i) Charlie May's document.

ii) The Lancet

iii)

iv)

v) Hep C - The facts

STATEMENT

"HAEMOPHILIA AND LIVER DISEASE" - HAY (BULLETIN) (MAY 1991)

HAY → KLENERMAN ; 7/10/91 (1382)

PROGRESSIVE LIVER DISEASE IN HAEMOPHILIA: AN UNDERSTATED PROBLEM?" HAY ET AL (LANCET) (JUNE 1985)

MEDICAL NOTE 724 ; CHEMICAL PATHOLOGY 16/1/92 ; CURIOSITIES CONCERNING HEPATITIS HISTORY

" " 841 ; "LIVER FAILURE"

HEPATITIS - THE FACTS - MIKE MAKRIS, 1996

HARTLEY → GILMORE ; 8/6/94

FREEMAN 22/8/94 "DISCUSSED WITH DR GILMORE"

FREEMAN 18/8/94 "WE WILL SIMPLY SAY WE HAVE FINISHED ASSESSMENT"

BASSENDINE → HAY "WE UNEARTHED AN ALPHA-FETOPROTEIN... 9280" ; 19/8/94

ULTRASOUND RLUH ; 20/7/94 ; "THERE IS A VERY WELL-DEFINED ROUND MASS"

RLUH AFP - 9280 ; 15/7/94

RLUH 8/6/92 ; "NOT AT ALL HAPPY FOR THIS MAN TO HAVE A FULL LIVER WORK UP"

HAY → PRESTON, 19/8/94 "THEY HAD BEEN DRAGGING THEIR FEET A BIT" P.T.O

GILMORE → HAM – POST MORTEM;
GILMORE → MUM – " " ; 9/9/94
HAM → MUM – " " ; 21/11/94

"A LIVER TRANSPLANT THAT CHANGED A LIFE" BULLETIN; SEP 1996
"WHY IS HEPATITIS C ALL IN THE MIND?" BULLETIN; SEP 1996
"TREATMENT OF HEPATITIS C"; U/K
"WHAT IS HEPATITIS C AND WHAT RELEVANCE IS IT TO PEOPLE WITH HAEMOPHILIA?"; BAGLIN; BULLETIN (MARCH 1996)
GILMORE TO HARTLEY – 13/7/94 (1428)
DISCHARGE SUMMARY – 8/6/92 "DR HAM CANCELLED" (191)
FREEMAN; 7CMS IN DIAMETER "LIKELY... HEPATOMA"
FREEMAN; AFP 1.00000ug/L; ~~23/8/94~~ 17/8/94

DIRECTORY
RE-ORDER CODE EN2437 RECYCLED

STATEMENT

From myself, Mrs Maureen Murphy, regarding my late husband, Mr William Murphy (Date of Birt GRO-C .34 / Date of Death 3.9.94) a haemophiliac, who died at the Royal Liverpool University Hospital as a result of:

i) **Hepatocellular carcinoma.**
ii) **Cirrhosis of the liver.**
iii) **Hepatitis C**
iv) **Haemophilia A.**

This statement has been made to support my pursuance of a medical negligence claim, through Irvings Solicitors, Liverpool, against the Royal Liverpool University Hospital.

After examining my late husband's medical records in detail, I wish to emphasise that it is my conviction that he was the subject of compounded medical negligence over a period of not less than 2 years and 10 months encompassing December 1991, to the date of his death, September 3 1994.

I have restricted details to the above period for the purposes of this statement only. I have done this both for ease and with a firm conviction that, although I am convinced my husband had certainly been the subject of medical negligence prior to December 1991, the clinical events in the last period of his life alone should provide enough evidence to substantiate my claim.

Although my statement concerns the 1991-94 period as stated, I have, as a matter of necessity, included occasional history and back-up references from prior to that period.

I base my statement around four key areas:

i) How was my husband allowed to undergo a knee-replacement operation in December 1991 when his haemotological / hepatological state clearly made him unfit for such a procedure ?

ii) Why, after diagnosis with cirrhosis of the liver in January 1992, followed by periods of oesophageal bleeding (varices), which are known indicators of the recognised medical state known as "liver failure" - which is one of the recognised starting points for consideration of liver transplantation - was all mention of such a possible procedure withheld until June 1994, when he was finally referred to a liver specialist ?

iii) Why, in July 1994, when preparations were underway to send my husband to the Freeman Hospital, Newcastle, for further tests re: a liver transplant, was the existence of cancer not noted at the RLUH ?

