# PAPERS AND SHORT REPORTS



## Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976-80: report on behalf of the directors of haemophilia centres in the United Kingdom

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**Abstract**

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

### Introduction

ORGANISATION OF TREATMENT

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

Each reference centre is responsible for the provision of an advisory clinical and laboratory service to individual haemophilia centres in a wide area (referred to as a "supraregion"). Some centres have staff, laboratory and clinical facilities, and funds specifically allocated for the haemophilia work, but most centres are run by the staff of haematology departments, medical departments, or blood transfusion centres as part of their routine service commitment. All haemophilia centres, irrespective of category, are expected to provide 24 hour emergency treatment for haemophilic patients. The number of patients treated each year by centres varies considerably (fig 1). One third of all

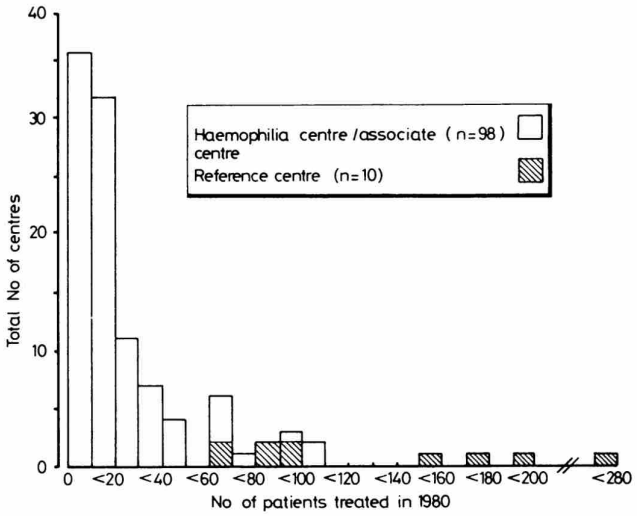


FIG 1—Numbers of patients treated during 1980 at haemophilia centres in United Kingdom.

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centres treated fewer than 10 patients in 1980 and two thirds treated fewer than 20.

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

## Report

### NUMBERS OF PATIENTS WITH HAEMOPHILIA A AND B

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

Tables IIm and IIIm show the age and severity groupings of the patients. To facilitate comparison with other reports these tables also show the total number of haemophiliacs in each age group in December 1974 and the percentage of male subjects in each age group in the normal male population (1971 Census). Of the 4321 known patients with haemophilia A and the 777 with haemophilia B, 1903 (44%) and 276 (36%) were severely affected. There was a preponderance of patients aged 10-40 when compared with normal males but a relative deficiency in patients aged less than 10 years or more than 40. When the severely affected patients (factor VIII value $<2\%$ of average normal) and mildly affected patients (factor VIII value $>2\%$ of average normal) were considered as separate groups there was, as expected, a much smaller proportion of severely affected patients aged above 50 compared with mildly affected patients. On the other hand, there seemed to be proportionately fewer patients aged less than 20 in the mildly affected group than in the severely affected group. This latter difference may have been due to delay in the diagnosis of the mild form of the condition. Compared to 1974 a larger proportion of haemophiliacs seemed to be reaching middle and old age; a quarter of the patients with haemophilia A in 1980 were more than 40 years of age compared with one fifth in 1974.

### AGE AT DEATH AND CAUSES OF DEATH

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

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

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

### AMOUNT AND TYPES OF THERAPEUTIC MATERIAL USED

Figures 2 and 3 show the long term changes in usage of the different blood products, and tables VIm and VIIm show in more detail the type and amount of the various therapeutic materials used in the management of haemophilia A and B during 1976-80. The total amount of factor VIII used steadily increased each year from $33{\cdot}716 \times 10^6$ units in 1976 to $57{\cdot}0 \times 10^6$ units in 1980. In 1976 nearly

### MINIPRINT TABLES Im-IVm

Im

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

| Year | Haemophilia A: Cumulative No of patients registered | Haemophilia A: Cumulative No (%) with factor VIII antibodies | Haemophilia A: No of new antibody cases detected | Haemophilia B: Cumulative No of patients registered | Haemophilia B: Cumulative No (%) with factor IX antibodies | Haemophilia B: No of new antibody cases detected |
|---|---|---|---|---|---|---|
| 1975 | 2839 | 182 (6·4) | 18 | 463 | 5 (1·1) | 0 |
| 1976 | 3192 | 195 (6·1) | 18 | 548 | 5 (0·9) | 0 |
| 1977 | 3546 | 208 (5·9) | 20 | 621 | 6 (1·0) | 1 |
| 1978 | 3914 | 225 (5·8) | 17 | 686 | 6 (0·9) | 0 |
| 1979 | 4122 | 245 (5·9) | 19 | 725 | 7 (1·0) | 1 |
| 1980 | 4321 | 258 (6·0) | 13 | 777 | 7 (0·9) | 0 |

