R.B.C.

HOUSE MESSAGE

B0000146/1

Armour Pharmaceutical Company Ltd.

Factorate Heat Treated file

To: D. Lewis
M. Cross
K. Dunbar
J. Vanhalle
M. Samuelsson

R. B. C.
15 JUL 1985

From: C.R. Bishop

Date: 12th July 1985.

Re: FACTORATE HEAT TREATED

Attached you will find a copy of a paper by Colombo et.al. entitled 'Transmission of Non-A, Non-B Hepatitis by Heat Treated Factor VIII Concentrate', The Lancet : Saturday 6th July 1985.

This is the result of the Travenol study and it is the first time that this has appeared as a complete paper in the Medical press. You will note it shows an 84% failure rate with a heat treatment procedure of 60°C for 72 hours.

There is a paper due to be published shortly by the Sheffield Group (E. Preston) on the results of our study last year in which you will recall that all three 'clean virgin' patients treated with our intermediate heat treated product acquired Non-A, Non-B Hepatitis. I am advised that this will be appearing within the next 3-4 weeks and the conclusion to the paper will be along the following lines:-

"Whilst all three of our patients have remained HTLV III antibody negative, it seems clear that at least from commercial sources the dry heated product remains disappointing".

This together with the Colombo paper is quite clearly an indictment of the dry heat treated processes in totally eliminating Non-A, Non-B, although in Chimpanzee studies both products showed effectivity against the Hutchinson strain of the Non-A, Non-B virus.

I have also been advised, unofficially, that in the Alpha trial which appeared to have been going so well, three patients have now gone down with Non-A, Non-B Hepatitis. All three patients were treated with material from one of the seven batches and to quote one of the Directors concerned:-

"If this batch had been used first and the results achieved as in the Armour Trial, this trial would have been stopped immediately - its just the luck of the draw".

2/....

What should be our strategy, therefore? Also enclosed for your information and study is a further paper from The Lancet dated June 29th 1985 entitled 'Progressive Liver Disease in Haemophilia : An Understated Problem?' by Charles Hay et.al. from Sheffield.

I have arrowed certain important paragraphs and would ask you to note the following:-

1. Leading workers conclude that liver disease in haemophilia is benign and non-progressive but the Sheffield Group question this.

2. Factor VIII therapy/consumption is unrelated to the severity and progression of liver disease.

3. Studies in patients who are not receiving regular supplies of blood products shows the same prevelance and frequency of progression as haemophiliacs being repeatedly challenged.

4. The Sheffield Group speculate that repeated exposures to viruses may, repeat may, modify the usually benign course of the disease.

5. The last sentence quite clearly and unequivocally states that any proven superior product is really only indicated in clean virgin untreated patients and there is little point in altering the treatment of those who have already been exposed to concentrates.

Although Alpha's unpublished evidence may look better, even with the three patients who have now succumbed to Non-A, Non-B, it is not the answer - it is still very much the luck of the draw which batch you get.

There may be a case for 'clean virgin' patients for Alpha but certainly not a case for universal change at a +16.6% increase in budgets (12-14p) or a risk of exposure of stabilised patients to new donor pools/antigens etc.

Use the above argument and the Hay paper to maximum effect when discussing the merits of the Alpha vs. the Armour product.

I will update you after the San Diego Meeting, at which various presentations will be will be made by the Companies.

GRO-C

C.R. Bishop.

cc: R.B. Christie / M. Rodell / A. Bessler / L. Lucas / R. Bursian
C. Schott / M. Cearnal / J.D. Michelmore / K.W. Fitch / M. Galvan

The Lancet · Saturday 6 July 1985

TRANSMISSION OF NON-A, NON-B HEPATITIS BY HEAT-TREATED FACTOR VIII CONCENTRATE

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Summary In-vitro and animal studies have shown that viral agents can be removed from or inactivated in clotting factor concentrates by physical or chemical treatment. However, clinical data have as yet not substantiated the results of these studies. 13 haemophilia A patients who had not been treated previously with blood or blood products were given a dry-heated factor VIII concentrate and were tested serologically over the next 12 months. Hepatitis developed in 11 patients (84%) and was invariably of type non-A, non-B. Morbidity was not related to the lot of the therapeutic material or to the number of infusions. The incubation period was either 5 or 8–11 weeks, and only 1 patient had symptoms. Aminotransferase elevation showed both monophasic and biphasic patterns. During the follow-up period signs of the disease disappeared in 10 patients (90%). These findings contrast with the absence of non-A, non-B hepatitis in chimpanzees given the same heated concentrate. Thus, clinical studies in first-exposure haemophiliacs are essential for the true evaluation of the safety of new "treated" concentrates.