It is medically known that the hopes for a liver transplant are seriously undermined, if not eradicated, by cancer. My husband's cancer, as can be proved, was in existence in July 1994 in the form of a 6.5cm (diameter) tumour with an Alpha-fetoprotein reading of 9280. Liverpool's failure to spot this crucial indicator was duly noted by the clinicians in Newcastle.

iv) Why, on return to Liverpool on August 19 1994, with said tumour likely to be in excess, at that stage, of 7cm (diameter), was chemotherapy treatment not due to be administered until September 6 1994, which, as it transpired, proved to be three days after his death ?

This represents an unacceptable waiting period of 19 days for a patient with seriously defined cancer. My husband was actually discharged from the RLUH following treatment for varices just four days before his death.

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1)

How was my husband allowed to undergo a knee-replacement operation in December 1991 when his haemotological / hepatological state clearly made him unfit for such procedure ?

In January 1992, as the medical records confirm, my husband was a patient at the Royal Liverpool University Hospital recovering from a knee-replacement operation, necessitated by his basic condition as a haemophiliac.

At this stage, and indeed for several years previously, I was inclined to believe, in the absence of information to the contrary, that my husband was free from infection due to contaminated NHS administered blood products.

We had known for some time that he was HIV negative, unlike his two haemophiliac brothers, who had both died of AIDS-related illnesses in 1989 and 1990.

We had previously been alerted to another possible blight on the haemophiliac community, known as *Hepatitis Non-a Non-b.* Ironically, the existence of this disease, later to be medically defined as Hepatitis C, was brought to our attention by Dr Charles Hay, the haematologist attending to my husband, in an article he had written for the *Haemophilia Society* bulletin earlier that year.

The article (enclosed) was entitled Haemophilia and Liver Disease and was by-lined to Dr C.R.M. Hay, Director of the Mersey Region Haemophilia Centre.

The central thrust of the article, is to the effect that research, conducted over a number of years, had led to the medical conclusion that a serious hepatological problem lay in store for haemophiliacs, who had been injected with infected blood products.

The author clearly makes the distinction between NEWER and OLDER haemophiliacs. Clearly my husband fell into the OLDER category, especially as it was known that he had suffered from 'transfusion hepatitis' in the late 1970s and then again in November 1981, following transfusions accompanying a duodenal ulcer at the Royal Liverpool University Hospital.

There had clearly been some concern about the likelihood of a newer hepatological problem for haemophiliacs for some years and as Dr Hay noted in his 1991 article:

"Increasing awareness of transfusion hepatitis during the 1970s led to the universal adoption of hepatitis B testing of all blood donations and the closure of American skid-row blood banks. This greatly reduced the frequency of hepatitis B after transfusion, but had little impact on the prevalence of transfusion hepatitis as a whole, since it was usually caused by non-A non-B hepatitis.

"The hepatitis C test is only now becoming widely available after the discovery of the virus in 1989 and all blood donations will be tested for this virus within the next few months."

The article later concludes by stating:

"For newly diagnosed haemophilic patients, haemophilic liver disease is of historical interest only, since current licensed concentrates are virologically safe. For older patients, it is usually not an active concern since most will have recovered or will have mild liver disease.

"A minority of patients are at risk from more serious problems and may require treatment with alph-interferon (sic) however, even though the role of such treatment is still under investigation.

"Certainly, it is one of the functions of every haemophilia centre to monitor all patients for evidence of chronic liver disease and the clinical problems that can result from this."

Therefore, with some justification, my husband and I safely assumed, prior to his admittance for the 1991 knee operation, that such monitoring had been ongoing and in the absence of information to the contrary, that he was a suitable candidate for major surgery.

The dangers of major surgery in haemophiliacs are well known and it could be sensibly assumed that such dangers would only be compounded, especially in a haemophiliac suffering from chronic liver disease.

My husband's admittance for his knee operation is, I believe, proof that he was judged to be in an adequate hepatological state.

Medical record sheet No. 1382 (enclosed) dated October 7 1991 would appear to back this up.

A letter from Charles Hay, the Consultant Haematologist, to Prof. L Klennerman of the RLUH Orthopaedic Dept, refers specifically to the prevailing conditions governing my husband's admittance for a knee-replacement operation.

