

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.

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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 biopsies²⁻⁴ 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

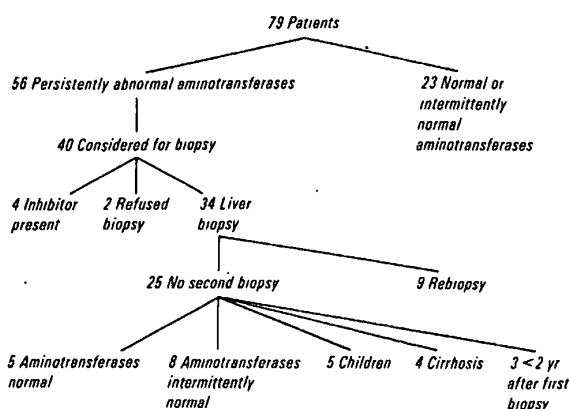


Fig 1—Factors in the decision to carry out liver biopsies.

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

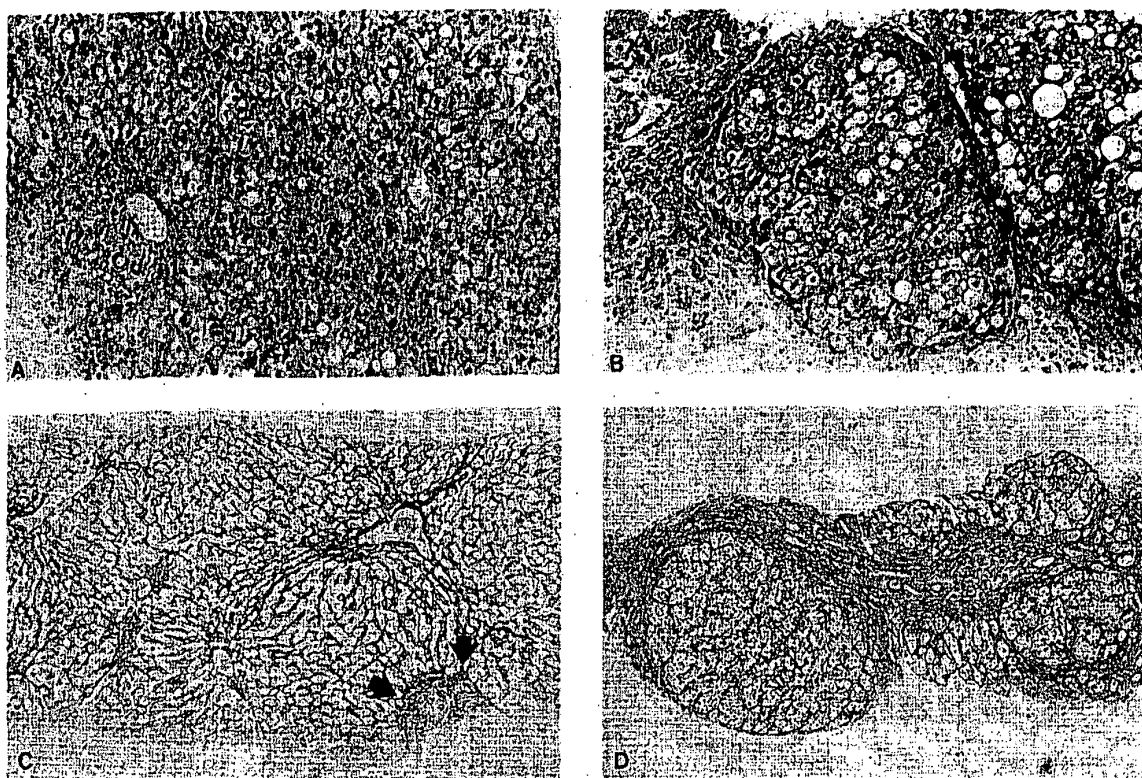


Fig 2—Serial liver biopsies showing progression from CPH or mild CAH to micronodular cirrhosis.

Patient 8 in 1979 (A) and 1981 (B): Steatosis and sinusoidal infiltration suggest NANB virus infection (haematoxylin and eosin, reduced by $\frac{1}{2}$ from $\times 215$). 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 $\frac{1}{2}$ from $\times 85$).

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-progressive²¹ 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.

We thank Dr J. S. Lilleyman, Sheffield Children's Hospital, for access to data from his patients.

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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 clergyman 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"

1. Dyer C. The Savage case: disciplining consultants. *Br Med J* 1985; **290**: 1894-95.
2. Note. Suspension of NHS obstetrician. *Lancet* 1985; **i**: 1463.

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

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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