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Introduction

CLOTTING factor concentrates manufactured from thousands of units of pooled plasma are likely to transmit viral infections to haemophiliacs. The risk of post-transfusion hepatitis B is reduced but not abolished by screening donors for hepatitis B surface antigen (HBsAg), and HBV vaccination may reduce this risk even further.[1] However, non-A, non-B (NANB) hepatitis, with an attack rate close to 100% in haemophiliacs not previously exposed to blood or blood derivatives (first-exposure, or "virgin", patients), remains a formidable problem.[2,3] Moreover, there is epidemiological and serological evidence that concentrates transmit human parvovirus[4] and the human T-cell lymphotropic virus HTLV III/LAV.[5-7]

During the past few years, several manufacturers have developed physical and chemical methods of eliminating or reducing concentrate infectivity with minimum loss of clotting factor activity.[8] One commercial manufacturer heated lyophilised factor VIII (FVIII) concentrate at 60°C for 72 h, a process thought to reduce concentrate infectivity, since no case of NANB hepatitis was found in chimpanzees treated with this preparation even when an NANB inoculum was added before the heating process.[9] However, the heating process does not completely inactivate HBV. Although deliberate contamination of the concentrate with small amounts (300 infectious doses) of HBV before heating did not cause hepatitis B in animals, contamination with extremely large amounts of HBV (30 000 infectious doses)[9] was followed after a lag period, by hepatitis B and the appearance of hepatitis B markers. Since this concentrate has been

CLINICAL CHARACTERISTICS AND INFUSION DATA FOR THE PATIENTS REGULARLY FOLLOWED-UP

Patient	Age (yrs)	F VIII level (%)	Body weight (kg)	Type of treatment	Total concentrate dose (U)	No of infusions	Lot	Hepatitis incubation period (weeks)	ALT peak (x upper normal limit)
1	2	1	10	Prophylaxis	20 100	67	820628A	Not assessable	8
2	1	1	11	Demand	8700	21	820628A	No hepatitis	2
5	3 months	1	6	Demand	3600	13	820628A	Not assessable	
11	11	2	50	Surgery	1650	1	820817A	10	33
12	15	16	80	Demand	22 000	11	820817A	8	44
13	3	1	12	Demand	1260	3	820817A 820628A	No hepatitis	9
14	22	11	82	Surgery	19 980	17	820628A	5	91
15	1	1	9	Demand	2130	4	820817A	8	7
16	58	18	70	Surgery	66 720	15	820817A	8	7
18	1	1	12	Demand	3000	6	820628A	11	53
19	1	1	12	Demand	4500	15	820628A 840120A	Not assessable	71
20	10	1	40	Demand	3600	2	840120A	5	48
21	1	1	10	Demand	620	2	830121A 833010A 820817A	8	17

marketed without infectivity studies being done in man, we have conducted a multicentre prospective clinical investigation to assess its likelihood of transmitting hepatitis to previously untreated haemophilia A patients.

Patients and Method

Concentrate

Five different lots of a heated FVIII concentrate ('Hemofil T', Hyland Therapeutics, Glendale, California) were used in this study. Each lot was made from pooled plasma collected in 1982, 1983, and 1984 from approximately 5000 North American plasmapheresis donors.

Patients

Haemophilia centres in Milan, Heidelberg, London, and Paris enrolled patients who needed treatment with FVIII concentrate. Only patients highly susceptible to post-transfusion hepatitis were considered—ie, those who had never received blood or blood products. Other inclusion criteria were normal serum levels of aminotransferases, no history or current evidence of liver disease, no medication likely to raise serum levels of liver enzymes, no HBV serum markers (except for anti-HBs in the 1 vaccinated patient [number 21]), and patient willingness to cooperate in a study demanding periodic blood sampling and visits to clinics over a 12-month period. 21 patients with severe, moderate, or mild haemophilia A met these criteria and gave their written informed consent.

Follow-up Procedure

Serum samples were obtained and full physical examinations were done before treatment, and then every 2 weeks during the first month, every 3 weeks for 6 months, and thereafter monthly until the end of the year's follow-up. Liver function tests included serum bilirubin, aminoaspartate tranferase (AST), and aminoalanine transferase (ALT), and were done in the central laboratories of each participating centre by automated spectrophotometric methods at 37°C.[10] Serum samples were also tested for HBsAg (anti-HBs) and hepatitis A IgM antibody (anti-HA) by the use of commercial radioimmunoassay kits (Abbott Laboratories, North Chicago, USA). Cytomegalovirus IgM antibody (anti-CMV) was detected by complement-fixation test or by enzyme-linked immunoabsorbent assay (Behring, Marburg, West Germany). Serum IgG antibody to the Epstein-Barr virus capsid antigen was measured by indirect immunofluorescence. At each visit, patients were questioned for symptoms of hepatitis and any other illness, and records were taken of current drug treatment. Portions of sera were also stored at −20°C for future studies. Diagnosis of post-transfusion hepatitis was made when ALT values greater than 2·5 times the upper normal limit at each laboratory were found on at least two consecutive occasions during the follow-up period. NANB hepatitis was diagnosed when no markers indicating recent hepatitis A or B, cytomegalovirus, or Epstein-Barr virus infections were detected and where no clinical or laboratory evidence of any other cause for increased ALT activity could be found.

Results

21 patients were included in the study. 13 were followed up regularly as planned; 7 missed some visits critical for the evaluation of post-transfusion hepatitis (5th and/or 11th week); and 1 was followed-up regularly for 37 weeks, then defaulted.