Dr Hay clearly states: **"There are no haemotological problems other than his haemophilia, so the whole thing should be very straightforward..."**

It is now clear that was far from the case. The operation, finally carried out on December 6 1991 had clearly run into complications as early as the mid-point of January 1992.

It is now clear that those complications surfaced because such a complex operation had been carried out on a patient suffering from Hepatitis C.

Naturally extensive testing was carried out in January 1992 and on the 14th of that month, I was informed, by the RLUH, that my husband was suffering from CIRRHOSIS OF THE LIVER and it was explained to me that this had been the result of ongoing Hepatitis C (formerly non A non B), most likely the result of infected 'preheat treatment era' blood transfusions during his duodenal ulcer operation at the same hospital in November 1981.

At that point I was told that my husband's condition was terminal. His condition also explained as to why the knee-replacement had not been the success expected, and indeed I was told, that if it had been known, prior to the operation, that my husband was suffering from Hepatitis C / cirrhosis, then most certainly he would not have been allowed to undergo surgery.

I find this explanation difficult to reconcile with the extensive medical research into the likely incidence of complicated liver disease, especially in patients such as my husband.

It is difficult to accept that my husband's condition had not been monitored, especially when the haematologist in charge of him, namely Dr Hay, had carried out such extensive research and stated publicly that "it is one of the functions of every haemophilia centre to monitor all patients for evidence of chronic liver disease and the clinical problems that can result from this."

Indeed to compound the dissatisfaction with the explanation given me the RLUH, the contents of an article in *The Lancet,* of June 29 1985 (enclosed), to which Dr Hay was one of four contributing haematologists, make it doubly unsatisfactory that I learned about my husband's terminal condition at such a late stage.

The introductory summary of the article clearly states that:

"It is anticipated that liver disease in haemophiliacs will become an increasing clinical problem in the future."

It goes on to say that:

"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."

It is my contention therefore, especially in the light of such knowledge, that my husband's condition had not been monitored satisfactorily.

The key-point of proof here, I believe, was his admission for knee surgery in December 1991. Given that he was deemed to be suffering from chronic liver disease in the December, it is hard to believe that advanced cirrhosis had developed by the following 14 January - a little over a month.

Therefore it is my contention that his hepatological monitoring was grossly inadequate and as such, in my opinion, was a contributing factor in ongoing medical negligence.

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2)

Why, after diagnosis with cirrhosis of the liver in January 1992, followed by periods of oesophageal bleeding (varices), which are known indicators of the recognised medical state known as "liver failure" - the recognised starting point for consideration of liver transplantation - was all mention of such a possible procedure withheld until June 1994, when he was finally referred to a liver specialist for the first time in 2.5 years?

Having accepted, in good faith, in 1992 that my husband was suffering from cirrhosis of the liver, I enquired as to how long he would have to live. I was told by Dr Hay that his life expectancy would be "maybe 2 weeks, 2 months or 2 years - in fact, he may never leave this hospital."

No mention was ever made of a transplant or any other avenues of hope.

I was not given any supplementary information relating to the manifestations of his condition. Therefore, it was something of a shock, when the first bout of oesophageal bleeding (varices) occurred in April 1992.

My husband was admitted to the RLUH with the condition which is a known indicator of 'liver failure'. He was admitted to a high dependency unit and was in a life threatening condition for three days.

Only after he rallied and was discharged,was it that we were informed of the nature of VARICES and it was explained that from then on, he would need to undergo surgical treatment, on a regular basis, to counteract the spontaneous oesophageal bleeding.

We were, at no stage, informed that he was in the medically defined state known as LIVER FAILURE. However medical record sheet No. 724 (enclosed) dated January 16 1992, just two days after I was informed that he had Hepatitis C / cirrhosis of the liver, clearly states "liver failure".

Another sheet, No. 841 (enclosed) dated May 5 1992, again clearly lists "liver failure"

Yet not only was no mention of a liver transplant mooted, my husband incredibly was still not referred to a hepatologist.

It is my contention that clearly my husband should have been referred to a hepatologist quite some considerable time before December 1991. If not, however, then surely such action should have been taken in January 1992 following the diagnosis with Hepatitis C / cirrhosis. In the event of the abject failure to refer on either of those two occasions then quite clearly he should have been referred at the latest by April 1992 following the first varices attack.

