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THIRD ANNUAL REPORT ON PROJECT NO J/S240/78/7 -

PRELIMINARY RESULTS

1) TITLE

Studies of the epidemiology and chronic sequelae of factor VIII and IX associated hepatitis in the United Kingdom.

2) AIM

a) To study the incidence and types of factor VIII and IX related hepatitis in the U.K. by requesting the Directors of Haemophilia Centres to report cases as soon as they occur to the Oxford Haemophilia Centre, using standard forms; the effect of batch size, HB_sAg screening of donors, the source and numbers of donors used to make each brand of concentrate are studied. Paired sera, faeces, urine and implicated batches of concentrate are collected for study where possible from acute non-B hepatitis cases. Studies of the incidence of acute hepatitis B, both overt and symptomless are carried out. An attempt is made to provide an early warning system to identify implicated batches of concentrate. Serological studies of the prevalence of HB_sAg, anti-HB_s, hepatitis A antibody, and antibodies to other viruses have been carried out at Oxford.

The 3 year study is now complete, and the reports for 1977-80 have been reviewed and compared with the 1974-5 Hemofil survey[1] and the results of Kryobulin associated hepatitis in 1976[2]. The preliminary results of a feasibility study for a prospective follow-up of transfusion hepatitis in haemophiliacs at Oxford carried out since March 1st, 1981 have been analysed, and the significance of the results in relation to the incidence and types of hepatitis reported in the retrospective study considered.

b) To assess the incidence of chronic liver disease due to factor VIII and IX associated hepatitis by following up patients who have received known infected batches of concentrate.

The results of the clinical survey are now complete.

3) COST AND DURATION

Approved budget £25,462. 43. Duration 3 years from September 1978. Three year surveillance now complete. The surveillance is now being continued with financial support from local funds for a further two years until permanent arrangements can be made.

4) PERSONS ENGAGED WHOLE OR PART-TIME ON THIS PROJECT

5) STAGES COMPLETED

a) Three years surveillance of cases of hepatitis reported to the Oxford Haemophilia Centre. Review of cases notified 1972-77. Review of Hemofil and Kryobulin surveys 1974-76.

b) Review of patients on long term factor VIII therapy at the Oxford Haemophilia Centre completed. Of 174 patients initially investigated, full information is available on 125 Haemophilia A patients, and 12 Haemophilia B patients. An assessment of the value of the serum bile acids as a measure of chronic liver disease in haemophiliacs showed no correlation with the degree of abnormality of liver function tests or other clinical criteria of liver disease. Liver biopsy studies were not carried out.

A retrospective study of hepatitis A and B serology and liver function tests in household contacts of haemophiliacs on home treatment was carried out. There was no evidence that household contacts contracted acute or chronic non-A, non-B hepatitis as a result of contact with haemophiliacs who have known chronic liver disease associated with these agents. There was no evidence of the subclinical spread of hepatitis B other than those incidents reported in the second annual report (page 9).

As part of the prospective study at Oxford already referred to, the adult household contacts of all patients are being investigated prospectively at the time of initial enrolement of the index case, and again 6-9 months after the initial transfusion of concentrate to the index case.

A preliminary study of liver function tests was started in Haemophilia A patients with mild coagulation defects and Von Willebrands Disease patients in 1980. The results of the survey led to the start of the prospective survey to see if NHS factor VIII manufactured at Oxford was associated with a lower incidence of non-A, non-B hepatitis (pool size = 500 donations) compared with the association with NHS factor VIII manufactured at Elstree (batch size = more than 3,000 donations). This study is of patients with mild coagulation defects who require one episode of transfusion to cover an operatio: or other procedure. They are followed prospectively for up to 2 years. Twenty patients have so far been enrolled for this study.

Preliminary results of this survey have prompted a review of all cases of non-B hepatitis reported to the Oxford Haemophilia Centre since 1974. This is in fact the cause of the late completion of the research report.

6) PROGRESS MADE IN RELATION TO THE RESEARCH PLAN

(1) Hepatitis Surveillance

In 1980, 49 overt and 12 symptomless cases associated with transfusion of factor VIII or IX were reported. See Table 2. Forty two of the overt cases were non-B hepatitis, and 9 of these were confirmed as non-A, non-B hepatitis by serological tests.