Of the 13 patients who were regularly followed up (see accompanying table) 9 were given FVIII on demand for treatment of acute bleeding episodes, 3 during surgical procedures, and 1 for prophylaxis. 9 received FVIII from the same concentrate lot throughout the whole follow-up period and 4 were given FVIII from two or three different lots (table). Clinical efficacy of the concentrate was as good as expected from the doses given and the FVIII level achieved. There were no immediate adverse reactions to the concentrate.

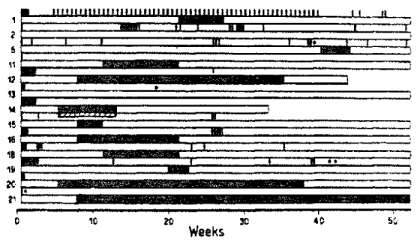

Fig 1—Pattern of non-A, non-B hepatitis in 14 patients infused with the heated factor VIII concentrate.

Each horizontal bar represents results for one patient. The length of the open bar indicates duration of follow-up. Solid bars indicate ALT more than 2·5 times the upper normal limit. The hatched bar indicates jaundice. Each vertical stroke indicates the infusion of one concentrate dose (for lack of space, the number of vertical strokes does not correspond to the number of infusions in patients 12, 14, and 16 (see table for exact numbers). Lot changes are indicated by black dots.

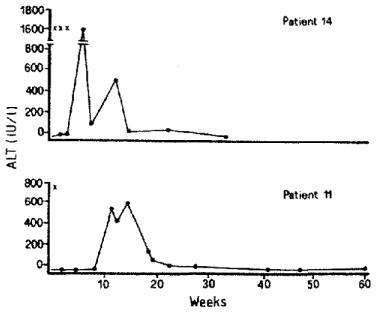

Fig 2—Pattern of ALT changes in 2 patients who had non-A, non-B hepatitis.

Upper panel: shorter incubation, biphasic pattern (patient 14). Lower panel; longer incubation, monophasic pattern (patient 11). Crosses indicate a dose of concentrate.

NANB hepatitis developed in 11 (84%) of the 13 patients who were regularly followed up (fig 1). In the others, ALT values were either intermittently raised, but not to the arbitrary value defined for hepatitis (patient 2), or reached this upper limit only in isolated instances (patient 13). The incubation period for hepatitis could be assessed in 8 patients given single or multiple infusions only during the first three weeks of the study (nos 11, 12, 14, 15, 16, 18, 20, 21). The incubation period (the interval between the first infusion of the product and the first abnormal ALT result) was 5 weeks in 2 cases (nos 14 and 20) and 8–11 weeks in 6 (nos 11, 12, 15, 16, 18, 21). 7 patients (nos 1, 11, 12, 15, 16, 19, 21) showed a monophasic pattern of ALT elevation and 4 showed biphasic rises (nos 5, 14, 18, 20) (fig 2). In patients in whom hepatitis developed, ALT rises were 7 to 91 times (median 33) the upper limit of normal values. Serum bilirubin ranged from 0·4 to 10·7 (median 1·2) mg/dl. In all but 1 patient (patient 14), the hepatitis did not produce symptoms. Patient 14 had anorexia and jaundice (peak bilirubin 10·7 mg/dl), which lasted for 8 weeks. During the follow-up period, ALT values returned to normal in 10 (90%) of the 11 patients who had hepatitis. Patients 14 and 12 were not followed up after ALT levels returned to normal at 32 and 44 weeks.

Among the 8 patients with incomplete follow-up, 2 had NANB hepatitis, 3 had sporadic ALT rises, and 3 showed no evidence of ALT elevation (not shown). All concentrate lots transmitted hepatitis (table). The frequency of hepatitis was not related to number of infusions (fig 1).

Discussion

The primary purpose of this study was to assess whether hepatitis could be transmitted by heat-treated FVIII concentrate. The enrolment of only patients previously untreated with blood or blood products is of critical importance for the accurate assessment of post-transfusion hepatitis, because previous exposure may confer protection against new attacks of NANB hepatitis.[2,3] Our decision to select only first-exposure patients meant that only a small number of patients with haemophilia A could be recruited. In addition, the adoption of strict criteria for follow-up, involving frequent and regular blood sampling, reduced the number of patients suitable for analysis to 13. However, studies of post-transfusion hepatitis are only meaningful when serial biochemical tests are done regularly, since ALT rises during NANB hepatitis are often short-lived[2,11,12] (fig 1) and hence might be missed with irregular follow-up.

There were many similarities between the clinical and biochemical patterns of NANB hepatitis seen in our study and those seen in haemophiliacs given unheated FVIII. Hepatitis occurred in 84% of our patients, a rate close to that (100%) previously observed in first-exposure haemophiliacs infused with unheated commercial concentrates.[2,3] Short (5 weeks) and longer (8–11 weeks) incubation periods were observed, as were monophasic and biphasic ALT patterns (fig 2). However, none of our patients had the very short incubation periods (1–2 weeks) that have previously been reported.[2,3] Two viral agents have been implicated in NANB hepatitis on the basis of cross-challenge studies in chimpanzees.[13,14] More recently, retrovirus or retrovirus-like agent(s) have also been implicated in NANB hepatitis transmitted by plasma products.[15] Our data show that these putative agents were not completely inactivated by heating the FVIII preparation to 60°C for 72 h.