It is known that varices is one of the classic indicators of 'advanced liver failure' and indeed the document *Hepatitis C - the facts* (enclosed) produced by the Haemophilia Society, in conjunction with Prof. Mike Makris, from the Royal Hallamshire Hospital, Sheffield, states thus.

Under the sub-heading *'Liver transplantation - when is a liver transplant considered ?'* the document states:

"Once there is advanced liver failure. Your doctor will discuss this with you if it is present. Features of liver failure include swelling of the abdomen (ascites), dilated veins (varices) in the gullet (oesophagus) which can rupture and cause vomiting of blood, or confusion (encephalopathy)."

It really is quite astonishing now to consider that my husband had reached such a stage and the possibility of a transplant was never mentioned. However it did not seem so to us at the time as the idea of a transplant had never crossed our minds as being even the remotest possibility in a haemophiliac.

It is even harder in retrospect to accept that my husband underwent two further very serious varices attacks - later on in April 1992 and then again in May 1992 and still the possibility of a transplant failed to materialise.

It is obvious to us now that such a possibility was not mentioned for the simple reason that my husband had not been referred to a hepatologist.

Only in the period after May 1992 were my husband's varices attacks controlled, by means of vein-strengthening injections (sclerotherapy), a procedure repeated at regular and frequent intervals until just 4 days before his death.

In the period between May 1992 (the control of the varices) and June 1994, in excess of two years, my husband's condition visibly deteriorated to the point where his quality of life was *nil.*

His medical records show repeated problems with a hernia, itchiness, leg ulcers, spontaneous and embarrassing tongue bleeds, ascites, acute digestive problems and chronic fatigue. All are known symptoms of advanced liver failure.

On a personal level, it was distressing for me to witness that by May 1994 my husband was longer able to wear formal clothes such was the distention of his abdomen. His only comfortable attire was loose-fitting leisure wear.

His social life, as a consequence, was completely indoors and was blighted by the tongue-bleed episodes. As a result, by that stage my husband and I were at a very depressed level such was his ongoing rapid debilitation and deterioration.

In June 1994 his condition had visibly worsened to the point where a referral to a liver specialist was medically inescapable.

It is to be noted though that medical record sheet No. 1425 (enclosed) dated June 8 1994, shows that Dr Ian Gilmore was consulted only on the advice of Mr Mark Hartley, a Senior Surgical Registrar in the RLUH Gastro' unit and not by the hematology department.

Pointedly Mr Hartley requests of Dr Gilmore:

"I would appreciate it if you could see him fairly soon in your clinic because of his discomfort."

It is important to stress here that at that point, it had not occurred to me or my husband that such, now seemingly obvious action, should have been taken at least two years earlier.

To our amazement and without any form of medical examination, Dr Gilmore immediately raised the idea of a liver transplant. In fact, Dr Gilmore, before even taking so much as my husband's temperature, informed us of exactly which hospital he wished my husband to attend - namely the Freeman Hospital, Newcastle. Consequently the process to transfer my husband to the north east began immediately.

It is my contention, that given that my husband was deemed a possible liver transplant candidate just four months before his death, that surely he should, in light of all the medical knowledge available at that time, have been considered for a transplant in January 1992.

I believe that the failure to refer my husband to a liver specialist for **TWO AND A HALF YEARS** is considerably evidential of medical negligence, especially when the idea of liver transplant was raised almost immediately upon doing so.

Serious questions must be asked as to how a University Teaching Hospital failed in such basically stark terms to a refer a patient, patently suffering with chronic liver disease, to a liver specialist for two-and-a- half years, when such a course of action would have seemed obvious even to the non-medically qualified.

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3)

Why, in July 1994, when preparations were underway to send my husband to the Freeman Hospital, Newcastle, for further tests re: a liver transplant, was the existence of cancer not noted at the RLUH ?

It is medically known that the hopes for a liver transplant are seriously undermined, if not eradicated, by cancer. My husband's cancer, as can be proved, was in existence in July 1994 in the form of a 6.5cm (diameter) tumour with an Alpha-fetoprotein reading of 9280. Liverpool's failure to spot this crucial indicator was duly noted by the clinicians in Newcastle.

After consultation with our daughter and son, my husband decided, with some degree of heightened anticipation, to undergo preliminary tests for a liver transplant.

