Oxfordshire Area Health Authority (Teaching)

OXFORD HAEMOPHILIA CENTRE

Copy of First Annual Report to DHSS as submitted on 3.12.79

WITH COMPLIMENTS

of

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First Annual Report on Project Number J/S240/78/7

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

2. Aims 1) 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 record forms: the effect of batch size, Hepatitis B Surface Antigen (HB_sAg) screening of donors, the source and number of donations used to make each brand of concentrate are studied. Paired sera, faeces, urine and implicated batches of concentrate are obtained 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 are under way.

Initially the hepatitis reports for 1977 have been reviewed. Annual Returns for 1977 have been received from 107 Haemophilia Centres and a provisional analysis of the data, showing the number of patients suffering from hereditary coagulation defects known to the UK Haemophilia

Centre Directors on 31.12.77 and the number of patients treated at Centres during 1977, is given in Table 1.

2) To assess the incidence of chronic liver disease due to factor VIII associated hepatitis by follow-up of patients transfused with known infected batches of concentrate: Patients are examined for clinical and laboratory evidence of chronic liver disease and are compared with matched controls. The incidence of the secondary spread of hepatitis B to household contacts of haemophiliacs is also being assessed.

So far 179 haemophiliacs on long term factor VIII and IX therapy at Oxford Haemophilia Centre have been studied according to the protocol - see appendix 2.

3. Cost and Duration

Approved budget £25,462.43. Duration 3 years, but the Research Fellow in Hepatitis at Oxford supported for two years only.

4. Persons engaged whole or part-time on the project

Dr. J. Craske, Consultant Virologist, Manchester Public Health Laboratory.

Dr. C.R. Rizza, Consultant Physician-in-charge, Oxford Haemophilia Centre.

Miss R.J.D. Spooner, Research Assistant, Oxford Haemophilia Centre.

Dr. S. Ghosh, Research Fellow in Hepatitis, Oxford Haemophilia Centre.

Dr. Joan Trowell, Lecturer in Medicine, Nuffield Department of Clinical Medicine, The John Radcliffe Hospital, Oxford.

Dr. S.H. Davies, Director, Haemophilia Centre, Edinburgh Royal Infirmary.

Dr. D. Ellis, Blood Products Laboratory, Elstree.

Dr. Davies retired on 1.10.79. He will continue to be associated with this project.

5. Stages Completed

(1) First year of three year surveillance of cases of hepatitis reported to the Oxford Haemophilia Centre. Review of cases notified in the years 1974-7.

(2) Review of patients on long-term factor VIII therapy at Oxford Haemophilia Centre:-
Total number of patients: 179. Initial liver function tests have been done for all patients.
Out of these 179 patients 120 patients have so far been tested for Hepatitis A and B serology.
Clinical Assessment: 32 out of 70 patients chosen for further follow-up after initial screening have so far been investigated.

6. Progress Made in relation to research plan

(1) Hepatitis Surveillance

Review of cases reported to the Oxford Haemophilia Centre since 1974 has enabled us to identify a total of 209 cases of hepatitis where adequate information was available for these to be included in the survey.

A further 30 reports were discarded as the information was not adequate. This covered the period 1.1.74 to 31.12.77, and included the cases reported in the Hemofil survey.

In addition the cases in the 1977 treatment year were further analysed as the first complete year of the survey. Directors of Haemophilia Centres were asked to indicate in their returns whether each patient had been transfused with one or more bottles of each of the different brands of factor VIII or IX, or had received cryoprecipitate or other products. This enabled us to calculate an attack rate for each product derived from the following formula expressed as a percentage:-

$$\frac{\text{No. of cases of overt non-B hepatitis, or hepatitis B associated with a brand of factor VIII or IX}}{\text{Total patients treated in any one year with that product}}$$

With the help of the Oxford Regional Health Authority Computer Unit, the above information has been analysed by computer and the preliminary results are shown in Table 2. It was found impossible to record attack rates in terms of batches of concentrate as was done for the Hemofil survey (1), as the clerical work involved did not justify the results obtained. Individual batches of selected products were investigated where there was a high index of suspician of an association

with hepatitis.