There were 5 cases of symptomatic hepatitis B reported in 1970. A notable feature since the beginning of 1980 has been the continued number of cases of symptomless and overt hepatitis B reported. For 1980 the cases are associated with those products most frequently used. Table 3 gives the

associated blood products for the period January 1980 - January 1982. In order to assess the effect of donor screening on the chance of acquiring hepatitis B from concentration, it is proposed to conduct a small survey to obtain information regarding the time between the transfusion of a patient's first dose of concentrate and the date of detection of hepatitis B infection, and the total amount of concentrate transfused (factor VIII units or batches) in patients contracting hepatitis B. This will be compared with information collected in the Hemofil survey, before RIA screening of donors was instituted in 1975. Preliminary information suggests that RIA screening of donors for HB_sAg may delay exposure to hepatitis B by 2-6 years in patients regularly treated with factor VIII, compared with patient treated with factor VIII prepared from plasma screened for HB_sAg by electrophoresis. The results suggest that further reduction in the incidence of hepatitis B in haemophiliacs will be difficult to achieve by further donor screening with RIA tests, e.g., for anti-HB_c, as the cost will be high for the prevention of so few cases. A better approach would be to immunise haemophiliacs with hepatitis B vaccine when they are first transfused.

(2) Non-B hepatitis

The pattern of non-B hepatitis was similar in 1980 to that in previous years. There is no evidence that the incidence related to any blood product has declined. Table 1 shows the cumulative attack rate for all types of hepatitis reported to Oxford since 1972. The previously reported higher attack rates in patients with Von Willebrands Disease observed in previous years is confirmed.

(3) NHS v Commercial Concentrate

In table 6 (page 18) of the second annual report, the attack rates of hepatitis in patients treated with only one product in any year was reported. This suggested that non-B hepatitis associated with NHS factor VIII had a considerably lower attack rate than that associated with commercial factor VIII. However, preliminary results of the prospective survey at Oxford have failed to confirm this. Of five patients with no previous exposure to concentrate, treated with a mean of approx. 12,000 factor VIII units of NHS concentrate during one treatment episode, 5 patients so far followed have developed non-A, non-B hepatitis with incubation periods of from 51 - 125 days. Of these, 2 were symptomatic and 3 symptomless. In the same survey 3/3 patients transfused with U.S. commercial concentrate, who had not received the product before, developed symptomatic non-A, non-B hepatitis (incubation period = 9-53 days). It is possible that the previously reported lower attack rate associated with NHS concentrate may be due in part to the fact that a higher proportion of non-A, non-B hepatitis cases associated with NHS factor VIII may be subclinical compared to those associated with U.S. commercial concentrate. These preliminary results suggest that there is a 90% chance of contracting non-A, non-B hepatitis when first transfused with either NHS or commercial concentrate.

(4) Multiple attacks of non-A, non-B hepatitis

In previous reports, and in reference 3, we presented evidence to suggest that one short incubation type of non-A, non-B hepatitis was associated with transfusions of U.S. commercial factor VIII and a second with Kryobulin or NHS factor VIII. Further evidence to be presented elsewhere

shows that NHS and Kryobulin are associated with 2 serotypes of non-A, non-B hepatitis, and U.S. commercial concentrate a single serotype.

It is proposed to consult the manufacturers as to the significance of these results as the most likely explanation is that the differences in the fractionation processes used in the preparation of the different products may account for these observations.

(5) Hepatitis A associated with factor VIII and IX transfusions?

Since 1978, 2 clusters of cases of hepatitis A have been identified. The first involved 4 Christmas Disease patients towards the end of 1978. Two patients developed hepatitis with jaundice, and the diagnosis was confirmed by the detection of hepatitis A specific IgM antibody in serum specimens from these patients. Two further symptomless infections were detected in Christmas Disease patients who were transfused with the same batches of NHS factor IX as the first two. It was not possible to show a single batch of concentrate was associated with these cases, so the source of these infections remains in doubt. However, there was no epidemiological or serological evidence of recent hepatitis A in household contacts of these patients and no significant common social contact.

