The Incidence of Jaundice and Antibodies in Patients in the United Kingdom

- A Six Year Survey -

The figures collected for 1974, which will complete the six-year survey, are not complete and so this is only a provisional report of the data which many of you have collected so faithfully over the last six years. I think that the best thing that I can do is to go through the provisional figures and indicate a few thoughts that occur to me about them. I should be grateful if you would then raise points of difference or agreement that I can take into account in drawing up a manuscript for publication. When this manuscript is drawn up I will circulate it to all of the Directors who have taken part in the survey and try to represent all points of view in the final copy. The first thing that I should say now is that in all years we receive reports from about $^{3}/_{4}$ of the centres and in each year we have data on about 1,100 patients. The centres from which we have no reports mostly differ from one year to another so that over all there are few centres from which no reports have ever been received. I am very well aware that at many centres very little provision is made for staff to make the records required for the survey. Should this be the main difficulty, I may be able to find funds to have an assistant to travel to the centre and collect data should this be helpful. The other point that I should like to make is that the inclusion of data in a National Survey does not exclude the separate publication of Regional data.

The Total Number of Patients Treated at the Centres

Over the 6 year period the number of patients known at the centres has increased from 1,046 to 2,450 (table 6). We previously estimated the probable number of patients in the country at 3,000, thus we should be approaching a situation where the majority of patients are known at the Haemophilia Centres. I feel that now may be the time to make an effort to identify the remaining patients who are not now registered at Haemophilia Centres. I will refer to this topic again in connection with an item later in the programme.

The Amounts and Varieties of Factor VIII used at the Centres making returns

The total amounts of factor VIII in tables 1, 2 and 3 are expressed as factor VIII units. The factor VIII units are defined as the factor VIII activity of 1 ml of an average, normal plasma collected for testing in the Laboratory. For cryoprecipitate the plasma derived from one blood donation provides about 70 units of factor VIII. For the NHS factor VIII the relationship is similar; that is, the product of one donation provides about 70 factor VIII units. For commercial human factor VIII the product of one donation is unlikely to provide more than 35 units of factor VIII. Thus cryoprecipitate and NHS intermediate potency factor VIII have an equal yield of factor VIII activity and will need the same amounts of donor blood to provide equal quantities of either preparation. The commercial, relatively high potency, factor VIII will need about twice the amount of donor blood to supply material equivalent in activity to a given amount of NHS factor VIII or cryoprecipitate. Over the 6 year period it will be seen that since 1969 the total amount of factor VIII used at the centres has doubled. During the last 2 years (tables 2 & 3) the amount of cryoprecipitate used at the centres has decreased slightly (8.91 to 8.55 million units). The amount of NHS concentrate used at the centres has increased a little from 1973 to 1974 (2.4 to 2.6 million units). The big change in the last year has been in the use of commercial human concentrates (none prior to 1973, 0.64 million in 1973 and 1.91 million in 1974).

I should like to digress slightly at this point to consider the use of concentrate in Oxford in the last 6 years (illustrated in Fig. 1). You will see that plasma has a source of factor VIII was phased out in 1972. The use of cryoprecipitate increased from 1969 to 1971, and thereafter decreased. The use of intermediate potency of NHS concentrate increased dramatically from 1971 to 1972 as a result of increased production by Dr. Bidwell who converted plasma previously collected for cryoprecipitate to freeze-dried concentrate. From 1973 to 1974 there there has been little increased production by Dr. Bidwell though her laboratory could well produce more. It has been found impossible to

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supply Dr. Bidwell with more plasma to fractionate. In 1973 and 1974 the deficit in Oxford has been made good by using commercial human concentrate. In respect of general pattern of types of material used at the centres other than Oxford it is my view that as soon as possible the cryoprecipitate should be phased out and replaced by NHS intermediate potency concentrate which has substantial advantages in comparison with cryoprecipitate (MRC working party report 1974). As will be seen this change was made in Oxford between 1972 and 1974.