The criteria used for assessing cases of hepatitis were given in the protocol of the research application (page 7). Appendix 1 gives the criteria by which the degree of association with a blood product or batch was assessed. The results of this analysis will be given in the second report. The attack rates given in Table 2 should be thought of as "cumulative attack rates", since the denominator for 1977 will include patients treated in previous years with many of the products received in 1977. The "true" or "first exposure" attack rate is derived as follows:-

$$\frac{\text{No. of cases of overt non-B or B hepatitis associated with a brand of factor VIII or IX}}{\text{No. of patients treated in any year for the first time with that product}} \times 100$$

The relationship of the first exposure to the cumulative attack rate is shown in Table 3 for the Hemofil survey (1). The first exposure attack rate for the cases reported in 1978 will be derived by subtracting from the total patients receiving each product in 1978 those patients who received the same product in 1977. Since three of the commercial products were first used in the U.K. in 1976, this will give a close approximation of the first exposure attack rates for these products. Reference to the records of the Hemofil and Kryobulin surveys of 1974-6 will enable us to

identify most of the patients who received transfusions of these products in these years. The least valid results will be obtained for NHS factor VIII and cryoprecipitate.

The two most obvious results of the 1977 returns are (1) The high association of Factorate with cases of hepatitis B compared with other brands of commercial concentrate. (2) The continued association of Hemofil and other brands of commercial concentrate with cases of non-B hepatitis.

(2) Non-A, non-B, Hepatitis

That the cases of non-B hepatitis reported in this survey are another variety of non-A, non-B, hepatitis is confirmed by the fact that tests for hepatitis A antibody were performed on sera obtained from 25 cases reported to Oxford in 1978-9. Patients were either hepatitis A antibody (Anti-HA) negative after the resolution of their hepatitis, or anti-HA positive in the acute phase serum with a negative test for hepatitis A specific IgM antibody. A further 20 cases were investigated in the original Hemofil survey (2). Therefore 45 episodes of acute non-B hepatitis investigated were found to be unrelated to hepatitis A.

(3) Chronic Hepatitis

A progress report of the follow-up of 179 patients on long term treatment with factor VIII

and IX concentrates is given in Appendix 2.

7. Variations from original research plan

Screening of patients for abnormal liver function was done using the Aspartate amino-transferase test as this is the routine test performed by the biochemistry laboratory at Oxford. Patients are also being reassessed using the alanine aminotransferase test as this may be a more sensitive and specific index of liver damage.

The original protocol described four categories for analysing the results of serum enzyme tests in the study of chronic hepatitis. The fourth category was originally those patients whose liver function tests reverted to normal values after the first abnormal result. This was intended to cover cases of symptomless acute hepatitis. It has been found, however, that about 36% of these patients have an occasionally abnormal serum enzyme test that do not follow any consistent pattern. This observation has been confirmed by similar results at the Lord Mayor Treloar College, Alton (3). Therefore the classes of results of serum enzyme tests were changed to those shown in Appendix 2.

8. Factors causing delay in execution of research plan

No significant problems have been encountered during the first year of this project.

9. Publications Proposed

A paper describing the results of the hepatitis A and B serological survey of patients treated at the Oxford Haemophilia Centre will be submitted for publication during the course of next year.

10. Expected date of completion:

September 1st 1981. Final report - October 1981.

References:-

(1) Craske, J., Kirk, P., Cohen, B. and Elise M. Vandervelde (1978) J. Hyg. Camb. 80, 327-336.

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

(3) U.K. Haemophilia Centre Directors' Hepatitis Working Party (1978). Unpublished Observations.