A further 2 cases have been detected in 1981 in the prospective survey. The first developed anicteric hepatitis 66 days after a transfusion of one batch of Oxford (NHS) factor VIII concentrate. No other product was transfused for six months after to this patient. A serological survey of patients also treated with this batch showed that 11 other patients were negative for anti-HAV by RIA in a serological survey conducted in 1979. Retesting of further sera taken within 6 weeks of transfusion of the implicated batches has detected one other symptomless case of hepatitis A. All the other 10 patients remained anti-HAV negative. A case of hepatitis A due to transfusion of whole blood has recently been detected in North West London (4).

It seems possible that a small proportion of NHS factor VIII and IX batches may contain hepatitis A virus. This may be a reflection of the increase in pool size of NHS factor VIII batches in recent years. The evidence is however still not conclusive. No other source of infection has been found for these cases. A further factor may be that haemophiliacs on regular factor VIII or IX therapy receive passively acquired anti-HAV antibody from factor VIII and IX concentrate and that this protects them from exogenous infection.

7) VARIATION IN THE ORIGINAL RESEARCH PLAN

The data from the prospective study at Oxford has confirmed earlier evidence that NHS factor VIII may contain a serologically distinct non-A, non-B agent from that associated with U.S. commercial concentrate. The incubation periods of the Oxford factor VIII related cases are also longer than those reported in the retrospective survey associated with U.S. commercial concentrate. Two cases of possible reinfection after first attacks of non-A, non-B hepatitis were seen in the prospective study. Closer evaluation of these cases has raised the question as to whether these illnesses may have some other cause or be due to other agents as the liver function tests have a different pattern to that seen in cases of non-A, non-B hepatitis after first transfusion of factor VIII concentrate.

As the result of these observations it has been decided to re-analyse the hepatitis reports with particular respect to reports in patients who have already been treated with several batches of factor VIII or IX concentrate. It is hoped to see if there are any differences by which these episodes can be distinguished from first attacks of non-A, non-B hepatitis. This will involve the use of a mini-computer recently acquired by the Manchester Public Health Laboratory.

8) FACTORS CAUSING DELAY IN THE EXECUTION OF THE RESEARCH PLAN

It has been found that the analysis of hepatitis reports where detailed information is required involves considerable delays if the Regional Health Authority computer at Oxford is used. Therefore, the use of the mini computer at Manchester, using selected patient data, should provide a more detailed analysis of the information collected in the retrospective and prospective surveys.

9) PUBLICATIONS PROPOSED

a) A report of the information collected in the first three years of the survey was given at a symposium on "Unsolved problems in haemophilia" given at the Royal College of Physicians and Surgeons in Glasgow in September 1980 (reprint enclosed).

b) A paper summarising the relationship of different types of non-A, non-B hepatitis to different brands of factor VIII.

c) A paper describing the incidence of hepatitis A and B in British haemophiliacs.

10) EXPECTED DATE OF COMPLETION

The retrospective survey is now complete. Funds are available to continue the surveillance programme for a further two years. The results so far obtained would justify continuance on a routine basis for the next five years.

The prospective survey has been financed so far out of non-NHS research funds. A project grant application was made last year to the Medical Research Council for this study but this was refused without any reason being given. Funds are available for a further six months for the prospective survey. Continuance of the survey after this will depend on the availability of research funds.

REFERENCES

1) Craske, J., Kirk, P., Cohen, B and Elise M. Vandervelde (1978) J. Hyg. Camb., 80, 329-336.

2)

3) Craske, J., Spooner, R.J.D., and Elise M. Vandervelde (1978) Lancet, ii, 1051.