The secondary objectives of this study were to ascertain the severity and tendency to chronicity of the post-transfusion hepatitis and any possible relation between infection and concentrate lot or dose. Occurrence of hepatitis was clearly not related to the lot number or to the number of infusions. The 90% recovery rate during the 12-month follow-up was similar to that which has been reported in first-exposure haemophiliacs given unheated FVIII.[2] Only 1 of our 11 patients became jaundiced and had symptoms. Whether the hepatitis in our patients was truly attenuated by the heat treatment of FVIII can only be established by a controlled study, but we did not think it justifiable to include a control group of patients treated with unheated FVIII, since chimpanzee studies have suggested that a safer product was available.[9] The high prevalence of NANB hepatitis and the absence of HBV transmission in our subjects are in contrast with the HBV transmission and absence of NANB hepatitis in chimpanzees given the same heated concentrate.[9] These differences indicate that the animal model is not reliable for NANB hepatitis transmission studies[16] and that prospective studies in first-exposure haemophiliacs are essential for the evaluation of the safety of new "treated" concentrates. HBV added in large doses to the concentrate withstood the heating procedure, and delayed-onset hepatitis B occurred in chimpanzees.[9] There are two possible explanations for the apparent absence of hepatitis B among our patients. Perhaps the concentrates contained a low bioburden which could be inactivated, or maybe NANB viral infections interfered with HBV expression.[17,18] There have been reports that first-exposure haemophiliacs in whom NANB hepatitis developed after exposure to unheated FVIII concentrates do not have signs of HBV infection.[2,3]

Our finding that NANB hepatitis is transmitted by a heated concentrate should not be taken as evidence that heat treatment is equally ineffective for other viral agents. We have seen, for instance, that none of these patients seroconverted to the retrovirus considered to be the putative agent of AIDS, whereas the rate of seroconversion was high in a group similar to ours in terms of amount of concentrate transfused but who received an unheated preparation.[19] Although this finding needs to be confirmed it is consistent with the observation of the thermolability of AIDS retroviruses.[20]

References at foot of next page

QUININE AND SEVERE FALCIPARUM MALARIA IN LATE PREGNANCY

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Summary Quinine dihydrochloride was given intravenously to 12 women with severe falciparum malaria in the third trimester of pregnancy. The initial dose consisted of 10 or 20 mg salt/kg over 4 h and was followed by 10 mg salt/kg every 8 h until patients were fit to swallow, when quinine sulphate tablets were given. Uterine activity showed little or no change despite rising quinine concentrations. Of 3 patients in labour, 2 proceeded normally while a third had a successful caesarean section for fetal distress. Late (type II) decelerations of the fetal heart rate were recorded in 6 patients before treatment but in most patients signs of fetal distress diminished as the maternal temperature fell. Hypoglycaemia and hyperinsulinaemia developed in 7 patients, in 2 before quinine was started. The important toxic effect of quinine in late pregnancy is not an oxytocic action but rather its capacity to release insulin.

Introduction

> "La plupart des auteurs admettent aujourd'hui qu'une femme enceinte, affectée de paludisme, est plus exposée à avorter si on ne lui donne pas de quinine que si on lui en donne."
>
> Laveran, 1907[1]

FALCIPARUM malaria can be a devastating complication of pregnancy.[2-4] In Thailand it is the commonest cause of maternal mortality.[2] 50% of pregnant women who become unrousable during the course of falciparum malaria die, and the fetus is stillborn in most of these cases irrespective of the maternal outcome (Warrell et al, unpublished).

In Southeast Asia, quinine has become indispensable for the treatment of severe chloroquine-resistant malaria, but its safety in pregnancy is uncertain. It was used successfully in pregnancy before synthetic antimalarials were developed[3,6,7] but it has also been given to induce abortion[8] and to augment labour.[9] It has been blamed for stillbirth[10] and acute renal failure in pregnancy.[11] Pregnant women seem particularly prone to quinine-induced hypoglycaemia.[12] In Thailand we are obliged to use quinine for all cases of severe malaria because there is no other effective drug available for intravenous use. We report here an investigation of the toxicity of quinine in women who had severe falciparum malaria in late pregnancy.

Patients and Methods

Patients

In 1982 and 1983, patients more than 29 weeks pregnant admitted to Pra Pokklao Provincial Hospital, eastern Thailand, were selected for study if they had *Plasmodium falciparum* malaria which was sufficiently severe to demand treatment with intravenous quinine. Patients or their relatives gave written informed consent to investigation and treatment. The study was approved by the ethical committee, Faculty of Tropical Medicine, Mahidol University, Bangkok. Patients were excluded if they had taken quinine within the previous 3 days or had detectable quinine in their blood on admission.