IIm

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

| Age (years) | Factor VIII value (%, average normal): <2 | 2-10 | >10 | NK | Total: No | Total: % | Figures for 1974: Total No | Figures for 1974: % | Normal males in UK population (%)* |
|---|---|---|---|---|---|---|---|---|---|
| <5 | 114 | 58 | 30 | 4 | 206 | 4·8 | 129 | 5·1 | 8·4 |
| 5-9 | 154 | 103 | 49 | 16 | 322 | 7·4 | 289 | 11·4 | 8·4 |
| 10-19 | 480 | 260 | 184 | 38 | 962 | 22·3 | 646 | 25·5 | 15·0 |
| 20-29 | 429 | 232 | 144 | 34 | 839 | 19·4 | 599 | 20·0 | 14·5 |
| 30-39 | 322 | 186 | 130 | 32 | 670 | 15·5 | 529 | 13·0 | 12·2 |
| 40-49 | 186 | 139 | 86 | 22 | 443 | 10·2 | 252 | 6·7 | 12·6 |
| 50-59 | 88 | 109 | 64 | 20 | 311 | 7·2 | 158 | 5·2 | 12·0 |
| 60-69 | 67 | 76 | 57 | 15 | 215 | 5·0 | 71 | 3·3 | 10·0 |
| ≥70 | 30 | 45 | 41 | 5 | 121 | 2·8 | 42 | 1·6 | 5·7 |
| NK | 23 | 28 | 14 | 167 | 232 | 5·4 | 130 | 5·1 | — |
| Total (%) | 1903 (44·0) | 1236 (28·6) | 829 (19·2) | 353 (8·2) | 4321 (100·0) | 100·0 | 2538 | 100·0 | 99·1 |

NK = Not known. *Figures from 1971 Census.

IIIm

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

| Age (years) | Factor IX value (%, average normal): <2 | 2-10 | >10 | NK | Total: No | Total: % | Figures for 1974: Total No | Figures for 1974: % | Normal males in UK population (%)* |
|---|---|---|---|---|---|---|---|---|---|
| <5 | 18 | 15 | 6 | 0 | 39 | 5·0 | 22 | 5·8 | 8·4 |
| 5-9 | 25 | 28 | 15 | 1 | 69 | 8·9 | 39 | 10·3 | 8·4 |
| 10-19 | 70 | 60 | 30 | 8 | 168 | 21·6 | 107 | 28·2 | 15·0 |
| 20-29 | 57 | 48 | 37 | 7 | 149 | 19·2 | 72 | 19·0 | 14·5 |
| 30-39 | 54 | 35 | 24 | 10 | 123 | 15·8 | 39 | 10·3 | 12·2 |
| 40-49 | 21 | 34 | 10 | 7 | 72 | 9·3 | 20 | 5·3 | 12·6 |
| 50-59 | 14 | 19 | 10 | 3 | 46 | 5·9 | 21 | 5·5 | 12·0 |
| 60-69 | 8 | 19 | 8 | 7 | 42 | 5·4 | 11 | 2·9 | 10·0 |
| ≥70 | 5 | 13 | 6 | 4 | 28 | 3·6 | 10 | 2·6 | 5·7 |
| NK | 4 | 5 | 2 | 28 | 41 | 5·3 | 18 | 4·8 | — |
| Total (%) | 276 (35·5) | 275 (35·4) | 151 (19·4) | 75 (9·7) | 777 (100·0) | 100·0 | 379 | 100·0 | 99·1 |

NK = Not known. *Figures from 1971 Census.

IVm

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

| | Age (years): <10 | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | ≥70 | NK | Total | Total at risk in severity groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Haemophilia A* | | | | | | | | | | | |
| Factor VIII value*: <2 | 4 | 2 | 12 | 13 | 7 | 7 | 9 | 4 | — | 58 | 1903 |
| 2-10 | 1 | — | — | 4 | 1 | 2 | 5 | 7 | — | 20 | 1236 |
| >10 | — | 1 | — | 1 | — | 1 | 2 | 3 | 1 | 8 | 829 |
| NK | — | — | — | — | 1 | — | — | 1 | 1 | 3 | 353 |
| Total | 5 | 3 | 12 | 18 | 9 | 10 | 16 | 15 | 1 | 89 | — |
| Total at risk in age groups | 528 | 962 | 839 | 670 | 443 | 311 | 215 | 121 | 232 | — | 4321 |
| *Haemophilia B* | | | | | | | | | | | |
| Factor IX value*: <2 | — | — | — | 1 | — | 2 | 3 | 1 | — | 7 | 276 |
| 2-10 | 1 | 1 | 1 | — | 2 | — | 2 | 1 | — | 8 | 275 |
| >10 | 1 | — | — | — | — | — | — | — | 2 | 3 | 151 |
| NK | — | — | — | 1 | — | — | — | — | 1 | 2 | 75 |
| Total | 2 | 1 | 1 | 2 | 2 | 2 | 5 | 3 | — | 18 | — |
| Total at risk in age groups | 106 | 168 | 149 | 123 | 72 | 46 | 42 | 28 | 41 | — | 777 |