4)

TABLE 1

JAUNDICE IN HAEMOPHILIAC PATIENTS IN THE UNITED KINGDOM

Year	Total number of treated patients	Number of cases of jaundice	Per Cent	
1969	1048	19	1.81	
1970	1041	25	2.40	
1971	1143	22	1.92	
1972	1191	17	1.42	
1973	1124	26	2.31 -	Hemofil first used
1974	1634	85(101)*	5.20 (6.18)	Kryobulin first used
1975	1609	42(51)	2.61 (3.17)	
1976	1886	56(61)	2.97 (3.24)	Other commercial products)
				Koate (Cutter))
				Factorate (Armour))
				Profilate (Abbott))
1977	1968	50(54)	2.54 (2.74)	
1978	2039	41(47)	2.01 (2.30)	
1979	1935	33(40)	1.70(2.06)	
1980	2117	40(51)	1.88 (2.40)	

Data from Biggs, R. (1974)
Biggs & Spooner (1976)
U.K. Haemophilia Survey 1977-79.

* Numbers in brackets include asymptomatic cases.

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TABLE 2 FACTOR VII AND IX ASSOC

PATIENT DIAGNOSIS AND MATERIAL RECEIVED	CASES OF HEPATITIS NON-B SYMPTOMATIC	SYMPTOMLESS	B SYMPTOMATIC
	HAEMOPHILIA A		
NHS ELSTREE	2 (0.21)	0	1 (0.10)
OXFORD	0	0	0
EDINBURGH	3 (2.19)	0	0
CRYOPRECIPITATE	1 (0.12)	0	0
COMMERCIAL			
HEMOFIL	4 (1.09)	1	0
FACTORATE	10 (1.22)	1	2 (0.24)
PROFILATE	0	0	0
KOATE	3 (0.99)	0	0
KRYOBULIN	6 (1.44)	1	0
CONCENTRATE:			
BRAND UNSPECIFIED	7	0	1
TOTAL	36 (1.70)	3	4 (0.19)
	HAEMOPHILIA B		
NHS IX	1 (0.32)	0	1 (0.32)
SECONDARY CASES	0	0	0
DEATHS	NONE		

DHF.003.0138

TABLE 2 FACTOR VIII AND IX ASSOCIATED HEPATITIS 1980

CASES OF HEPATITIS NON-B SYMPTOMATIC	NON-B SYMPTOMLESS	B SYMPTOMATIC	B SYMPTOMLESS	TOTAL SYMPTOMATIC ONLY	TOTAL TRANSFUSED	CASES OF HEPATITIS NON-B (SYMPTOMATIC)	B (SYMPTOMATIC)	TOTAL TRANSFUSED
HAEMOPHILIA A						VON WILLEBRANDS DISEASE		
2 (0.21)	0	1 (0.10)	1	3(0.31)	942	1 (4.55)	1 (4.55)	22
0	0	0	0	0	188	0		9
3 (2.19)	0	0	2	3(2.19)	137	0		2
1 (0.12)	0	0	0	1(0.12)	841	1 (0.51)		198
4 (1.09)	1	0	1	4(1.09)	366	1 (20.00)		5
10 (1.22)	1	2 (0.24)	2	12(1.46)	818	1 (8.33)		12
0	0	0	0	0	144	0		5
3 (0.99)	0	0	0	3(0.99)	302	1 (25.00)		4
6 (1.44)	1	0	0	6(1.41)	414	0		5
7	0	1	2	8	NOT RELEVANT	1		NOT RELEVANT
36 (1.70)	3	4 (0.19)	8	40(1.88)	2117	6 (2.53)		237
HAEMOPHILIA B								
1 (0.32)	0	1 (0.32)	1	2(0.64)	309			
0	0	0	0					
NONE								

DHF.003.0139

TABLE 3

HEPATITIS B: CASES REPORTED FROM 1.1.80 TO 1.1.82 RELATED TO PRODUCT IMPLICATED

CLINICAL FEATURES	PRODUCT IMPLICATED					HISTORY OF PREVIOUS CONCENTRATE		
	NIIS	ARMOUR	HEMOFIL	NIIS FACTOR IX	CONCENTRATE BRAND UNKNOWN	YES	NO	NK
SYMPTOMLESS	3	2	1	1	4			
ANICTERIC	1	2	0	1	3	20	3	2
JAUNDICED	2	3	0	0	2			
TOTAL	6	7	1	2	9	TOTAL	25	

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