Clinical Assessment

Patients were admitted to the obstetric intensive-care unit and were seen by both an obstetrician and physician. History and physical examination, including a detailed obstetric assessment with an estimate of gestational age, were recorded on standard forms. A doctor remained with the patient throughout the study.

Treatment

The initial dose of quinine dihydrochloride (Government Pharmaceutical Organisation, Thailand) given was either 10 mg or (in 2 cases) 20 mg of the salt/kg (equivalent to 8·3 and 16·7 mg base/kg, respectively) diluted in 500 ml of normal saline and infused over 4 h; this was followed by further 4 h infusions of 10 mg of the salt/kg every 8 h. As soon as they could swallow, patients took quinine sulphate tablets until they had completed 7 days of quinine treatment.

Investigation

A 'Teflon' catheter was inserted into an antecubital vein and kept patent with heparinised saline. Blood was taken for baseline parasite count, haematocrit, white-cell count, blood urea nitrogen, serum creatinine, albumin, globulin, total and direct bilirubin, and serum aspartate aminotransferase.

M. COLOMBO AND OTHERS: REFERENCES

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Australian MRSA and would be expected if either was used alone. Resistance to vancomycin is, so far, a laboratory phenomenon but, if vancomycin is more widely used, resistance may become a problem.

Several authors have reported failure to contain MRSA infection without an isolation unit:[1,2,14] hospitals without such facilities or, as at this hospital, unable to finance the staffing of a unit may find that this epidemic MRSA will pose a considerable threat to their clinical practice.

We thank Miss Sarah Picton, RGN, infection control nursing officer, and Miss M. Pereira, BSc, for their expert epidemiological and laboratory assistance.

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Occasional Survey

PROGRESSIVE LIVER DISEASE IN HAEMOPHILIA: AN UNDERSTATED PROBLEM?

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Summary In an 8-year study of 79 unselected patients with haemophilia who had received clotting factor concentrates, there was evidence of chronic progressive liver disease in at least 17 (21%). 8 patients had chronic active hepatitis and 9 had cirrhosis (5 with oesophageal varices). Histological evidence suggested that non-A non-B hepatitis was mainly responsible, although the influence of other viruses could not be excluded. Serial liver biopsies showed progression from chronic persistent hepatitis to chronic active hepatitis and cirrhosis within 6 years, suggesting that chronic persistent hepatitis in haemophiliacs is not as benign as hitherto supposed. Symptoms and abnormal physical signs were uncommon in these patients. There was no relation between degree of abnormality of serum aminotransferase levels and severity of the underlying liver disease. It is anticipated that liver disease in haemophiliacs will become an increasing clinical problem in the future.

INTRODUCTION

ABNORMAL liver function tests have been reported in 20–100% of patients with haemophilia who have received blood products.[1–6] In many patients these abnormalities are transient and probably reflect acute self-limiting hepatitis, but they persist in a substantial proportion. Liver biopsies have shown that these biochemical abnormalities reflect various types of chronic inflammatory disease, including chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and cirrhosis.[1–6]

Little concern has been expressed about the long-term implications of liver disease associated with haemophilia;[1,6-8] few clinical features of chronic liver disease have been reported in haemophiliacs and few deaths attributed to it. Liver biopsy studies have shown CPH in most of these patients, leading various workers to conclude that liver disease in haemophilia is benign and non-progressive.[1,6-8] Moreover, the recent publicity about AIDS in haemophilia has overshadowed the problem of liver disease.

We now report our observations in a group of haemophilic patients who have been followed prospectively for several years, with specific attention to their liver status.

PATIENTS AND METHODS

Since 1977 we have regularly screened haemophilic patients for clinical and biochemical evidence of liver disease. The series comprised 65 patients with haemophilia A and 13 with haemophilia B, and also included 1 patient with von Willebrand's disease. All had received blood products at some time.

Percutaneous liver biopsies[2-4] were done in 34 patients with elevated aminotransferase levels that had persisted for longer than 6 months without any evidence of returning to normal. Serum aminotransferase levels were considered abnormal if they fell outside the reference range; the degree of abnormality did not influence the decision to do the biopsy. All patients gave written informed consent. Contraindications to biopsy included the presence of a factor VIII or IX inhibitor and psychological unsuitability. One liver sample was obtained post mortem in a patient with a high-titre factor VIII inhibitor. Mean age of the patients was 31·6 years (range 3–70) at the time of their first biopsy. 31 had haemophilia A, 2 had haemophilia B, and the series also included the patient with von Willebrand's disease who acquired acute hepatitis after receiving factor VIII concentrate.[4] 24 of the haemophiliacs were severely affected (factor VIII or IX <2%). All had received factor VIII or IX concentrate at some time; their consumption in the 3 years prior to biopsy was calculated from the hospital records.