Table 1

Haemophilia A and B (Christmas Disease) patients known to the U.K. Haemophilia Centre Directors on 31.12.77

Diagnosis	Total Patients in UK	Total Transfused in 1977
Haemophilia A	3699	1968
Haemophilia B (Christmas Disease)	650	340
Haemophilia A Carriers	Not Available	42
Von Willebrand's Disease	Not available	236

Table 2

Factor VIII and IX Associated Hepatitis - 1977 Attack Rates

Patient Diagnosis and Material Received	Cases of Hepatitis				Total No. Patients Transfused in 1977
	Non-B Overt Only	B		Total Overt Only	
		Overt	Symptomless		
HAEMOPHILIA A					
Factor VIII Concentrate					
NHS					
Elstree	6 (0.66)	3(0.33)	1	9(0.99)	908
Oxford	5 (2.78)	0	0	5(2.78)	180
Edinburgh	0	1	2	1(0.81)	123
Commercial					
Hemofil	11 (2.48)	0	1	11(2.48)	444
Factorate	5 (1.58)	6(1.90)	0	11(3.49)	315
Profilate	1 (3.70)	0	0	1(3.70)	27
Koate	1 (0.41)	1(0.41)	0	2(0.83)	241
Kryobulin	0	1(0.33)	0	1(0.33)	306
Unspecified	2	0	0	2	Not relevant
Cryoprecipitate	2 (0.15)	1(0.075)	0	3(0.23)	1329
Plasma	0	0	0	0	4
TOTAL	33(1.68)	13	4	46(2.34)	1968*
HAEMOPHILIA B					
Factor IX Concentrate					
NHS Oxford	4 (1.35)	1(0.33)	0	4**	296
NHS Edinburgh	0	0	0	0	62
Commercial	0	0	0	0	4
Plasma	0	0	0	0	5
TOTAL	4	1	0	4**	340*

(cont.)

Figures in parenthesis indicate percentages

* Adjusted for duplicates

** 1 Case Non-I ollowed by B

Table 2 (cont.)

Patient Diagnosis and Material Received	Cases of Hepatitis				Total No. Patients Transfused in 1977
	Non-B Overt Only	B		Total	
		Overt	Symptomless		
CARRIERS OF HAEMOPHILIA A					
Factor VIII Concentrates					
NHS Oxford	0	0	0	0	11
NHS Elstree	0	0	0	0	4
NHS Edinburgh	0	0	0	0	1
Commercial					
Koate	0	0	0	0	1
Hemofil	0	1	0	1	1
Cryoprecipitate	0	0	0	0	22
Plasma	0	0	0	0	1
TOTAL	0	1	0	1 (2.44)	41
CARRIERS OF HAEMOPHILIA B	0	0	0	0	9
VON WILLEBRANDS DISEASE					
Factor VIII Concentrate					
NHS Elstree	0	1 (3.70)	0	1	27
Oxford	0	0	0	0	8
Edinburgh	0	0	0	0	3
Commercial					
Hemofil	0	0	0	0	5
Factorate	0	1(20.00)	0	1	5
Profilate	0	0			0
Koate	1 (12.5)	0	0	1	8
Kryobulin	0	1(12.5)	0	1	8
Cryoprecipitate	0	0	0	0	196
Plasma	0	0	0	0	16
FEIBA	1	0	0	1	1
TOTAL	2	3	0	5 (2.12)	236
Hepatitis not due to blo products	1	0	0	1	-

(cont.)

Table 2 (cont.)