The Supply Equated to the Need

Fig. 2 represents the average use of factor VIII united per patient. There is no indication that supply is approaching saturation. The average use per patient in the U.K. in the Haemophilia centres is now about 12,000 units annually. The estimated need made by the MRC working party was for 15,000-20,000 units per patient annually. The Scottish estimate as indicated by Dr. Cash (1975) in Helsinki is for 18,000 units/patient and the U.S.A. estimate (1973) was for 20,000 units per patient. Our experience with patients so far on home therapy is that each one uses on average 25,000 units annually. We thus still probably have a substantial deficit in factor VIII even although the National supply may at present be being supplemented by as much as 6 million units of commercial factor VIII.

25,000
3000
75,000

25
12,000
3 000
36,000,000

The Incidence of Jaundice in Patients having Haemophilia

Introduction

The occurrence of hepatitis in patients receiving transfusion therapy is quite a complicated problem which requires analysis from several points of view. These are:-

1. The types of viruses that may occur in plasma or plasma fractions.
2. The incidence of these viruses in relation to the type of blood collected and the type of product.

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2000 - 6000

150
1750 donors

3. The susceptibility of the recipient to infection.

4. The relationship between dose of virus received and the manifestation of disease.

1. The types of virus known to occur in plasma are types B & A and there are also probably unidentified long incubation type viruses. In a recent review Prince (1975) suggests that a high proportion (80% of hepatitis cases) may be due to long incubation type viruses other than type B. The evidence is that on average only 20% of hepatitis cases show positive serological evidence of type B infection and so presumably 80% are not type B. This conclusion is supported by the observation that if all of the donations serologically positive for type B virus are excluded using the most modern test systems then only 20% of the hepatitis infections are prevented. (?)

2. The incidence of virus type B and other viruses in donor blood plasma fractions made from this blood has been shown to vary very much from one population to another. There is also great difference between commercial and volunteer donor blood. Commercial donors may have 10 times higher incidence ov virus type B antigen than volunteer donor blood. There is also evidence (Prince 1975) that commercial donor blood may be 10 times as likely to contain the unidentified long incubation viruses as volunteer donor blood. In the United Kingdom the incidence of virus type B antigen is of the general order of 1 per 1,000 donations. Clearly the pooling of plasma from many donations will increase the probability of an infected sample being included in the pool whether the pool is made from voluntee or commercial donor blood. X new donors are

3. The susceptibility of the recipient to infection by hepatitis viruses is an important feature controlling the incidence of disease. Patients who have never previously been transfused and who receive an infected donation have about a 1 in 2 chance of contracting the disease. Patients who have haemophilia as a class are relatively immune to infection. In the previous survey only about 5% of those probably exposed to virus

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developed jaundice. It would seem reasonable to suppose that at least those patients who have detectable antibodies to virus type B will be immune to this particular virus. About 30% of haemophilic patients have antibody to virus type B and could reasonably be treated with commercial human factor VIII.

4. The relationship between the dose of virus and the manifestation of disease. There is evidence from early inoculation studies that the occurrence of clinical disease may be related to dose. This conclusion was supported by the Directors survey (1973) which showed a higher incidence of jaundice in relation to probable donor-exposure in patients receiving cryoprecipitate compared to those receiving concentrate.

These introductory remarks have been included in the hope of helping the participants to understand and evaluate the discussions on hepatitis which may occur during the day.

The Statistical Data on the Incidence of Jaundice in Haemophilic Patients

The statistical data on the incidence of jaundice in Haemophilic patients is given in table 4. The Oxford figures have been separated from the total since the Oxford patients have always shown a somewhat higher incidence of hepatitis than those at other centres. Until 1973, only patients showing clinical jaundice were included in the survey; in 1974 many centres reported patients with raised LFTs. These are shown in brackets after the figures and should not be included in the statistics which are comparable to previous years.

It will be seen that in 1974 there was an increase in the incidence of jaundice at all centres. This increase may well be related to the use of commercial factor VIII concentrates. These concentrates are made from large pools of commercial donor plasma. It is not, however, easy at the present time to attribute the infection to particular types of concentrate in individual patients since most patients receive

4/19A

more than one type of concentrate and since the overall amounts of treatment are increasing. For example, of the 16 cases of jaundice recorded in Oxford, (table 5), 10 had received both NHS and commercial factor VIII, 4 received only NHS factor VIII and 2 only commercial factor VIII. Thus in only 2 cases could the jaundice be safely attributed to commercial concentrate and one of these developed jaundice actually during his only course of treatment during that year. The illness in this case had zero incubation period and is difficult to attribute to virus infection.