9 patients had a second liver biopsy. Patients were considered for a repeat biopsy if they showed new physical signs of liver disease or if their aminotransferase levels remained persistently abnormal for at least a further 2 years after the first biopsy. Repeat biopsies were not done in children, patients with established cirrhosis, and those in

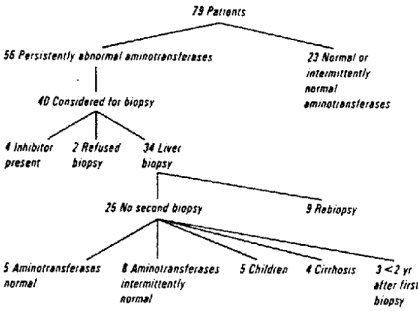

Fig 1—Factors in the decision to carry out liver biopsies.

whom liver function tests had become normal or were only intermittently abnormal (fig 1).

Liver Biopsies

Cores of liver tissue were fixed in neutral buffered 10% formalin for routine histology and light microscopy. Small fragments were fixed in neutral buffered 3% glutaraldehyde for electron microscopy. Paraffin sections for light microscopy were stained with haematoxylin and eosin, orcein, periodic acid/Schiff after diastase treatment, silver impregnation for reticulin, Masson's trichrome, and rhodanine. Each biopsy was classified by means of standard criteria for histological diagnosis of chronic liver disease.[9] The presence of microvesicular steatosis, sinusoidal infiltration, and periductal infiltration was taken as evidence of non-A non-B (NANB) hepatitis.[10,11]

RESULTS

Initial biopsy in 34 patients showed CPH in 20, chronic lobular hepatitis (CLH) in 1, CAH in 9, and established micronodular cirrhosis in 4. One patient with cirrhosis admitted to 60–80g of alcohol/day and had histological features consistent with alcohol abuse. None of the other biopsies had features of alcoholic liver damage. Further details of these cases will be published elsewhere.

9 patients had a second biopsy; the relevant features are shown in the table, and the histology of 2 patients is shown in fig 2. Only 1 of the serially biopsied patients (patient 7) showed partial resolution of CAH. We have also included a child whose initial liver biopsy showed CAH and who subsequently manifested spider naevi, splenomegaly, and radiological evidence of oesophageal varices over the next 3 years; we conclude that this 12-year-old had cirrhosis. Thus, cirrhosis was present in at least 9 of the 34 patients.

RESULTS OF SERIAL LIVER BIOPSIES

Patient	First biopsy	Second biopsy	Age at first biopsy (yr)	Interval between biopsies (mo)	Factor VIII or IX consumption (U/kg/yr)
1	CPH	CPH	30	49	28
2	CPH	CPH	31	25	74·4
3	CPH	CAH	33	56	653·6
4	CPH	CAH	22	27	687·4
5	CPH	Cirrhosis	67	58	294·8
6	CPH	Cirrhosis	48	69	34·5
7	CAH	CPH	26	93	501·3
8	CAH	Cirrhosis	36	31	29·4
9	CAH	Cirrhosis	55	45	142·2
10*	CAH	*	9	..	Unavailable

*Second biopsy not done but unequivocal signs of cirrhosis and portal hypertension developed within 3 yr of first biopsy.

24 patients had histological evidence of NANB hepatitis, including 7 who had a second biopsy. None had histological or serological evidence to indicate that they were chronic hepatitis B virus (HBV) carriers.

Biochemistry

In 56 of the 79 haemophiliacs screened regularly, the aminotransferase levels were elevated for more than 6 months. This abnormality persisted for at least a further 2 years in 40 patients. Of the remaining 39, the aminotransferase levels became normal in 20 and intermittently abnormal in a further 19. By definition, persistently abnormal aminotransferase levels were present in all patients who had liver biopsies; the degree of aminotransferase elevation bore no relation to the liver histology.

Clinical Features

2 patients died, both from intracerebral haemorrhage; both had histological evidence of cirrhosis. 1 of these patients had a mild confusional state, attributed to hepatic encephalopathy. He was also known to have radiological evidence of oesophageal varices and had a haematemesis shortly before he died. Only 3 of the patients with cirrhosis had spider naevi; although 8 had splenomegaly and 5 had hepatomegaly, both these physical signs can be seen in patients with lesser degrees of liver disease. The spleen was palpable in 3 patients with CPH and 1 with CLH; hepatomegaly was seen in 3 patients with CAH. 5 of the 9 cirrhotic patients had radiological evidence of oesophageal varices.

Factor VIII Therapy

Severity and progression of the liver disease was unrelated to factor VIII consumption in the 3 years prior to liver biopsy.

DISCUSSION

Our observations show that progressive liver disease is a potentially serious problem in haemophilia. Of 79 haemophilic patients, selected solely on the basis of previous exposure to blood products, 17 had evidence of progressive liver disease (9 cirrhosis, 8 CAH). Serial liver biopsies showed progression of CPH to CAH and cirrhosis within a period of 2–6 years.