Hepatitis type unknown:	1
Symptomless Non-B:	1
Chronic Hepatitis:	3

Table 3

Factor VIII Associated Non-B Hepatitis: True and Cumulative Attack Rates

Batch of Hemofil	Number Cases Of Non-B Hepatitis	No. Patients First Exposed to Hemofil With This Batch		Cumulative No. Of Patients Treated With Hemofil	
		No.	Attack Rate	No.	Attack Rate
P	0	30	0	30	0
R	2	38	5.2%	68	2.9%
Q	6	56	10.7%	124	4.8%
S	10	74	13.5%	198	5.0%
T	12	68	17.6%	266	4.5%
U	9	37	24.3%	303	3.0%
V	4	34	11.8%	337	1.2%
W	3	22	13.6%	359	0.83%
X	2	22	9.1%	381	0.52%
Y	1	12	8.3%	393	0.25%
Z1	2	25	8.0%	418	0.48%
Z2	1	29	3.4%	446	0.22%

APPENDIX 1

U.K. HAEMOPHILIA HEPATITIS WORKING PARTY: HEPATITIS SURVEILLANCE

Criteria for assigning a casual relationship between a batch or type of product of Factor VIII or IX concentrate and cases of hepatitis occurring in patients treated with the suspect batch.

1. DEFINITION OF HEPATITIS

A patient is considered to be suffering from hepatitis when 3 or more symptoms or signs compatible with a diagnosis of hepatitis are present as indicated on the sickness record form C1, together with evidence of abnormal liver function tests. These are considered abnormal when a figure at least twice the upper limit of normal serum aspartic or alanine aminotransferase or both, as obtained by the local biochemistry laboratory, is present within 3 weeks of the onset of symptoms. A presumptive diagnosis in the absence of enzyme tests can be accepted if all the other criteria of acute hepatitis are satisfied. A serum bilirubin is considered abnormal if a figure of at least twice the upper limit of normal was obtained on the same occasion. Subclinical cases of hepatitis are not included in the analysis of attack rates of Factor VIII related hepatitis, but we encourage Haemophilia Centre Directors to report cases they consider to be subclinical cases of hepatitis. Symptomless cases of hepatitis B are defined below.

Cases of hepatitis are defined as B or non-B. The evidence on the basis of serological tests on 20 cases of non-B hepatitis suggests that hepatitis A virus is rarely,

if ever, involved with transfusion hepatitis. Hepatitis B is considered to be present when a serum is positive for hepatitis B surface antigen (HB_sAg) by RPHA or RIA within 1 month of the onset of symptoms. The same patient should previously have been HB_sAg negative and hepatitis B surface antibody negative where the result is known. Non-B hepatitis is considered to be negative when all serum specimens from a patient with acute hepatitis are negative for HB_sAg as defined above.

For symptomless hepatitis B infections, either a positive test for HB_sAg or seroconversion to anti-HB_s positive by RIA or passive haemagglutination and hepatitis B core antibody (anti-HB_c) by electrophoresis is considered to be evidence of recent hepatitis B infection.

2. DEFINITE ASSOCIATION WITH A BATCH OF FACTOR VIII OR IX CONCENTRATE

a) Instances where at least 3 cases of either B or non-B hepatitis occur in patients transfused with the suspect batches within the known incubation periods of each type of hepatitis. One of these cases should have been transfused with the suspect batch only, within the incubation period, and have received no other product. The strongest association will be demonstrated if cases of hepatitis associated with one batch of factor VIII are found in more than one Haemophilia Centre, as this makes other sources of hepatitis B, e.g., contact with other cases or staff in the Centre, most unlikely.

b) In the absence of the latter type of case the occurrence of 4 cases in the incubation period as defined above will constitute definite association.

3. POSSIBLE ASSOCIATION

a) With batches: One or 2 cases of B or non-B hepatitis occurring after transfusion with a batch of concentrate where no other cause of hepatitis is known. b) With brand or type of product: Cases are observed where it is not possible to identify the batch involved, owing to the large number of batches transfused. In such instances it may be possible to identify the brand or type of product involved, e.g., cryo-precipitate, Elstree Factor VIII.

4. NO LIKELY ASSOCIATION

a) The diagnosis of hepatitis is not confirmed. b) The limits of the incubation periods (see below) for B or non-B hepatitis are exceeded. c) A case of non-B hepatitis is confirmed by serological tests to be hepatitis A. So far sera from 20 cases of Factor VIII associated non-B hepatitis have been examined and none have proved to be due to hepatitis A. d) Some other more likely cause is found for the patient's hepatitis, e.g., a family outbreak of infectious hepatitis.