It needs to be stressed here that the whole idea of a transplant came as a complete shock to all of the family. Essentially though, it raised all our hopes by no inconsiderable measure. Not only would it have meant that my husband's life might be prolonged, maybe for another 10-15 years but also that such a life extension could be haemophilia free, thanks to a new liver.

The massive psychological leaps here cannot be understated. The feelings of euphoria were difficult to suppress although we knew we must do so, in case our hopes were dashed. Nevertheless, we had our own confidences that, at last, our hopes and prayers were being answered and the end to my husband's suffering could well be near.

It was therefore with some anticipation that we waited for transference to Newcastle.

Shatteringly though, in early August 1994, my husband underwent a serious bout of HEPATOLOGICAL ENCEPHALOPATHY. In much the same way as I was not informed back in April 1992 about the varices attacks, I was again subjected to a quite frightening episode, whereby my husband slipped into encephalitic coma overnight, without me realising or even suspecting a problem until a very advanced comatose state had developed.

At no stage since cirrhosis was diagnosed in January 1992 were my husband and I warned about the dangers of encephalitic coma episodes.

My husband's medical records confirm that his life was seriously threatened for several hours, until the coma was eventually treated at the RLUH following his admittance to the Accident & Emergency unit.

The hospital's records will confirm that in August 1994 the A&E dept was undergoing extensive reconstruction and was in a quite chaotic state. My husband, a haemophiliac, suffering from cirrhosis of the liver, and, unknown to us at that time - the end stages of liver failure - was left on a trolley for almost six hours, whilst myself and my family were asked rudimentary questions about his health, such as "is an asthmatic ?"

Had we have been informed of the likely incidence of coma, we would have been able to inform the overstretched A&E dept staff of the true nature of my husband's condition.

Once my husband's condition eased the next day, we were left to consider what remained of the transplant possibilities.

We were informed, rather confusingly, that my husband was now in the FINAL PART of the END STAGES of LIVER FAILURE. As far as we were aware, up to that point, my husband had not even entered liver failure.

It is clear to us now that liver failure had been in existence prior to the first varices attack in April 1992. From that point onwards, his liver had entered the "end stages" process - as highlighted by varices. Indeed those end stages were now coming to a conclusion with the onset of coma. Yet my husband had only been recommended for a liver transplant five weeks earlier.

Within five days of the coma episode, my husband and I were transferred, via hospital limousine, to the Freeman Hospital, Newcastle. It is fair to say that upon leaving Liverpool, facing the unknown in strange surroundings, that we were both in quite an emotional state.

It must also be stressed that a journey, which later proved to be utterly pointless, was a very tiring endurance for my husband. It is also distressing now to reflect that it was a sheer waste of precious days.

Tests with a view to a liver transplant started immediately and were progressing well on the following Tuesday, when the transplant co-ordinator explained to my husband, myself and our children, who had travelled north that day, the precise details of the operation.

We were given a step-by-step introduction to the whole process, even down to the point where we were told we would be receiving a bleep in order to let us know that a donor liver had been found.

Although it would have been quite impossible for my husband to have even considered a holiday abroad - it is interesting to note that the plans for a transplant had reached such a developed stage in Newcastle that we were told that under no circumstances must my husband leave the country.

It is fair to say then that the process of preparing for a transplant had reached an advanced and very detailed stage and it was accepted by all that if a donor organ became available then my husband would undergo procedure.

The whole family was very optimistic.

It was therefore with a sickening shock, the extent of which I cannot emphasise adequately, that my husband and I learned, just hours after watching our elated children return to Liverpool full of hope, that that transplant was an impossibility because a liver scan had revealed a tumour some 7cm in diameter.

It is important to record here that when the Newcastle staff were breaking the news to us, they pointedly asked my husband how long it had been since his last liver scan. When they learned that it had only been three weeks earlier in Liverpool, they seemed more than a little surprised.

However before breaking the shattering news to us, the clinicians at Newcastle had obviously discussed the likely impact. Quite naturally they were concerned about how we would react to such news so far away from home, and understandably a decision was taken not to inform us and leave it to the more familiar Liverpool staff.

The medical records submitted from Newcastle Nos 1 and 2 (enclosed), dated August 18 1994 seem to confirm this. It is clear from the clinical notes that Newcastle had decided to discuss the findings with Dr Gilmore at Liverpool and "we will simply say we have finished assessment and will let him know outcome."