The Occurrence of Factor VIII antibodies in Haemophilic Patients

The incidence of anti-factor VIII antibodies in haemophilic patients is shown in table 6. It will be seen that there is as yet no increase in the incidence of anti-factor VIII antibodies despite the increased treatment.

Christmas Disease Patients

The material given to Christmas disease patients in Oxford is given in table 7. It will be seen that there is no general upward trend in the amount of material given to patients in the last 5 years. The incidence of jaundice in Christmas disease patients is given in table 8. The incidence of jaundice is similar to that in haemophilic patients before the introduction of commercial factor VIII concentrate.

Discussion

The final report should probably include an analysis of patients according to age that was given in the first report. Considering the increased incidence of jaundice and the probable contribution of commercial factor VIII we should probably try and analyse the incidence of jaundice in mildly and severely affected patients. The mildly affected patients being less often treated may be found to be more susceptible to hepatitis viruses.

The survey has grown and developed over the years and it seems that the data collection forms are becoming rather numerous and perhaps confusing. The time has now probably come to review the types of forms to be used, and perhaps to consider collecting the data about jaundice

in more careful detail and with some attempt to limit the number of different kinds of factor VIII received by one patient. I have in mind that perhaps we should continue to collect data as follows:-

1. The numbers of patients treated at different centres and particularly notification of newly identified patients and we have made a simple return on which newly discovered cases may be returned.

2. The amounts of various types of therapeutic material used.

3. The incidence of factor VIII antibodies.

Then the study of jaundice could be the subject of a separate and more careful study which could perhaps be organised by Dr. Kirk in co-operation with the virus reference laboratory.

All of the evidence so far collected suggests that there is not a high incidence of jaundice in patients who receive NHS factor VIII concentrate or NHS factor IX concentrate. I, therefore, feel that every effort should be made to increase the supply of intermediate potency concentrates made from United Kingdom blood.

I should be most grateful for ideas about data which should be collected or analysed and for topics which you would like to see discussed or recommended as a result of our study.

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Table 1

Material used to treat haemophilic patients in 1974.

Year	Number of Centres making returns	Number of Patients	Total amount of material used(Factor VIII units)	Average no. of Factor VIII units used per patient
1969	37	1046	6,286,700	6,010
1970	34	1038	7,589,036	7,311
1971	36	1141	9,513,080	8,337
1972	33	1195	10,247,540	8,575
1973	32	1124	12,247,373	10,896
1974	31	approx. 1100	13,434,820	12,213

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Table 2

Materials used to treat 1,124 Haemophilic patients at 32 Haemophilia Centres in 1973

Type of Material	Number of Centres	Factor VIII Units		
		Oxford	Other Centres	Total
NHS Factor VIII	18	1,471,215	917,860	2,389,075
Commercial Human Factor VIII	7	400,350	240,250	640,600
Cryoprecipitate	32	368,630	8,544,210	8,912,840
Plasma	16		304,858	304,858
Totals	32	2,240,195	10,007,178	12,247,373

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Table 3

Materials used to treat about 1,100 haemophiliacs at 31 centres during 1974.

Type of Material	Number of Centres	Factor VIII units		
		Oxford	Other Centres	Total
NHS Factor VIII	17	1,500,480	1,067,535	2,568,015
Commercial Human Factor VIII	20	874,095	1,036,930	1,911,025
Cryoprecipitate	31	89,710	8,458,190	8,547,900
Plasma	8		407,880	407,880
				13,434,820

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Table 4

The occurence of Jaundice in haemophiliac patients.

Year	All Cases			Oxford		
	patient Treatment Years	Number of Cases	%	Patient Treatment Years	Number of Cases	%
1969	1048	19	1.81	174	4	2.30
1970	1041	25	2.40	166	5	3.01
1971	1143	22	1.92	179	8	4.47
1972	1191	17	1.42	207	3	1.45
1973	1124	26	2.31	217	8	3.69
1974	1100	40 (59)	3.63 (5.45)	219	16 (20)	7.31 (9.1)
Mean	1108	28	2.01 (2.54)	194	7.3 (8.0)	3.79 (4.05)

x The bracketed figures include the patients who were not ill, but who had abnormal liver function tests.