Other factors to be considered are:

(i) Incubation period

Previous experience with Factor VIII transfusion hepatitis suggests the following limits to incubation periods:

Non-B hepatitis	7 - 110 days
Hepatitis B	49 - 200 days

(ii) The age of the patient

Hepatitis B reports to the Communicable Disease Surveillance Centre of the PHLS suggest that this illness is uncommon in persons below the age of 14 years unless it has arisen as

a complication of medical treatment. Cases of hepatitis B reported in haemophiliacs below 14 years of age therefore have a strong association with blood products. The age incidence of non-A, non-B hepatitis in non-haemophiliac patients in the U.K. is at present unknown.

(iii) Severity of coagulation defect

The attack rates of hepatitis associated with suspect batches of concentrate is higher in mild and moderate haemophiliacs (factor VIII level >2% of normal) compared with severe haemophiliacs (factor VIII level <2% of normal). This is related to the frequency of past treatment with blood products, i.e., the chance of previous exposure to B or non-B hepatitis viruses.

(iv) Change of type of Factor VIII therapy

Past experience suggests that cases of hepatitis are also commonly associated with a change in the type of factor VIII treatment a patient receives. Two common instances are 1) Transfusion with large pool freeze dried Factor VIII for the first time when starting home treatment. 2) Transfusion to cover an operation where large pool material is used in patients normally maintained on cryoprecipitate. Modifications may have to be made to these criteria in the light of further experience.

Dr. J. Craske.
17.1.79.

APPENDIX II

Liver disease in Haemophiliacs - a progress report

According to the agreed protocol of Haemophilia Centre Directors Hepatitis Working Party, 179 patients with severe haemophilia A have been studied. The patients were given a general physical examination with particular attention to signs associated with liver diseases and medical history was taken regarding their general health and symptoms associated with chronic liver disease. Blood samples were collected at the interval of 3 to 6 months for liver function tests. HB_sAg, HB_sAb, HA Ab and other viral studies.

The results of the medical history, physical examination and liver function tests were analysed. The asymptomatic patients with normal liver function tests at least on two consecutive occasions were dropped from regular follow-up and transferred to routine follow-up clinic when they will be checked at yearly intervals. Those patients were classified in 4 different groups depending on their AST level.

Group 1. Always normal
Group 2. Occasionally abnormal
Group 3. Persistently abnormal (between 35 (upper limit of normal) and 70 i.u./l)
Group 4. Persistently abnormal (more than 70 i.u./l)

In the last two groups probably chronic liver disease was suspected. 32 of these groups had been seen at the Liver Clinic by Dr. Trowell where the possibility of a chronic liver disease was evaluated.

Results

In spite of multiple transfusions and large numbers of grossly abnormal liver function tests, very few patients showed any stigmata of chronic liver disease. 14 of these patients (7.8%) had palpable spleen. 3 had spider nevi and only one had gynaecomastia of any significance. Total protein was raised in more than 10% of cases, all of these were associated with raised globulin fraction and none of these patients showed abnormally low albumin.

As discussed earlier, patients were classified into 4 different groups on the basis of their AST level (table 1)

Table 1.