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

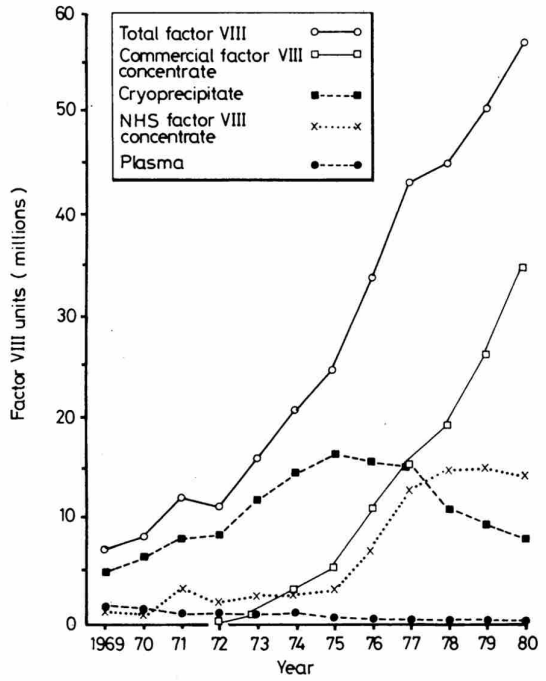


FIG 2—Amount of different types of materials containing factor VIII and total amount of factor VIII activity units used each year during 1969-80 by haemophilia centres in United Kingdom to treat patients for haemophilia A.

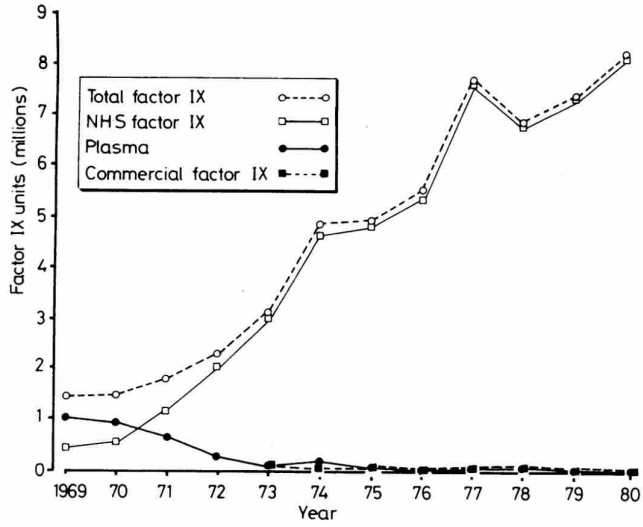


FIG 3—Amount of different types of materials containing factor IX and total amount of factor IX activity units used each year during 1969-80 by haemophilia centres in United Kingdom to treat patients for haemophilia B.

half of the factor VIII used was in the form of cryoprecipitate. Usage of this material decreased during the survey period and in 1980 accounted for only 14% of the total number of factor VIII units given. The use of commercial factor VIII concentrate, on the other hand, showed a steady increase each year and in 1980 represented 60% of the total factor VIII used.

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

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

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

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

## MINIPRINT TABLES Vm–IXm

Vm

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

| Causes | Haemophilia A | Haemophilia B |
|---|---|---|
| Cerebral haemorrhage/"stroke" | 26 (5) | 4 (1) |
| Other types of bleeding | 11 (6) | 1 |
| Postoperative complications | 6 (2) | — |
| Suicide | 5 | — |
| Neoplasm | 7 | 3 |
| Pulmonary embolism | 2 | — |
| Pneumonia | 4 | — |
| Hepatitis | 1 (1) | 1 |
| Myocardial infarct | 1 | 3 |
| Accidents | 4 | 2 |
| Not known | 11 (1) | 4 |
| Miscellaneous non-haemorrhagic conditions | 11 (5) | — |
| Total | 89 (20) | 18 (1) |