However, it is clear that this decision was reversed at some stage during the day and later notes state that "COR has informed patient and his wife," and "suggested that surgery was probably not now and option..."

It was fortunate for us that Newcastle reversed their decision and informed us, as it is quite possible that my husband and I would never have discovered that the cancer was already in existence at the time of the previous liver scan in Liverpool.

The day following Newcastle's discovery, Prof. Bassendine's letter to Dr Gilmore (enclosed) dated 19 August 1994, confirmed the existence of the tumour during the Liverpool scan.

Detailing that my husband, as part of his work-up, had an NMR scan, Prof. Bassendine reports that Newcastle had discovered "a lesion of approximately 7cm in the left lobe, possibly penetrating the capsule".

Prof. Bassendine goes on to state: "On review of his Liverpool medical records we unearthed an alpha-fetoprotein from blood taken on 15th July of 9280, confirming that he has developed a hepatocellular carcinoma on the background of his Hepatitis C cirrhosis."

Interestingly I find that Prof. Bassendine's letter revealing Liverpool's failure to spot cancer was not in the medical records file submitted to me by the RLUH. My only access to this information came via the submission of records from the Freeman Hospital.

One is left to wonder why such an important document is missing. I also find curious the remark made by Dr Hay (August 26 1994) upon my husband returning to Liverpool, insisting that there was no cancer prior to Newcastle. Indeed Dr Hay, obviously referring to the gap between the Liverpool and Newcastle scans went on to say that "a lot can happen in three weeks."

However in the records submitted from Liverpool, Sheets 106 and 373 (enclosed) confirm Prof. Bassendine's report. Sheet 106 (a blood test, taken on 18 July 1994 - 20 days prior to the encephalopathy episode) clearly shows the Alphafeto Protein level of 9280. The only medical conclusion here is that my husband was suffering from cancer.

The consultant named was C.R.M. Hay.

Worse though, is the liver scan result (Sheet 373, July 20 1994 - enclosed. i.e. subsequent to the revelation of the AFP level):

Dr GRO-D , the Senior Registrar, reports to the named clinician, Dr I.T. Gilmore that the ultrasound has revealed "a very well defined round-mass (6.5cm in diameter) in the left lobe of the liver. This has no characteristic appearances and it is not possible to differentiate between a regenerative nodule and tumour."

At face value, this would appear to suggest that the RLUH is incapable of diagnosing cancer ? Even given the apparent identification problems, three things, in my opinion, point towards medical negligence / incompetence.

Firstly, given the medical knowledge available, the likelihood that the "very-well defined round mass..." (appearing on the the liver of a Hepatitis C suffering haemophiliac, with cirrhosis of the liver) was cancer must have been very high indeed and certainly worth consideration.

Secondly, if the inability to identify the cancer on the ultrasound at Liverpool is to be accepted, the one would suggest that the AFP level, as revealed on the blood count, would surely in itself be an aide to identification.

One can only assume that either the two were not matched-up, or that the likely incidence of cancer had simply not been contemplated - otherwise my husband would most certainly not have been transferred to Newcastle.

Thirdly, Newcastle's reading of AFP, at the time of the cancer diagnosis, was some 10,000 and the size of the tumour was some 7cm. When Liverpool failed to spot the tumour, it was 6.5cm with a reading of 9280. The increase to 10,000 would seem compatible with a 0.5 cm increase in tumour size.

It is difficult to accept that just 0.5cm made the crucial diagnosis. It is my contention that all three of the above areas constitute medical negligence.

It is absolutely abhorrent to realise that my husband and I built up our hopes for a transplant to such an extent, only to have them dashed by the revelation that he was suffering from cancer all the time.

Accordingly, the staff at Newcastle informed my husband that a transplant was no longer possible. I believe that there is also a question of finances here. The tests carried out at Newcastle were a sheer waste of health service money.

It is clear that my husband should have been considered for a transplant in 1992 and as such would likely have undergone procedure had an organ been found because, even at such a well developed stage of liver failure in August 1994, the medics at Newcastle confirmed that only the presence of a tumour prevented them from recommending my husband for surgery.

Ironically, sheet 194 from my husband's medical records dated 8/6/92 confirms that clinicians were in fact considering my husband for a liver work-up -- so obvious was the need.

