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APPENDIX B

REPORT OF THE HAEMOPHILIA CENTRE DIRECTORS' HEPATITIS WORKING PARTY - 1978.

It is fifteen months since I was invited by the Directors to become Chairman of the newly formed Hepatitis Working Party. During this time we have laid the foundations of what I hope will be a significant contribution to our knowledge of transfusion hepatitis in British haemophiliacs and its sequelae.

The Working Party at present consists of the following persons:-

Myself as Chairman

Miss R. Spooner

Dr. Howard Davies, Director, Edinburgh Haemophilia Centre.

Dr. Drummond Ellis, representing the Blood Products Laboratory, Lister Institute, Elstree.

Dr. Joan Trowell, Lecturer in Medicine, The Radcliffe Infirmary, Oxford.

We have held three meetings of the Working Party and at present aim to meet 2 - 3 times a year.

FINANCE

It became apparent soon after the Working Party was formed that the available money from the hepatitis fund started by Dr. Biggs, would be exhausted by August, 1978. Therefore, an application for a Research Grant was made to the D.H.S.S. in April of this year to provide financial support for the Surveillance Programme for hepatitis at the Oxford Haemophilia Centre, and for a pilot project to investigate the incidence of chronic liver disease in patients treated with Hemofil in 1974-5. Approval has now been given to this project which will last for three years, and a Research Fellow, Dr. Susanta Ghosh, has been appointed to run the clinical side of the project.

HEPATITIS SURVEILLANCE

Since our original work on hepatitis associated with Hemofil and Kryobulin, we have carried out a review of cases of hepatitis reported as part of the collaborative study since 1974. The aim of this is to try and assess the change in prevelance of hepatitis since the introduction of Hemofil. Unfortunately, it will not be possible to compare the incidence before and after the introduction of Hemofil, as the different criteria used for the collection of

data before and after 1974 do not allow a direct comparison. Table 1 shows the reports of jaundice for the years 1972 to 1976 related to the total number of patients treated in any year. Apart from the increase in the cases associated with the introduction of commercial concentrates, the incidence of jaundice has remained fairly constant since 1974.

We should have revised figures for the incidence of hepatitis between 1974 and 1977 in time for the annual meeting of the U.K. Haemophilia Centre Directors' in November. Table 2 shows a provisional analysis of the relation of different types of hepatitis to the implicated brands of concentrate. We cannot make any deductions as to the relative incidence between different products without details of the numbers of patients treated, but it can be seen that approximately one half of the cases reported have been associated with Hemofil, mostly due to the highly contaminated batches in use in 1974-5. Out of a total of 207 overt episodes of hepatitis, 135 (65.2%) were non-B and 72 (34.8%) hepatitis B.

EVIDENCE IN FAVOUR OF THE EXISTENCE OF 2 TYPES OF NON-B HEPATITIS

a) Multiple Attacks of Hepatitis

One interesting observation is the number of patients who have had multiple attacks of hepatitis. Nineteen patients have so far been identified: (table 3). Brand 'L' is Hemofil and Brand 'M' is Kryobulin.

Eighteen patients had two attacks of hepatitis; sixteen of these had non-B hepatitis and hepatitis B. Two other patients who were known to be anti-HB_s positive had two attacks of non-B hepatitis; the first patients contracted non-B hepatitis associated with Hemofil followed by Kryobulin associated non-B hepatitis one year later. The second patient had NHS factor VIII associated non-B hepatitis in 1973 followed by Hemofil associated non-B hepatitis in 1974. One patient had 3 attacks of hepatitis; - non-B followed by hepatitis B due to Hemofil followed by non-B hepatitis associated with Kryobulin one year later. There was no consistent order in the successive attacks of hepatitis, supporting the view that these were distinct infective agents.

Sera from six of these patients have so far been tested for hepatitis A antibody (HAVAB) by a commercial solid phase radioimmunoassay test which has recently become available. Four of these patients, who contracted non-B hepatitis followed by hepatitis B, were negative by this test in specimens taken after their attack of non-B hepatitis. A fifth patient was positive for HAVAB in a serum specimen taken before the onset of his non-B hepatitis. The sixth patient, who was one of the patients who contracted 2 attacks of non-B hepatitis, seroconverted from negative to positive for HAVAB between his first and second attacks of non-B hepatitis. Presumably he had a subclinical illness due to Hepatitis A virus.