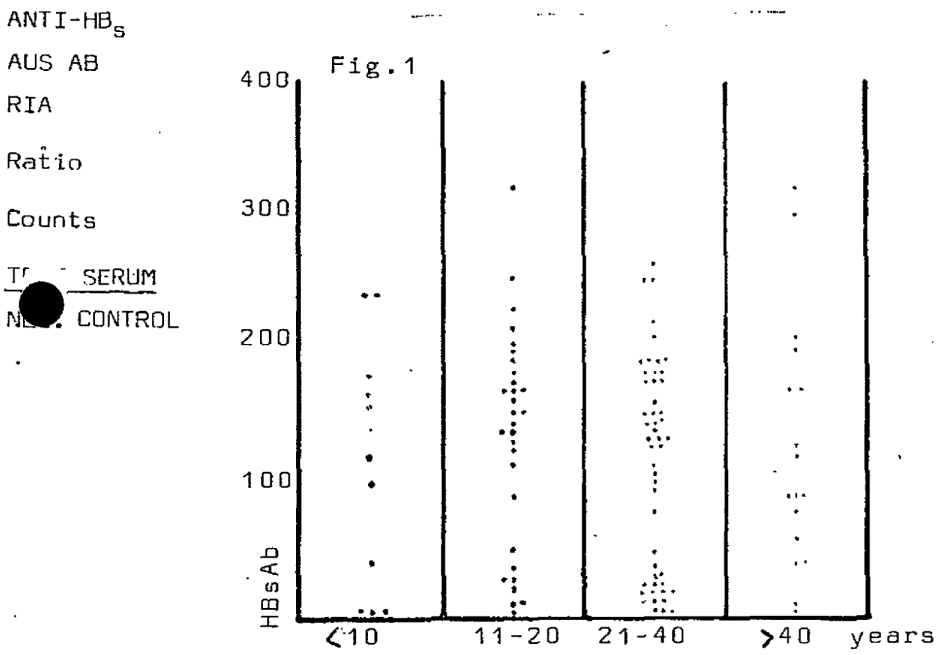
	No. of patients	Percent
Group 1.	41	23.6
Group 2.	63	36.2
Group 3.	47	27.0
Group 4.	23	13.2

70 (40.2%) out of 174 patients, for whom details liver function tests were available, had persistently abnormal liver function tests. 32 of these have been seen at the Liver Clinic and 20 of them (62.5%) most probably had significant chronic liver disease as judged by their clinical features and further investigations like proteins and BSP retention.

During this period of study (March, 1978 to August, 1979) 7 of these patients (3.9%) developed overt jaundice and 2 of these (28%) were HB_sAg positive. In 6 out of 7 cases the liver function tests rapidly returned to normal or pre-jaundice level. The other one showing persistently abnormal liver functions.

88 out of 107 patients studied had raised $HB_sAb.$, evidence of past infection with Hepatitis B, (82.2%). Prevalence of HB_sAb increased from 75% (8 out of 10 tested) in the 6 - 10 year age group to 93.75% in the 31 - 40 year age group though this is not a significant difference.

Fig. 1.



Only two of these patients were shown to have persistence of HB_sAg with raised LFTS, and were regarded as carriers of HB_sAg. There was no significant difference in liver function tests between those with high level of HB_sAb and those negative for HB_sAb or with a low level of HB_sAb. (Table 2).

Table 2

	Liver function				
	Group 1.	Group 2.	Group 3.	Group 4.	Total
HB_sAb Ratio* >20	15 (19%)	32(40.5%)	25(31.6%)	7(8.9%)	79
HB_sAb Ratio <20 or negative	5 (20%)	14(56%)	2(8%)	4(16%)	25

* RIA results of HB_sAb level as expressed as ratio of RIA count of the test specimen of the serum and RIA count in negative control specimen.

No significant difference in liver function tests were shown in patients treated with NHS Factor VIII compared with the LFTs of those treated with commercial Factor VIII (Table 3).