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Table 5

Cases of Hepatitis in Oxford.

Cases	Material Given to Patients		Probable donor exposure
	NHS	Commercial	
1	1	2	2,200
2	12	-	2,400
3	7	3	4,400
4 xx	9	1	2,800
5 xx	3	1	1,600
6	3	1	1,600
7	4	1	1,800
8	1	-	200
9 xx	3	2	2,600
10	4	2	2,800
11	2	-	400
12	2	-	400
13 x	-	2 -	2,000
14	3	2	2,600
15 x	-	1 -	1,000
16	7	1	2,400

Cases 1 to 9. showed some change of HB Ab or HB Ag at the time of developing hepatitis, patients from 10 to 16 had no change in HB Ab or HB Ag.

x The patients only received commercial concentrate but one patient developed jaundice while actually receiving the material.

xx By careful analysis hepatitis in these patients could have been due to one batch of commercial concentrate but two of them also received suspect batches of NHS concentrate.

Table 6

Incidence of Factor VIII Antibodies in Haemophilic Patients

Year.	Cumulative number of patients in Survey		% with Antibodies	Number of new cases detected during the year.
	Total	With Antibodies		
1969	1046	71	6.78	20
1970	1263	89	7.04	18
1971	1639	107	6.52	15
1972	1914	120	6.27	12
1973	2327	131	5.63	11
1974	Approx. 2450	147	6.00	13

? evidence of death

4/27

Table 7

Therapeutic material given to Christmas disease patients in Oxford.

Year	Factor IX units	Number of patients	Factor IX units per patient
1969	418,433	36	11,623
1970	355,545	35	10,158
1971	553,392	26	21,284
1972	771,732	38	20,309
1973	654,884	43	15,230
1974	492,740	35	14,071

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Table 6

The incidence of Jaundice in Christmas disease patients.

year	All cases		Oxford	
	Number of Patients	Number Jaundiced	Number of Patients	Number Jaundiced
1969	138	2	36	1
1970	121	0	34	0
1971	129	1	23	2
1972	160	4	37	1
1973	165	1	43	0
1974	170	5 (2)	35	0
Total	833	13 (1.56%)	171	4 (2.34%)