VIm

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

| Material | Factor VIII units | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1976 | | 1977 | | 1978 | | 1979 | | 1980 | |
| | Amount | % Total | Amount | % Total | Amount | % Total | Amount | % Total | Amount | % Total |
| Plasma | 15 000 | < 0·1 | 1 000 | < 0·1 | 5 000 | < 0·1 | 32 000 | < 0·1 | 1 000 | < 0·1 |
| Cryoprecipitate | 15 717 000 | 46·6 | 15 226 000 | 35·3 | 10 980 000 | 24·4 | 9 414 000 | 18·1 | 8 153 000 | 14·2 |
| NHS factor VIII concentrate | 6 915 000 | 20·5 | 12 949 000 | 30·0 | 14 800 000 | 32·9 | 15 092 000 | 30·0 | 14 366 000 | 25·1 |
| Commercial factor VIII concentrate | 11 069 000 | 32·8 | 15 017 000 | 34·8 | 19 273 000 | 42·8 | 26 178 000 | 53·0 | 34 749 000 | 60·7 |
| Total | 33 716 000 | 100·0 | 43 193 000 | 100·0 | 45 058 000 | 100·0 | 50 716 000 | 100·0 | 57 271 000 | 100·0 |
| No of patients treated | 1 866 | — | 1 975 | — | 2 048 | — | 2 053 | — | 2 107 | — |
| Average amount of factor VIII used per patient | 17 877 | — | 21 870 | — | 22 000 | — | 24 703 | — | 27 181 | — |

VIIm

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

| Material | Factor IX units | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1976 | | 1977 | | 1978 | | 1979 | | 1980 | |
| | Amount | % Total | Amount | Total | Amount | % Total | Amount | % Total | Amount | % Total |
| Plasma | 18 000 | 0·3 | 31 000 | 0·4 | 28 000 | 0·4 | 3 000 | 0·1 | 1 000 | 0·1 |
| NHS factor IX concentrates | 5 533 000 | 99·5 | 7 621 000 | 98·9 | 6 789 000 | 99·4 | 7 362 000 | 100·0 | 8 194 000 | 99·1 |
| Commercial factor IX concentrates | 12 000 | 0·2 | 52 000 | 0·7 | 11 000 | 0·2 | Nil | — | 77 000 | 0·9 |
| Total | 5 561 000 | 100·0 | 7 704 000 | 100·0 | 6 827 000 | 100·0 | 7 365 000 | 100·0 | 8 272 000 | 100·0 |
| No of patients treated | 296 | — | 332 | — | 330 | — | 344 | — | 355 | — |
| Average amount of factor IX used per patient | 18 794 | — | 23 205 | — | 20 688 | — | 21 410 | — | 23 301 | — |

VIIIm

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

| | 1977 | 1978 | 1979 | 1980 |
|---|---|---|---|---|
| | *Haemophilia A* | | | |
| No of patients with antibodies treated | 114 | 131 | 124 | 121 |
| Human factor VIII | 2 589 000 | 3 249 000 | 4 011 000 | 4 491 000 |
| Porcine factor VIII | 16 000 | | 279 000 | 378 000 |
| NHS factor IX | 266 000 | 124 000 | 50 000 | 214 000 |
| Commercial factor IX (Prothrombplex*) | 10 000 | 12 000 | 3 000 | |
| Activated prothrombin complex concentrates | | | | |
| †EEIBA* | 2 329 000 | 1 928 000 | 821 000 | 647 000 |
| Proplex* | 2 467 | 149 000 | | |
| Autoplex* | | | | 81 000 |
| | *Haemophilia B* | | | |
| No of patients with antibodies treated | 3 | 2 | 1 | 2 |
| NHS factor IX concentrate | 37 000 | 34 000 | 36 000 | 85 000 |

*Units of activity as defined by manufacturers concerned.

IXm

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

| Age (years) | Factor VIII value (% average normal) | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <2 | | 2-10 | | >10 | | Not known | | | |
| | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT |
| 5 | 84 | 7 (8·3) | 27 | 2 (7·4) | 4 | 0 — | 0 | 0 — | 115 | 9 (7·8) |
| 5-9 | 119 | 69 (58·0) | 96 | 33 (22·4) | 18 | 1 (5·6) | 3 | 2 (67·0) | 198 | 85 (42·9) |
| 10-19 | 398 | 293 (73·6) | 138 | 31 (22·5) | 45 | 2 (4·3) | 4 | 0 — | 585 | 326 (55·5) |
| 20-29 | 322 | 206 (64·6) | 94 | 18 (19·2) | 29 | 0 — | 4 | 0 — | 449 | 226 (50·3) |
| 30-39 | 234 | 154 (65·8) | 56 | 7 (11·9) | 31 | 2 (6·5) | 1 | 0 — | 325 | 163 (50·2) |
| 40-49 | 137 | 73 (53·3) | 41 | 4 (9·8) | 16 | 0 — | 4 | 0 — | 198 | 77 (39·3) |
| 50-59 | 75 | 31 (41·3) | 42 | 6 (14·3) | 19 | 0 — | 2 | 0 — | 138 | 37 (26·8) |
| 60-69 | 33 | 8 (24·2) | 18 | 2 (11·1) | 8 | 0 — | 2 | 0 — | 61 | 10 (16·4) |
| ≥70 | 15 | 3 (20·0) | 12 | 0 — | 5 | 0 — | 0 | 0 — | 32 | 3 (9·4) |
| NK | 2 | 1 (50·0) | 5 | 1 (20·0) | 1 | 0 — | 8 | 0 — | 16 | 2 (12·5) |
| Total | 1419 | 847 (59·7) | 494 | 84 (17·0) | 176 | 5 (2·8) | 28 | 2 (7·1) | 2117 | 938 (44·3) |
| Total treated as % of total known* | 74·6 | — — | 40·0 | — — | 21·2 | — — | 7·9 | — — | 49·0 | — — |

NK = Not known *See table IIm.

