K.	1959	+	7/62	75	5	188,000	*0.1*	88	0	100	86	90	0.33
208	IV : 1	A (moderate)	P.S.	1960	+	8/62	22	2	276,000	*3*	115	0	110	115	101	0.38
209	IV : 3	A (severe)	B.Å.A.	1961	+	8/62	42	4	—	*0.8*	79	0	—	79	62	0.20
210	—	A (severe)	L.G.L.	1936	0	8/62	30	8	179,000	< *1*	103	0	72	105	109	0.31
212	IV : 9	A (mild)	B.L.	1910	+	10/62	—	2	228,000	*8*	85	0	34	140	106	0.36
	IV : 11	A (mild)	L.L.	1901	+	12/62	—	5	142,000	*8*	103	0	46	105	163	0.37
	IV : 13	A (mild)	B.A.L.	1910	+	12/62	—	4	203,000	*9*	78	0	37	144	161	0.30
	IV : 14	A (mild)	E.L.	1920	+	12/62	—	6	124,000	*6*	60	0	50	93	183	0.27
213	IV : 4	A (severe)	L.E.H.	1953	+	9/62	> 60	2		*1.9*	70	0	—	81	67	0.32
						8/63	> 60			*0.5*						
						8/63	> 60			*0.5*						
214	—	B (mild)	J.J.	1942	?	11/62	12	5	—	54	*5*	0	—	70	89	0.26
215	IV : 32	B (severe)	S.P.	1957	+	11/62	150	—	—	77	*0*	0	—	83	99	0.35
216	IV : 4	A (mild)	I.E.	1953	+	9/64	—	3	290,000	*13*	86	0	—	97	60	0.30
	IV : 8	A (mild)	G.M.	1955	+	12/62	—	3	162,000	*8*	85	0	—	138	96	0.30
217	III : 1	A (mild)	E.K.	1911	+	3/63	11	—	—	*23*	105	0	—	108	118	0.41
	III : 4	A (mild)	S.K.	1926	+	3/63	10	—	—	*32*	75	0	—	89	110	0.37
	IV : 7	A (mild)	L.C.	1950	+	1/63	13	5	—	*36*	92	0	—	118	120	0.45
						2/63	13	—	—	*34*						
218	IV : 13	A (mild)	K.R.	1917	+	12/60	14	7	—	*21*	67	0	16	110	100	0.33
						12/62	15	4	—	*35*	140	0	—	118	200	0.32

Fam. No.	Coordinate No.	Type of haemophilia	Case	Year of birth	Heredity None=0 Pos. = +	Mth/yr of invest.	Coagulation time min.	Bleeding time (Duke) min.	Platelets per mm³	AHF % of normal	B-factor % of normal	Circulating anticoagulant	Prothrombin consumption residual %	P&P (pro-thrombin + f. VII) %	Factor V % of normal	Fibrinogen g/100 ml
219	IV : 10	A (mild)	F.P.	1933	0	2/58	10	3—5	—	*36*	105	0	—	78	70	
						1/63	8	6		*39*	63	0		110	135	0.22
						2/65	6			*40*						
220	II : 5	A (mild)	E.N.	1908	+	7/63	12		34,000	*21*[4]	93	0		60	71	0.46
				†1963		7/63				*15*[4]						
	III : 5	A (mild)	A.H.	1928	+	6/63	19	2	276,000	*11*	118	0	27	110	94	0.36
						6/64				*12*						
	III : 8	A (mild)	S.Å.A.	1937	+	6/63	19	3	272,000	*11*	118	0	57	81	93	0.38
						6/63				*9*						
221	VII : 2	B (mild)	T.H.	1957	+	7/63	16	3	272,000	177	*14*	0	42	114	119	0.35
222	IV : 2	A (mild)	B.J.	1936	+	4/64	8	6	n	*6*	84	0	patol.	93	101	0.22
	IV : 7	A (mild)	M.N.	1930	+	6/63	8	2	—	*5*	88	0	—	91	85	0.18
	IV : 8	A (mild)	Y.N.	1931	+	4/63	9	1	195,000	*6*	56	0	—	75	63	0.26
	V : 2	A (mild)	J.R.	1958	+	4/64	8	2	n	*7*	108	0	patol.	102	103	—
223	IV : 14	A (mild)	H.N.	1933	+	5/63	15	4		*21*	66	0	—	98	135	0.28
						6/63	7			*9*						
						10/63				*12*						
	IV : 15	A (mild)	G.N.	1935	+	2/63	13	4	—	*9*	67	0	—	97	98	0.21
	IV : 16	A (mild)	R.N.	1937	+	8/63	6	3	—	*12*	72	0	—	85	108	0.22
						10/63				*10*						
	IV : 17	A (mild)	C.N.	1946	+	8/63	12	6	—	*14*	66	0	—	84	115	0.21
						10/63				*14*						
224	IV : 9	A (mild)	L.G.T.	1960	+	5/63	10	3	240,000	*5*	98	0	—	99	113	0.24
	IV : 11	A (mild)	T.O.	1959	+	10/63	6	3	218,000	*14*	89	0	—	102	129	0.32
225	IV : 9	A (mild)	J.O.L.	1952	+	11/63	10	1	250,000	*35*	113	0	—	89	102	0.30
						12/63				*18*						

226	IV : 22	A (mild)	K.S.	1949	+	10/62	11	4		*25*	—	—	—	83	—	0.25
	IV : 25	A (mild)	R.W.	1950	+	11/63	10	1		*23*	96	—	—	84	69	0.23
227	IV : 22	A (severe)	M.L.	1961	+	12/64	—	—		*0.5*						0.25
228	III : 2	B (mild)	J.K.	1938	+	2/64	12	3	218,000	87	*21*	0	75	91	112	0.31
229	II : 1	B (mild)	J.H.	1934	0	12/63	22	5	298,000	115	*16*	0	26	102	120	0.43
230	—	A (mild)	V.N.	1913	?	10/63	9	3	—	*10*	78	0	—	99	82	0.29

[1] Blood sampling not adequate
[2] It has not been possible to check the value
[3] The test performed on a mailed blood sample
[4] After blood transfusion
n=Normal value

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