Table 3

	Liver function				
	Group 1.	Group 2.	Group 3.	Group 4.	Total
N.H.S. factor VIII	25(30%)	28(33%)	22(26%)	9(11%)	84
Commercial factor VIII	12(32%)	10(27%)	11(30%)	4(11%)	37

The patients treated with different types of factor VIII (N.H.S. and Commercial) showed no significant differences in their HBs Ab level. (Fig. 2)

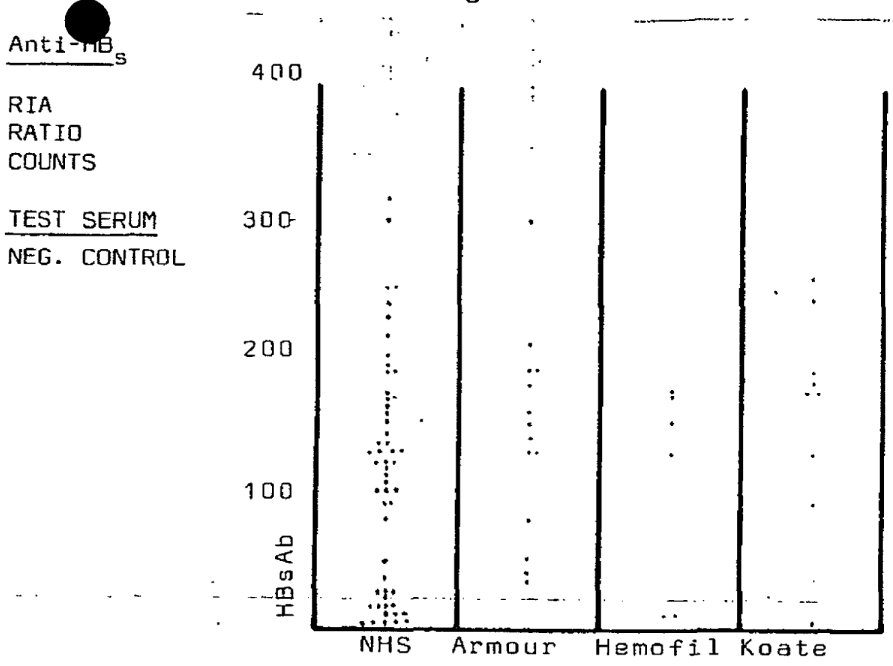


Fig.2
No.of patients on NHS factorVIII-53
Mean HBsAb level-111
SD-80.6

Patients treated with commercial factor VIII-29
Mean HBsAb level-139
SD-72
p>0.1

but HB_sAb level showed an inverse relation with the time interval between the last dose of factor VIII and the day on which the sample was taken (fig. 3). This is being investigated further.

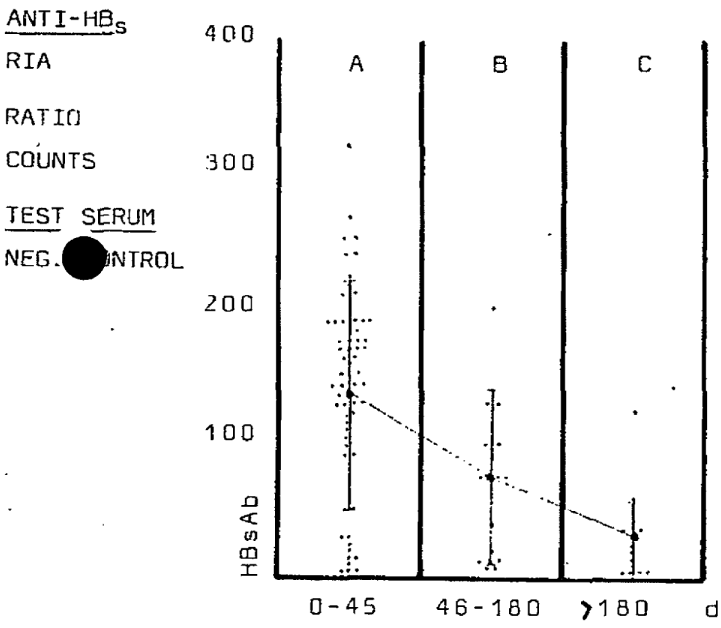


Fig.3
Total number of patients-93
Group-A=65
Group-B=15
Group-C=13
SD for Gr.-A=77
Gr.-B=59
Gr.-C=35
p value between Gr.A and Gr.C $<$0.001
Gr.B and Gr.C $<$0.01