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

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

### HOME TREATMENT

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

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

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

Information about carriers and patients with von Willebrand's disease treated by haemophilia centres has been collected since 1976. Table XIIIm gives the total numbers of carriers of haemophilia A and patients with von Willebrand's disease treated during 1976-80 and the amounts and types of blood products used. With regard to types of material used to treat carriers of haemophilia A, the use of cryoprecipitate and NHS factor VIII fluctuated greatly from year to year but there was a steady increase in the use of commercial factor VIII. In addition to the patients treated with blood products, four mildly affected carriers of haemophilia A were treated with desmopressin only. The total amount of factor VIII used in any one year for the treatment of carriers of haemophilia A accounted for less than 1% of the total factor VIII used in Britain. Throughout the period of the survey cryoprecipitate was the therapeutic material most used for the treatment of von Willebrand's disease, accounting for 75-90% of the factor VIII given to those patients. Besides preparations containing factor VIII other materials were infrequently used: in 1977 a patient with von Willebrand's disease and antibodies against factor VIII was treated with an activated prothrombin complex concentrate (FEIBA; "factor eight inhibitor bypassing activity") and porcine factor VIII, and in 1977, 1978, 1979, and 1980 desmopressin was given to two, four, nine, and nine patients, respectively. The total amount of factor VIII used in any one year to treat carriers of haemophilia A and patients with von Willebrand's disease accounted for only 3-4% of the total factor VIII used in Britain.

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

### HEPATITIS

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

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

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

## Discussion

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

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

### MINIPRINT TABLES Xm-XIVm

**Xm**

TABLE X—*Materials used for home treatment of patients with haemophilia A during 1980*

| Material | Total factor VIII units used for all patients | Factor VIII units used for home treatment only | % of material used for home treatment |
|---|---|---|---|
| Plasma | 1 000 | Nil | — |
| Cryoprecipitate | 8 153 000 | 1 043 000 | 12·8 |
| NHS factor VIII concentrate | 14 368 000 | 7 458 000 | 51·9 |
| Commercial factor VIII concentrate | 34 749 000 | 17 679 000 | 50·9 |
| Total units | 57 271 000 | 26 180 000 | 45·7 |
| No of patients treated | 2 107 | 938 | 44·5 |
| Average amount used per patient | 27 181 | 27 910 | — |

In addition 11 500 units factor eight inhibitor bypassing activity (1·7% of total FEIBA used) was supplied for home treatment.

**XIm**

TABLE XI—*Numbers of patients with haemophilia B treated by haemophilia centres during 1980, showing severity of coagulation defect, age, and proportion receiving home treatment*

| Age (years) | Factor IX value (% average normal) | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <2 | | 2-10 | | >10 | | Not known | | | |
| | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT | No treated | No (%) on HT |
| <5 | 14 | 1 (7·1) | 8 | 0 | 1 | 0 | 0 | 0 | 23 | 1 (4·4) |
| 5-9 | 20 | 14 (70·0) | 13 | 2 (15·4) | 4 | 0 | 0 | 0 | 37 | 16 (43·2) |
| 10-19 | 58 | 39 (67·2) | 32 | 12 (37·5) | 7 | 1 (14·3) | 1 | 0 | 98 | 52 (53·1) |
| 20-29 | 45 | 25 (55·6) | 19 | 3 (15·8) | 8 | 1 (12·5) | 0 | 0 | 72 | 29 (40·3) |
| 30-39 | 37 | 24 (64·9) | 7 | 2 (28·6) | 6 | 0 | 5 | 0 | 55 | 26 (47·3) |
| 40-49 | 18 | 9 (50·0) | 13 | 2 (23·1) | 1 | 0 | 2 | 1 (50·0) | 34 | 12 (35·3) |
| 50-59 | 9 | 2 (22·2) | 7 | 1 (14·3) | 0 | 0 | 2 | 0 | 18 | 3 (16·7) |
| 60-69 | 4 | 1 (25·0) | 4 | 0 | 0 | 0 | 1 | 0 | 9 | 1 (11·1) |
| ≥70 | 3 | 1 (33·3) | 3 | 2 (66·7) | 0 | 0 | 1 | 0 | 7 | 3 (42·9) |
| NK | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 0 |
| Total | 208 | 116 (55·8) | 106 | 24 (22·6) | 28 | 2 (7·1) | 13 | 1 (7·7) | 355 | 143 (40·3) |
| Total treated as % of total known* | 75·4 | | 38·6 | | 18·5 | | 17·3 | | 45·7 | |

NK = Not known. *See table IIIm.