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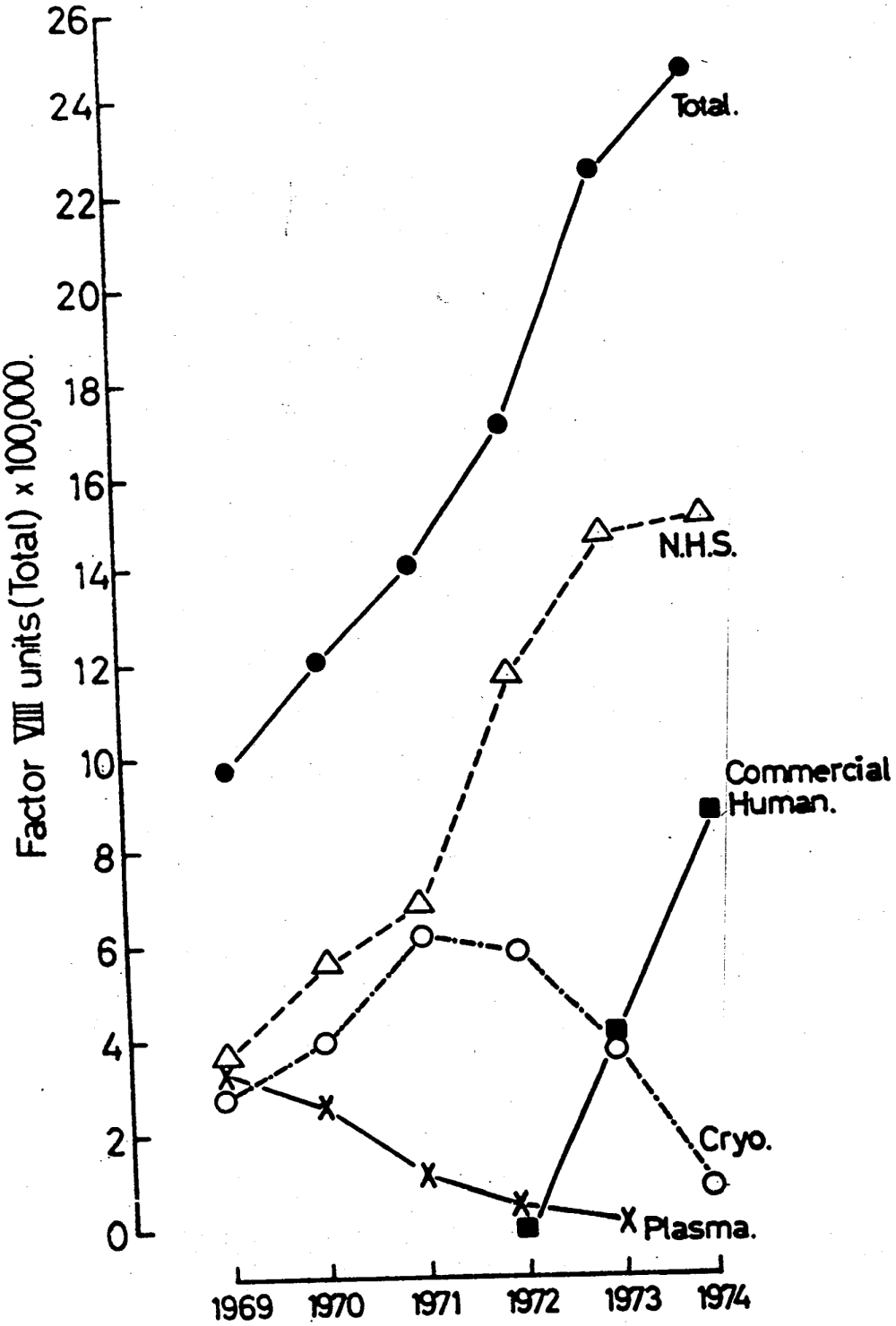

FIG. 1

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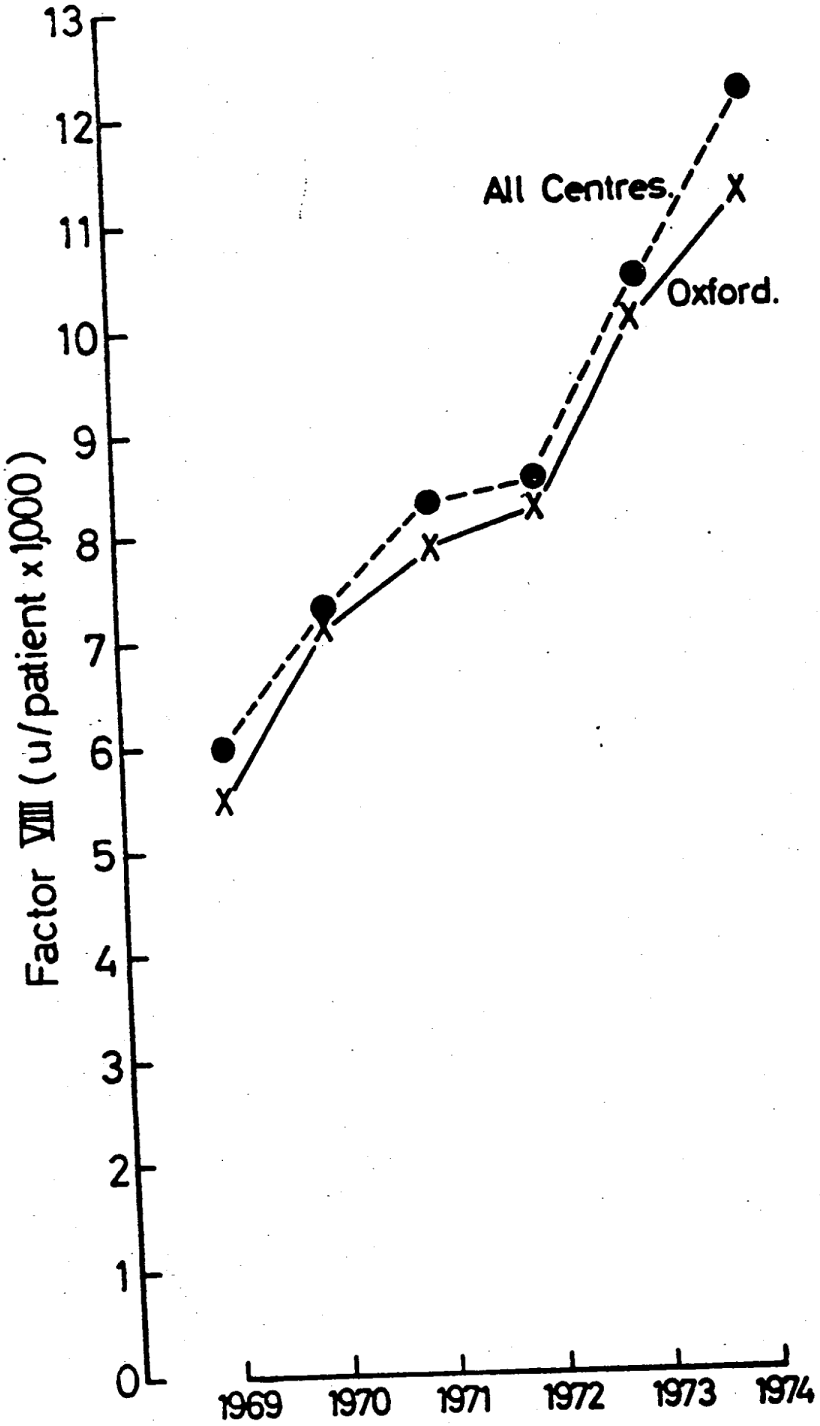