Non-B hepatitis associated with transfusions of factor VIII is therefore another example of "non-A, non-B hepatitis".

b) Hemofil associated non-B hepatitis

Evidence that non-B hepatitis associated with Hemofil is predominantly due to an agent of one serotype is shown in table 4. This shows that 52 of the first 55 cases observed were associated with the first transfusion of Hemofil that each patient received. The 52 cases had incubation periods of between 8 and 67 days, with a mean of 29 days, computed from the incubation periods of 35 cases where patients received only one batch of Hemofil during the incubation period. Those of the other 3 cases were greater than 80 days which is three standard deviations above the mean of 29 days. Since these 3 cases of hepatitis received more than one batch of Hemofil during the incubation period, they can be thought of as instances where transfusions of more than one batch was necessary before these patients contracted hepatitis. The alternative possibility that these patients had a coincidental attack of hepatitis A has been excluded in two out of three cases by testing sera from these patients for HAVAB.

Table 4 shows the cases associated with different batches of Hemofil in the approximate order in which batches came into use in British Haemophilia

Centres in 1974-6 according to whether they were associated with a transfusion of the first (columns 2 and 3) or subsequent (columns 4 and 5) batch of Hemofil that a patient received. In patients receiving a first transfusion of Hemofil, a total of 417 patient exposures in 11 infected batches (excluding batch P) produced 52 cases of hepatitis. In patients who had previously received a transfusion of Hemofil a total of 497 patient exposures in 10 infected batches produced 3 cases of hepatitis. Therefore, 37.9 first patient exposures per batch produced 4.72 cases per batch, whereas 49.7 second or subsequent patient exposures per batch produced 0.3 cases of hepatitis per batch used. Thus one case of hepatitis occurred every 8.0 first patient batch exposures compared with one case every 165.6 patient batch exposures in second or subsequent batches of Hemofil a patient received. Therefore, a patient was 20.3 times less likely to contract overt hepatitis if he had previously received a transfusion of a batch of Hemofil known to have been associated with other cases of non-B hepatitis. This may possibly be due to a subclinical infection acquired after a previous transfusion, and is consistent with the view that all cases of Hemofil associated non-B hepatitis occurring after first transfusions in this survey were due to an infective agent of the same serotype. All the Hemofil associated non-B cases which occurred in patients who experienced multiple attacks of hepatitis occurred after the first transfusion of Hemofil that these patients received.

These results suggest that the non-B hepatitis associated with Kryobulin may be of a different serotype from that associated with Hemofil, and possibly that the NHS factor VIII non-B cases are also distinct from the Hemofil cases. There may therefore be 2 types of non-B factor VIII associated hepatitis, i.e. 3 viruses involved, including hepatitis B virus. A crucual question yet to be answered is the relative role of each of these agents as a cause of chronic liver disease in haemophiliacs.

c) Incubation periods

Table 5 shows the incubation periods of non-B hepatitis associated with different products in cases where the affected batch is known with reasonable certainty. There is no significant difference in incubation periods between Hemofil associated hepatitis and other products including Kryobulin, suggesting that the 2 types of non-A, non-B hepatitis associated with factor VIII cannot be distinquished by means of differences in their incubation periods. Whether the long incubation period hepatitis described by Prince et al (1974) is also associated with factor VIII therapy remains to be seen. Further studies over the next 3 years may enable us to clarify the number of agents involved.

CHRONIC HEPATITIS

A follow up of Hemofil associated non-B hepatitis and hepatitis B has started at the Oxford Haemophilia Centre, and it is intended to follow up as many cases as possible. It is also intended to compare patients who received Hemofil with matched controls using clinical evaluation and laboratory investigation for chronic liver disease. This is part of the project financed by the H.D.S.S.

In the last few months, we have received reports of patients in several Haemophilia Centres who are thought to have evidence of chronic liver disease. It is important to collect as much information as possible about these patients and, therefore, we will submit to the Haemophilia Centre Directors' Meeting a draft protocol for the collection of information about the incidence of chronic liver disease in British haemophiliacs. The question of liver biopsy in the investigation of liver disease in haemophiliacs is controversial at the moment, and each Director must make up his own mind as to whether it is justified as a help in the clinical management of each individual patient.

We are at present analysing the results of the prospective study undertaken in 1975-6 and the results should be available shortly.

I have recently visited the Department of Medicine at the University of North Carolina at Chapel Hill during a visit to the U.S.A., and had the

opportunity to discuss the problem with Dr. Roberts and his colleagues. They have carried out almost 100 liver biopsies on patients with chronically elevated serum transaminases in a collaborative survey, and nearly 50% of these have histological changes compatible with cirrhosis , chronic active or chronic persistent hepatitis. These patients have had up to ten years of treatment with freeze dried factor VIII concentrates of different brands. There is controversy as to whether these changes are the sequel to acute virus hepatitis, or are due to some other cause, but Dr. Roberts and many other physicians are of the opinion the virus hepatitis is the main factor. The elucidation of this problem, therefore, remains the most urgent one from the patient's point of view.