The prevalence of abnormal liver function tests in haemophiliacs increased rapidly with the widespread introduction of factor VIII and IX concentrates in the mid-1970s.[12-14] These abnormalities are believed to arise as a sequel to viral infection transmitted by blood products.[5-8] Since the introduction of HBV testing of blood donations and HBV vaccination, HBV has become a much less frequent cause of liver disease in haemophilia, although most patients still have markers of previous exposure to this virus.[1-5] Almost all previously untreated haemophiliacs acquire NANB hepatitis after the administration of factor VIII concentrate, and regular users may have multiple attacks from more than one NANB agent.[15,16]

In agreement with other workers, we found that persistent elevation of aminotransferase levels for more than 6 months occurred in over half the patients.[2,3,5,13,17] Symptoms and abnormal physical signs were usually absent, and, when present, were sometimes misleading. Spider naevi were seen in a minority of patients with cirrhosis, whereas splenomegaly and hepatomegaly occurred in several patients without cirrhosis. A palpable spleen is sometimes found in haemophiliacs and may not be related to liver disease. Neither the degree of biochemical abnormality nor the physical signs

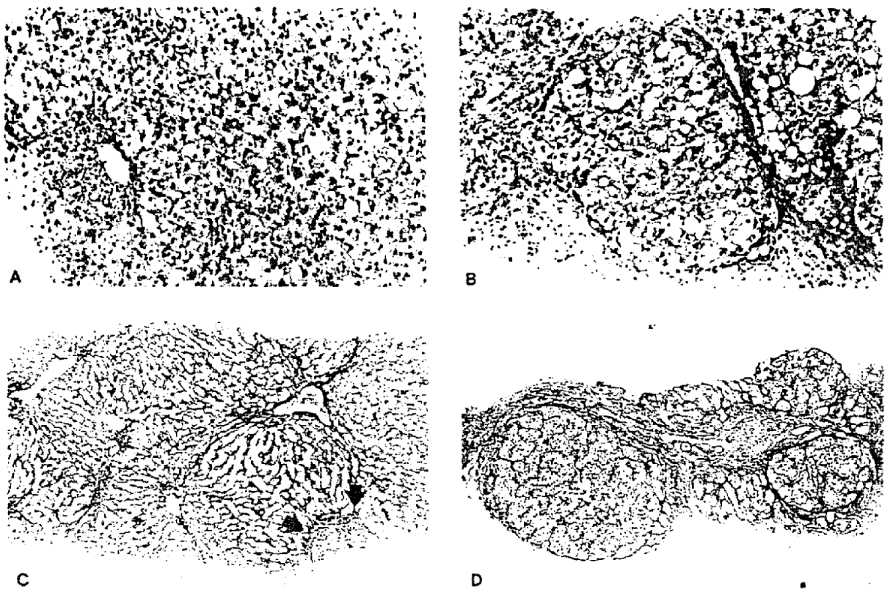

Fig 2—Serial liver biopsies showing progression from CPH or mild CAH to micronodular cirrhosis.

Patient 8 in 1979 (A) and 1981 (B): Steatosis and sinusoidal infiltration suggest NANB virus infection (haematoxylin and eosin, reduced by ½ from × 215). Patient 5 in 1979 (C) and 1983 (D): Portal tract (arrowed) in first biopsy shows no erosion of limiting plate; cirrhosis subsequently confirmed at necropsy (silver impregnation for reticulin, reduced by ½ from × 85).

gave a reliable indication of the nature of the underlying liver disease. Liver biopsy is therefore the only means of establishing the diagnosis.

There is only one previous report of serial liver biopsies in haemophiliacs, in which Mannucci et al reported partial resolution of CAH in 4 of 11 patients who had serial biopsies, although 1 patient with cirrhosis died from bleeding oesophageal varices.[1] Their findings contrast with our own: they studied predominantly patients whose aminotransferase levels were intermittently elevated and often returned to normal, whereas our patients had persistent aminotransferase elevation and may therefore represent a group with a much greater prevalence of chronic liver disease. Nevertheless, chronic progressive liver disease may occur in patients whose liver function tests are only intermittently abnormal; since we did not consider such patients for liver biopsy, we have probably underestimated the number of patients with CAH and cirrhosis. A further difference between our study and those previously reported is the length of follow-up. Cirrhosis may take several years to develop and it is consequently not surprising that cirrhosis was more common in our series than in earlier studies with shorter periods of follow-up.[1,5-7] This is especially important in view of the fact that the high prevalence of liver disease probably dates from the introduction of factor VIII concentrates. Studies in non-haemophilic patients with NANB show a prevalence of chronic liver disease and frequency of progression to CAH and cirrhosis comparable with the observations in our series.[18-20]

A notable feature of our series is that 4 patients with CPH have shown progression to CAH and cirrhosis; this is at variance with the generally accepted view that CPH is benign and non-progressive[21] and leads us to speculate that repeated exposure to hepatitis viruses may modify the usually benign course. The size of the liver biopsy sample, together with the nature of the histological changes, makes us confident that the progression is genuine and unrelated to sampling variability. No other causes of liver disease were identified in most of the patients and none of those who had two liver biopsies abused alcohol, analgesics, or narcotics.