FIG. 2

Haemostasis Club

von Willebrand Disease Survey

Background

In 1974 a Task Force of the International Committee on Thrombosis and Haemostasis was formed under the Chairmanship and Co-Chairmanship of Professor John Graham and Professor Ilsley Ingram in order to examine the nomenclature and activities of factor VIII and its sub-units. In order to assist the Task Force with a specifically British contribution, the Haemostasis Club has decided to try to obtain information on as many UK patients as possible who have been diagnosed as suffering from vWd.

In order to pursue these objects the Haemostasis Club established a small informal working party with Dr. A. L. Bloom as Chairman and Dr. J. Leslie as Hon. Secretary.

Objects

The objects of the survey are as follows:-

(1) To determine incidence of patients diagnosed as suffering from "vWd" in UK.

(2) To determine methods in use to detect various abnormalities attributable to factor VIII defects

eg BT Platelet count
VIIIC
VIIIRP (WF antigen)
mobility of antigen
ristocetin aggregation tests
glass bead retention
(platelet aggregation)

(3) To retrospectively determine the incidence and distribution of the above abnormalities in patients as locally determined.

(4) To prospectively study a few large families (both normal and abnormal members) using standardised methods with reference laboratories as appropriate in order to detect and classify possible types of vWd and variants of factor VIII.

IMMUNOLOGICAL STUDY OF SYNOVIAL FLUID & SYNOVIAL MEMBRANE

Haemophilic boys suffer from repeated intra-articular bleeding. Many of these patients develop an arthritis in which plasma cells are sometimes a conspicuous feature in the synovial membrane, suggesting the presence of an antigenic stimulus. In approximately 5/10% of cases of haemophilia the presence of rheumatoid factor can be demonstrated. Furthermore, acquired haemophilia is seen in some cases of rheumatoid arthritis due to the development of an antibody to factor VIII.

In co-operation with the MRC Rheumatoid Research Unit at Taplow, a research project is to be conducted by Dr. S.G. Rainsford to ascertain the antigen against which the plasma cells are reacting in the haemophilic synovial membrane. Dr. Rainsford would, therefore, appreciate advance information of any boy, suffering from haemophilia or Christmas disease, who is to undergo any open operation on any joint since it is important that specimens of synovial membranes can be collected and examined at Taplow. Would Haemophilia Centre Directors whose Surgeons are willing to assist with Dr. Rainsford's project and provide samples from patients who undergo surgery, please contact Dr. Rainsford at Lord Mayor Treloar College, Froyle, Alton, Hants for further details of the project.