PREVENTION OF VIRUS INFECTIONS

a) Screening tests for HB_sAg

Further studies have been carried out over the past year with batches of factor VIII suspected of being contaminated with hepatitis B virus in collaboration with Dr. D.S. Dane of the Virus Laboratory, The Middlesex Hospital, London. Since 1975, all batches of concentrate known to be associated with cases of acute hepatitis B have been negative for HB_sAg by radioimmunoassay. However, despite improved donor screening in the U.S.A., cases of overt hepatitis B still occur associated with every brand of large pool factor VIII, including NHS factor VIII.

It is evident, therefore, that screening tests for HB_sAg are not sensitive enough to detect all donor plasma infected with hepatitis B virus, even when the concentrate is prepared from donations of plasma from volunteer donors. Even though the number of infected batches has declined, severe haemophiliacs receive so much concentrate that there is still a high chance of exposure to hepatitis B virus. This is reflected in the fact that just under one third of the overt cases of hepatitis which are reported are due to hepatitis B.

Efforts are being made to increase the sensitivity of screening tests, but it seems unlikely that this will significantly reduce the incidence of

hepatitis B from the present level.

b) Hepatitis B Vaccines

Work by at least 4 different groups of workers in the U.S.A. has been undertaken to prepare a vaccine for hepatitis B in the past three years. One vaccine, consisting of a preparation of formalin treated hepatitis B surface antigen, prepared from plasma from carriers of HB_sAg with normal liver function tests, is at present undergoing human trials in the U.S.A. Should these prove successful, I think we should consider whether haemophiliacs would benefit from such a vaccine. Other groups who might benefit would be medical and other staff at Haemophilia Centres and the household contacts of haemophiliacs particularly those administering treatment to patients.

c) Non-A, non-B Hepatitis

Inoculation experiments in chimpanzees in the U.S.A., have produced hepatitis like disease in animals inoculated with plasma from cases of acute hepatitis and patients thought to be carriers of non-A, non-B hepatitis. One report describes the production of non-B hepatitis in chimpanzees after the intravenous injection of factor VIII concentrate. The incubation periods in the chimpanzees are similar to those of Hemofil associated hepatitis in haemophiliacs. In two instances, material from the first animal passage has produced hepatitis on inoculation into a second set of animals.

During my visit to the U.S.A., I visited the Hepatitis Laboratory at the Bureau of Biologics, Bethesda, Near Washington. As a result of this we intend to undertake some collaborative work which will involve attempts to reproduce non-A, non-B hepatitis in chimpanzees by transfusion of suspect batches of factor VIII identified in surveys in the U.K.

d) Household contacts of Haemophiliacs

As part of the follow up of the chronic sequelae of hepatitis at the Oxford Haemophilia Centre, we hope to obtain evidence of the incidence of jaundice and antibodies to hepatitis A and B viruses in the household contacts of haemophiliacs. A recent case shows that the families of haemophiliacs have

an increased risk of contracting hepatitis, which can have unforseen consequencies:-

The mother of a haemophiliac developed acute hepatitis B two months after pricking herself while administering factor VIII to her son, who has remained symptomless. One month before becoming ill, the mother donated a pint of blood at a regular blood donor session. This has since been used to transfuse a patient. We do not yet know whether the patient will develop acute hepatitis B. The son has since been found to be an e-antigen positive carrier of HB_sAg. It is obviously important to exclude the household contacts of haemophiliacs from being blood donors, as in addition they could also transmit non-A, non-B hepatitis in this way.

e) Future Research

As part of the programme to identify the agents associated with factor VIII associated non-A, non-B hepatitis, we are interested in obtaining specimens of faeces and urine, together with pre-illness, acute and convalescent sera from suspect cases of acute hepatitis. The faeces and urine should be collected as early as possible after the onset of symptoms. Anybody interested should get in touch with me at the Public Health Laboratory, Withington Hospital, Manchester, M20 8LR, tel: 061-445-2416.

As a result of the first year's work of the Hepatitis Working Party the problem of hepatitis from the point of view of the haemophiliac is more clearly defined, but there remains much work to be done to devise methods to prevent the threat of chronic liver disease clouding the undoubted benefits that large pool concentrates have brought.

We would like to thank all the staff of Haemophilia Centres for their devoted filling in of returns and replies to our letters. The next few years, I hope, will see some benefit to the patient in the form of a reduced risk of hepatitis associated with factor VIII therapy.