Although few reports of death attributable to liver disease in haemophilia have appeared, we predict that this will become more common. The introduction of virus-free or synthetic factor VIII concentrates cannot be expected to make a significant impact for several years. Although these products may well benefit hitherto untreated haemophiliacs, it is doubtful whether they will influence the progression of liver disease in those in whom it is already established.

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In England Now

MARCHING FOR WENDY SAVAGE, THE SUSPENDED OBSTETRICIAN[1,2]

IT seemed more like a festival than a protest. Children with balloons, babies in pushchairs, friendly groups chatting and smiling as the crowd grew in the grassy square near Mile End Hospital. There were medical students, GPs, hospital doctors, and midwives, but it was the people of the East London borough of Tower Hamlets who made the greatest impression. It was as much a celebration of the work of Wendy Savage as a protest at her suspension. Her recent honour—a fellowship from the Royal College of Obstetricians and Gynaecologists—seemed irrelevant compared with the overwhelming warmth and spontaneity of her defence from the local community.

Local GPs carried placards, ready to march side by side with their patients. "We can always reach her when we need her. She comes out to us to give care where it is needed, and we know the quality of care she gives" said one, when I expressed surprise. "I didn't want no caesarean" said a forthright mother of twins. "Wendy let's you have 'em natural, the way it ought to be, and she's with you helping all the way." So much for the obstetricians who say it is only the intellectual middle class who care about natural childbirth.

The crowd, now quiet and serious, formed into an orderly line and set off to march to the London Hospital, followed by a gaily decorated bus carrying some of the Asian women, who had come out in support even though it was Ramadan. "Wendy is best—investigate the rest!" and "Bring back Wendy, we shall not be moved" we chanted and sang along the main road while women waved from tall blocks of flats that have replaced little houses and corner shops.

Six of us (one a medical student) were allowed to meet the chairman of the health authority when Beverley Beech presented a letter asking for the immediate reinstatement of Wendy Savage and an investigation into local obstetric services. A hospital doctor brought a letter from his colleagues at Mile End. "Where are you from?" the chairman repeatedly asked the women wearing saris. "Tower Hamlets" they replied, "And where are you from?"

In the health authority meeting Wendy Savage was not on the agenda but the people could not be ignored. The crowd outside, now in heavy rain, were still chanting "Bring back Wendy" while members floundered to find a formula which would mollify the protesters. They were unused to discussing obstetric services in the presence of breastfeeding mothers and babes in arms. A locum was suggested "*No!* Only Wendy—she gives us the care we want." A venerable clergymen said no criticism of Mrs Savage was intended. "And if the bishop was to suspend you, vicar" said a robust cockney voice, "You wouldn't think it was any criticism of you, would you?" At last there was a decision to obtain "another professional opinion" as a matter of urgency. "Ask the Royal College!" shouted the women.

Perhaps the RCOG should be asked to do more than suggest an expert. There have been two major demonstrations in London on obstetric care: one at the Royal Free protesting against high-technology obstetrics; and one supporting Wendy Savage. The local women were not just fighting the injustice they felt had been done, they were demanding the kind of care they wanted. Why did they feel that "only Wendy" could provide it?

JEAN ROBINSON,
Past chairperson, The Patients Association

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Now that I am retired I naturally have to spend most of my time looking for my spectacles, trying to remember the names of my grandchildren, and wondering what I meant to do when I opened the cupboard door just now. But at intervals I manage to wander along to the medical library to see how far they have gone to the dogs without my regular patronage.

I first frequented medical libraries in the golden era when they were peaceful temples of helpful information; the annual input to the *Index Medicus* was contained in a single manageable volume, and symposia had not yet begun to breed. I was allowed by silver-haired librarians to sit in a comfortable chair in a dimly lit corner and occupy myself with a few slim books or journals. Clocks ticked, dust motes floated, and an occasional cough merely drew attention to the blissful silence.

Nowadays things are different. The present librarian has not a single silver hair (librarians, like policemen, grow younger every year). The stacks are in a constant state of flux, so that nothing is where it was last time, and every desirable current journal is either at the binders or has been stolen. The construction of the plastic seats bears no vestige of relationship to the construction of the bodies they are supposed to support, and the strip lights dazzle the eyes of the reader. Borrowing a book has become an electronic intelligence test which I cannot pass, and there is constant noise pollution from slot-machine copiers. In all directions lurk the cold glares of visual display units; Big Brother is still watching us, even though it is now 1985.

But these are minor hazards; it is the printed page itself that distresses me most. Once upon a time readers sat down to articles like On the comparative structure of the cortex cerebri, or Traité de la venin de la vipère; on y a joint un description d'un nouveau canal de l'oeil, in the confident expectation of enjoying a rattling good yarn. Today even the lists of contents of most of the journals are incomprehensible because of esoteric chemical formulae, arcane hormonal axes, and mysterious immunological or genetic jargon; I never dare to look inside. Nor do the Recent Acquisitions cheer me up; these 800-page monsters merely reinforce my resentment that so many people know so much about things of which I am entirely ignorant.

However, I am glad to say that I can still (usually) understand every word in In England Now, and this enables me to return home somewhat comforted.

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