**XIIm**

TABLE XII—*Materials used for home treatment of patients with haemophilia I during 1980*

| Material | Total factor IX units used for all patients | Factor IX units used for home treatment only | % of total of each material used for home treatment |
|---|---|---|---|
| Plasma | 1 000 | | Nil |
| NHS factor IX concentrate | 8 194 000 | 4 170 000 | 50·9 |
| Commercial factor IX concentrate | 77 000 | 75 000 | 97·4 |
| Total units | 8 272 000 | 4 245 000 | 51·3 |
| No of patients treated | 355 | 143 | 40·3 |
| Average amount used per patient | 23 301 | 29 685 | |

**XIIIm**

TABLE XIII—*Type and amount of materials used by haemophilia centres in 1976-80 to treat patients with von Willebrand's disease and carriers of haemophilia A*

| Human blood products used | Factor VIII units | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1976 | | 1977 | | 1978 | | 1979 | | 1980 | |
| | Total used | % total | Total used | % total | Total used | % total | Total used | % total | Total used | % total |
| *Patients with von Willebrand's disease* | | | | | | | | | | |
| Plasma | 9 000 | 1·1 | 10 000 | 0·6 | 16 000 | 1·2 | 9 000 | 0·6 | 4 000 | 0·3 |
| Cryoprecipitate | 674 000 | 84·7 | 1 419 000 | 89·1 | 1 030 000 | 79·5 | 984 000 | 63·5 | 1 074 000 | 74·1 |
| NHS factor VIII concentrate | 41 000 | 5·2 | 86 000 | 5·4 | 171 000 | 13·2 | 221 000 | 14·3 | 113 000 | 7·8 |
| Commercial factor VIII concentrate | 72 000 | 9·1 | 78 000 | 4·9 | 79 000 | 6·1 | 335 000 | 21·6 | 258 000 | 17·8 |
| Total | 796 000 | 100·0 | 1 593 000 | 100·0 | 1 296 000 | 100·0 | 1 549 000 | 100·0 | 1 449 000 | 100·0 |
| No of patients treated | 186 | | 231 | | 240 | | 247 | | 244 | |
| Average amount used per patient | 4 280 | | 6 896 | | 5 400 | | 6 271 | | 5 939 | |
| *Carriers of haemophilia A* | | | | | | | | | | |
| Plasma | 1 000 | 1·8 | 3 000 | 1·5 | | | | | | |
| Cryoprecipitate | 16 000 | 28·1 | 26 000 | 46·4 | 141 000 | 71·9 | 61 000 | 45·5 | 31 000 | 21·7 |
| NHS factor VIII concentrate | 36 000 | 63·2 | 22 000 | 39·3 | 25 000 | 12·8 | 43 000 | 32·1 | 24 000 | 16·8 |
| Commercial factor VIII concentrate | 5 000 | 8·8 | 7 000 | 12·5 | 27 000 | 15·8 | 30 000 | 23·4 | 88 000 | 61·5 |
| Total | 57 000 | 100·0 | 56 000 | 100·0 | 196 000 | 100·0 | 134 000 | 100·0 | 143 000 | 100·0 |
| No of patients treated | 19 | | 42 | | 30 | | 28 | | 28 | |
| Average amount used per patient | 3 000 | | 1 333 | | 6 533 | | 3 526 | | 5 107 | |

**XIVm**

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

| Coagulation defect | 1976 | | | 1977 | | | 1978 | | | 1979 | | | 1980 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total No of patients treated | Cases of hepatitis | | Total No of patients treated | Cases of hepatitis | | Total No of patients treated | Cases of hepatitis | | Total No of patients treated | Cases of hepatitis | | Total No of patients treated | Cases of hepatitis | |
| | | No | % of treated patients | | No | % of treated patients | | No | % of treated patients | | No | % of treated patients | | No | % of treated patients |
| Haemophilia A | 1886 | 61 | 3·2 | 1975 | 70 | 3·5 | 2048 | 57 | 2·8 | 2053 | 34 | 1·7 | 2107 | 52 | 2·5 |
| Haemophilia B | 296 | 7 | 2·4 | 332 | 8 | 2·4 | 330 | 3 | 0·9 | 344 | 3 | 0·9 | 355 | 2 | 0·6 |
| von Willebrand's disease | 186 | 4 | 2·2 | 231 | 4 | 1·7 | 240 | 10 | 4·2 | 247 | 9 | 3·6 | 235 | 9 | 3·8 |
| Haemophilia A carrier | 19 | 1 | 5·3 | 42 | 1 | 2·4 | 30 | Nil | | 28 | Nil | | 28 | Nil | |
| Haemophilia B carrier | 5 | Nil | | 9 | Nil | | 7 | Nil | | 9 | Nil | | 12 | Nil | |
| Total | 2392 | 73 | 3·1 | 2589 | 83 | 3·2 | 2655 | 70 | 2·6 | 2681 | 46 | 1·7 | 2737 | 63 | 2·3 |