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August, 20th, 1978.

Reference

Prince, A.M. et al (1974) Lancet, ii. 241-246.

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TABLE 1. JAUNDICE IN HAEMOPHILIAC PATIENTS IN THE UNITED KINGDOM.*

TREATMENT YEAR.	TREATED PATIENTS	No. OF CASES.	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)	← KRYOBULLIN 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)

*DATA FROM BIGGS, R., (1974) Brit J. Haemat. 26, 313-29.
BIGGS, R., (1977) & SPOONER R. J.D. (1977) Brit J. Haemat. 35, 487-504.

TABLE 2.

FACTOR VIII ASSOCIATED HEPATITIS. 1974-8.

CASES ASSOCIATED WITH DIFFERENT BRANDS. (PROVISIONAL RESULTS)

TYPE OF HEPATITIS.	TRAVENOL. HEMOFIL.	IMMUNO KRYOBULIN.	ARMOUR FACTORATE.	CUTTER KOATE.	ABBOTT PROFILATE.	NHS LISTER	NHS OXFORD.	CRYOPRECIPITATE.	NHS IX	UNKNOWN.
B.	36 (34%)	7 (33%)	3 (30%)	1 (25%)	3 (50%)	8 (50%)	4 (29%)	6 (66%)	2 (33%)	5 (33%)
NON-B.	70 (66%)	14 (66%)	10 (70%)	3 (75%)	3 (50%)	8 (50%)	10 (71%)	3 (33%)	4 (66%)	10 (66%)
TOTAL	106	21	13	4	6	16	14	9	6	15

A TOTAL OF 207 INCIDENTS OF HEPATITIS AFFECTED 186 PATIENTS : 19 HAD TWO ATTACKS : ONE PATIENT HAD THREE ATTACKS.

TOTAL CASES 207 ; NON-B. 135 ; HEPATITIS B 72.

TABLE 3

FACTOR VIII ASSOCIATED HEPATITIS.

MULTIPLE ATTACKS.

FIRST ATTACK	SECOND ATTACK	THIRD ATTACK	NUMBER OF PATIENTS.
BRAND 'L' - NON-B. * HEPATITIS.	BRAND 'M' HEPATITIS B.		13 (10 ICTERIC ; 3 SYMPTOMLESS HEPATITIS B)
NHS FACTOR VIII - HEPATITIS B.	BRAND 'L' NON-B HEPATITIS.		1
BRAND 'L' - HEPATITIS B	NHS FACTOR VIII NON-B HEPATITIS.		1
NHS FACTOR VIII NON-B HEPATITIS	NHS FACTOR VIII HEPATITIS B.		1
BRAND 'L' NON-B HEPATITIS	BRAND 'M' NON-B HEPATITIS.		1
NHS FACTOR VIII - NON-B HEPATITIS.	BRAND 'L' NON-B HEPATITIS.		1
BRAND 'L' NON-B HEPATITIS.	BRAND 'L' HEPATITIS B.	BRAND 'M' NON-B HEPATITIS.	1
			19.

* BRAND 'L' = HEMOFIL
BRAND 'M' = KRYOBULIN.

TABLE 4

NON-B HEPATITIS IN PATIENTS TRANSFUSED WITH ONE OR MORE BATCHES OF BRAND 'L' (HEMOFIL)

BATCH OF BRAND 'L'	NO. OF PATIENTS RECEIVING EACH BATCH EITHER ALONE OR FOLLOWED BY ONE OR MORE DIFFERENT BATCHES	NO. OF CASES OF NON-B HEPATITIS	NO. OF PATIENTS RECEIVING EACH BATCH AFTER PREVIOUS TRANSFUSION WITH A DIFFERENT BATCH	NO. OF CASES OF NON-B HEPATITIS
P	30	NIL	NIL	NIL
R	38	2 (5.2)*	17 (excluded)	NIL
Q	56	6 (10.7)	30	1
S	74	10 (13.5)	43	NIL
T	68	12 (17.6)	50	1
U	37	9 (24.3)	38	NIL
V	34	4 (11.8)	46	NIL
W	22	3 (13.6)	55	NIL
X	22	2 (9.1)	65	1
Y	12	1 (8.3)	17	NIL
Z1	25	2 (8.0)	61	NIL
Z2	29	1 (3.4)	92	NIL
TOTAL	417 (excluding batch P)	52 (12.5)	497 (excluding batches P and R)	3 (0.6)

* Percentage attack rates in parenthesis

TABLE 5. NON-B. HEPATITIS: INCUBATION PERIODS.

BRAND OF CONCENTRATE