However, as sheet 194 reports, my husband's haematologist, again Dr Hay, refused permission for a work-up.

The notes describe that Dr Hay was "not at all happy" for my husband "to have a full liver work-up". The notes go on to say that Dr Hay's refusal was "fully explained" to my husband with an apology as my husband was under the impression that he WAS to undergo a work-up.

It is difficult to accept that a work-up was refused whilst my husband was relatively well and yet a work-up was recommended two years later - when he was a man so obviously approaching death.

It is my firm conviction that the failure to refer my husband to a hepatologist until June 1994, the omission to explain about encephalopathy, the failure to diagnose cancer and the earlier refusal of a work-up, are all examples of ongoing medical negligence.

It is important to note that medical records 1433 and 1434, (both enclosed), which form a letter from Dr Hay to Prof GRO-D at the Royal Hallamshire Hospital , dated 19 August 1994: Dr Hay concedes that my husband had undergone varices treatment for the last 18 months. However, he goes on to report that my husband's "AFP have been negative and ascitic tap showed no abnormalities suggestive of underlying carcinoma". This was clearly not the case.

Interestingly Dr Hay then reports that "we have been considering hepatic transplantation with our hepatology for 2/3 months" and the delay in submission to Newcastle was down the the hepatologists "dragging their feet a bit".

It is difficult to understand as to what the purpose of this letter was, yet it clearly indicates that my husband's transference to Newcastle was too late.

Another record from my husband's file, medical record No. 1437 (enclosed), a letter from Dr Gilmore to Dr Hay, dated 20 October 1994, six weeks after my husband's death is difficult to comprehend.

Apart from the fact that it was Dr Gilmore who suggested that myself, my daughter and my son should meet him - the letter seems to indicate otherwise - it is difficult to see as to what purpose Dr Gilmore is pursuing. However, as with Dr Hay, Dr Gilmore seems to indicate that the timing of the decision to consider was husband for transplantation was far from satisfactory.

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4)

Why, on return to Liverpool on August 19 1994, with said tumour likely to be in excess, at that stage, of 7cm (diameter), was chemotherapy treatment not due to be administered until September 6 1994, which, as it transpired, proved to be three days after his death ?

This represents an unacceptable waiting period of 19 days for a patient with seriously defined cancer. My husband was actually discharged from the RLUH following treatment for varices just four days before his death.

Following my husband's return to Liverpool, after being diagnosed with cancer, it was accepted that chemotherapy would need to be administered as soon as possible.

It is unacceptable that my husband returned on 19 August 1994 and by the date of his death on 3 September 1994 he still hadn't received treatment. In fact his first chemotherapy session was not scheduled until 6 September 1994 - and may I stress that it was most disturbing to receive a telephone call from the RLUH on that day, informing me that my husband had failed to appear for his appointment.

It is difficult to accept that Newcastle were willing to keep my husband at the Freeman Hospital and commence chemotherapy treatment immediately whilst the RLUH did not consider it necessary for a further 18 days.

In Dr Hay's letter to Professor GRO-D (Medical Record No. 1433) , he refers to the "urgency" in sending my husband to Newcastle for transplant assessment. However, no such urgency is sensed in treating my husband for cancer, the eradication of which was the condition for a return to transplant assessments.

It is particularly unacceptable that on the Monday before my husband's death he was admitted to the RLUH for his varices to be treated. I was informed that it was the variceal check-up that forced the delay in chemotherapy as the oncologist only visited the RLUH once a week on a Tuesday.

A likely appointment for the commencement of chemotherapy on the Tuesday before my husband's death was cancelled by the variceal check-up which revealed no change in condition.

As the reports state, my husband had a level of AFP sufficient to suggest a serious cancerous growth on July 19th. yet by September 3 he had still not received any chemotherapy - a period touching on SEVEN WEEKS.

That seven week figure (at the inside) depends on my husband having achieved an AFP level @ 9280 in just one day, namely July 19. However, the likelihood is that my husband had started to develop cancer considerably earlier, which means that for the whole of the last three months of his life - and probably more - he was suffering from Hepatocellular Carcinoma and subsequently died without the relevant treatment.

I find that difficult to accept in the case of my husband, a patient who was so obviously in need of constant monitoring and who, ironically, spent most of that time in hospital.