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

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

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

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

We are grateful to Dr A Barr and Mr J Ennis, of the Oxford Regional Health Authority's statistics department, for constructing the life tables (see appendix Im) and for much useful advice and discussion. We thank the directors and staff of the haemophilia centres for their help with the survey (see appendix IIm). We are also grateful to the staff of the Oxford Regional Computer Unit for setting up and maintaining a confidential computer system for handling the patient data, Mrs Patricia Lawrence for typing the manuscript, and Mr R H Matchett for drawing the diagrams.

## References

1 Biggs R. Jaundice and antibodies directed against factors VIII and IX in patients treated for haemophilia or Christmas disease in the United Kingdom. *Br J Haematol* 1974;**26**:313-29.
2 Biggs R, Spooner RJD. Haemophilia treatment in the United Kingdom from 1969 to 1974. *Br J Haematol* 1977;**35**:487-504.
3 Biggs R, Spooner RJD. Haemophilia centre directors' annual statistics for 1975. *Br J Haematol* 1977;**36**:447-9.
4 Biggs R, Spooner RJD. National survey of haemophilia and Christmas disease patients in the United Kingdom. *Lancet* 1978;i:1143-4.
5 Hill A Bradford. *Principles of medical statistics*. 8th ed. London: Lancet, 1966.
6 Armitage P. *Statistical methods in medical research*. Oxford: Blackwell Scientific, 1971.

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## MINIPRINT APPENDICES I AND II

### APPENDIX Im

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

In preparing the life tables for patients with haemophilia A (tables XVm-XVIIIm) the "not knowns" were assigned proportionately throughout the age and severity groupings. Person-years at risk were calculated from the number of patients in the register at the mid-point of each year. Also the assumption was made that mortality operated constantly through the age bands. See Hill[5] and Armitage[6] for further details of methods used.

#### XVm

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

| Age group (years) | Factor VIII value (... average normal) | | | |
|---|---|---|---|---|
| | <2 | 2–10 | >10 | Total |
| 0 | 1479 | 780 | 315 | 2 574 |
| 10–19 | 2518 | 1271 | 782 | 4 572 |
| 20–29 | 2184 | 1028 | 620 | 3 833 |
| 30–39 | 1543 | 848 | 439 | 2 830 |
| 40–49 | 968 | 614 | 419 | 1 901 |
| 50–59 | 558 | 510 | 234 | 1 302 |
| 60–69 | 282 | 309 | 251 | 843 |
| ≥70 | 99 | 191 | 129 | 408 |
| Total | 9531 | 5542 | 3280 | 18 354 |

#### XVIm

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

| Age group (years) | Factor VIII value (... average normal) | | | |
|---|---|---|---|---|
| | <2 | 2–10 | >10 | Total |
| 0 | 4 | 1 | — | 5 |
| 10–19 | 2 | — | 1 | 3 |
| 20–29 | 13 | — | — | 13 |
| 30–39 | 13 | 4 | 1 | 18 |
| 40–49 | 5 | 3 | 1 | 9 |
| 50–59 | 7 | 2 | 1 | 10 |
| 60–69 | 9 | 5 | 2 | 16 |
| ≥70 | 4 | 6 | 5 | 15 |
| Total | 60 | 21 | 8 | 89 |

#### XVIIm

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

| Age group (years) | Factor VIII value (... average normal) | |
|---|---|---|
| | <2 | 2–10 |
| 0 | 0·0027 | 0·0013 |
| 10–19 | 0·0009 | * |
| 20–29 | 0·0060 | * |
| 30–39 | 0·0054 | 0·0047 |
| 40–49 | 0·0092 | 0·0036 |
| 50–59 | 0·0125 | 0·0039 |
| 60–69 | 0·0319 | 0·0162 |
| ≥70 | 0·0408 | 0·0442 |
| All age groups | 0·0063 | 0·0038 |

*No deaths in group.

#### XVIIIm

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

| Age (years) | Haemophilia A (factor VIII value as ... average normal) | | Normal males* |
|---|---|---|---|
| | <2 | 2–10 | |
| 0 | 10 000 | 10 000 | 10 000 |
| 10 | 9 733 | 9 871 | 9 813 |
| 20 | 9 656 | 9 871 | 9 756 |
| 30 | 9 092 | 9 871 | 9 667 |
| 40 | 8 356 | 9 417 | 9 547 |
| 50 | 7 619 | 8 787 | 9 207 |
| 60 | 6 718 | 8 012 | 8 200 |
| 70 | 4 858 | 5 508 | 5 983 |
| 75 | 3 945 | 4 038 | 4 363 |
| 80 | 3 203 | 4 816 | 2 653 |
| Median life | 69·1 | 79·2 | 72·8 |

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

*From table 23 of *Mortality Statistics 1979*, series DH1 No 8, Office of Population Censuses and Surveys, London.

### APPENDIX IIm

APPENDIX II

The following directors of haemophilia centres contributed data to the survey: Dr W S A Allan, The Royal Hospital, Wolverhampton; Dr S Ardeman, Edgware General Hospital, Edgware, Middlesex; Dr A Aronstam, Treloar Haemophilia Centre, Alton, Hants; Dr B Attock, North Devon District Hospital, Barnstaple; Dr P Barkhan, Guy's Hospital, London SE1 9RT; Dr A M Barlow, Huddersfield Royal Infirmary, Huddersfield, Yorks; Dr A J Barrett and Professor J G Humble (now retired), Westminster Hospital, London SW1P 2AP; Dr C J T Bateman, St Richard's Hospital, Chichester, Sussex; Dr O H A Baugh, Chelmsford and Essex Hospital, Chelmsford; Professor A J Bellingham and Dr R A McVerry, Royal Liverpool Hospital, Liverpool; Dr B Bennett and Dr A A Dawson, University Medical Buildings, Foresterhill, Aberdeen; Dr L Bernstock, St Helier Hospital, Carshalton, Surrey; Dr T Bird and Dr T Whitehead, West Cumberland Hospital, Whitehaven; Dr T B Blecher and Dr E A French, University Hospital, Nottingham; Professor A L Bloom, University Hospital of Wales, Cardiff; Dr R P Britt, Hillingdon Hospital, Uxbridge, Middlesex; Dr D Burman and Dr G L Scott, Bristol Children's Hospital; Dr D G Chalmers, Addenbrooke's Hospital, Cambridge; Dr I Chanarin and Dr Diana M Samson, Northwick Park Hospital, Harrow, Middlesex; Dr P Chipping and Dr P Hilgard, Hammersmith Hospital, London W12 0HS; Dr Morag Chisholm, Southampton General Hospital, Southampton; Dr I A Cook, Raigmore Hospital, Inverness; Dr E R Craven, General Hospital, Kettering, Northants; Dr P E Crome, Queen Mary's Hospital, Roehampton, London SW15 5PN; Dr T J Deeble and Dr A Inglis (now retired), Cumberland Infirmary, Carlisle; Dr I W Delamore and Dr R T Wensley, The Royal Infirmary, Manchester; Dr J A Easton, Wexham Park Hospital, Slough, Berks; Dr J O P Edgcumbe, Royal Devon and Exeter Hospital, Exeter; Dr D I K Evans, Royal Manchester Children's Hospital, Pendlebury; Professor P T Flute, St George's Hospital, London SW17 0QT; Dr B E Gillver, County Laboratory, Dorchester; Dr A H Goldstone, Dr J D M Richards, and Professor T A J Prankerd (now retired), University College Hospital, London WC1E 6AU; 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GARDEN TANSY flowers in June and July.

Dame Venus was minded to pleasure women with child by this herb, for there grows not an herb, fitter for their use than this is; it is just as though it were cut out for the purpose. This herb bruised and applied to the navel, stays miscarriages; I know no herb like it for that use: Boiled in ordinary beer, and the decoction drank, doth the like; and if her womb be not as she would have it, this decoction will make it so. Let those women that desire children love this herb, it is their best companion, their husbands excepted. Also it consumes the phlegmatic humours, the cold and moist constitution of Winter most usually affects the body of man with, and that was the first reason of eating tansies in the Spring. The decoction of the common Tansy, or the juice drank in wine, is a singular remedy for all the griefs that come by stopping of the urine, helps the stranguary and those that have weak reins and kidneys. It is also very profitable to dissolve and expel wind in the stomach, belly, or bowels, to procure women's courses, and expel windiness in the matrix, if it be bruised and often smelled unto, as also applied to the lower part of the belly. It is also very profitable for such women as are given to miscarry. It is used also against the stone in the reins, especially to men. The herb fried with eggs (as it is the custom in the Spring-time) which is called a Tansy, helps to digest and carry downward those bad humours that trouble the stomach. The seed is very profitably given to children for the worms, and the juice in drink is as effectual. Being boiled in oil, it is good for the sinews shrunk by cramps, or pained with colds, if thereto applied. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)