GUIDE TO APPENDICES

i) "Haemophilia and liver disease". Article written by Dr. C R M Hay. Haemophilia Society bulletin (May 1991).

ii) Royal Liverpool University Hospital medical references No 1382. Letter from Dr C R M Hay dated (7.10.91) to Professor L Klennerman requesting consideration for knee replacement operation. Statements from Dr Hay " that there are no haemotological problems " .

iii) Occasional Survey : " Progressive liver disease in Haemophilia - an understated problem?". The Lancet (June 1985).

iv) Royal Liverpool University Hospital medical reference No 724. First recorded note of existence of " liver failure " (16.1.92).

v) Royal Liverpool University Hospital medical reference No 841 . Further recorded note of existence of " liver failure " (5.5.92)

vi) "Hepatitis C: The facts" . Produced by the Haemophilia Society. in conjunction with Professor Mike Makris. of the Royal Liverpool University Hospital. Lists the timescale for consideration of liver transplant.

vii) Royal Liverpool University Hospital. medical reference No 1425. Letter from Mr. Mark Hartley. Senior Surgical Registrar. to Dr. Ian Gilmore. hepatologist. requesting his involvement with my Husband (8.6.94).

viii) Newcastle Freeman Hospital medical records. clinical record by Professor M. Bassendine. ruling out possibility of transplant. (18.8.94).

ix) Newcastle Freeman Hospital medical records, letter from Professor M. Bassendine to Dr. Ian Gilmore. confirming the existence of cancer prior to Liverpool's referal to Newcastle. (19.8.94)

x) Royal Liverpool University Hospital medical reference No. 1061. Relevant blood count test prior to Liverpool's referal to Newcastle. confirming the existence of cancerous tumor via Alpha Feto Protein reading of 9280. (15.7.94).

xi) Newcastle Feeman Hospital medical records. clinical details showing increase in cancerous tumour since Liverpool's failure to recognise it via alpha Feto Protein reading of 10.000 (23.8.94)

xii) "Hepatitis C - The facts ". Produced by the Haemophilia Society in conjunction with Professor Mike Makris of the Royal Hallamshire Hospital stating that patients with cirrhosis should be recommended for alpha feto protein test readings at four monthly intervals.

xiii) Royal Liverpool University Hospital medical reference No. 373. Original ultra sound report following liver scan in Liverpool stating existence of " Well- defined round mass (6.5cm in diameter) ". (20.7.94).

xiv) Newcastle Freeman Hospital medical records, MRI liver scan dated 16.8.94 confirming 7cm mass, likely to represent hepatoma (cancer).

xv) Royal Liverpool University Hospital medical reference No. 194. Dated (18. 6.92) - clinical confirmation listing Dr. Hay's refusal for liver work -up.

xvi) Royal Liverpool University Hospital medical reference No. 191. Discharge summary (18.6.92) detailing further refusal for liver work-up as vetoed by Dr. Hay due to "limited likely benefit".

xvii) Royal Liverpool University Hospital medical reference No. 1433/1434 letter from Dr. Hay to Professor GRO-D Department of Haemotology, Royal Hallamashire Hospital, confirming Liverpool's failure to recognise cancerous tumour. Statement that "Alpha feto proteins have been negative" when in fact the opposite was the case.

xviii) Statement by my late Husband in his own handwriting detailing the deteriorating quality of his life in January 1994 for Social Security purposes.

xix) Royal Liverpool University Hospital medical reference No. 1409. letter of support from Dr. Hay, again for Social Security purposes, confirming poor quality of life.

xx) Letter of support from Royal Liverpool University Hospital Social Worker, Mrs. Linda Smith, confirming poor quality of life.

xxi) Personal correspondence from Dr. I. Gilmore to myself passing his condolences on my Husbands death. Statement to the effect that my Husband's "hopes were raised" by the late referral to transplant.

xxii) Correspondence between Dr. I Gilmore and Dr. C R M Hay refering to myself and my family's visit to Dr. I. Gilmore.

xxiii) Pesonal correspondence from Dr. Hay to myself.

HAEMOPHILIA AND LIVER DISEASE

By Dr C.R.M. Hay,
Director,
Mersey Region
Haemophilia Centre,

INTRODUCTION

Post-transfusion jaundice, caused by hepatitis viruses, became a problem as soon as blood transfusion became relatively commonplace during the second world war. Blood products were also found to cause jaundice when many thousands of GIs were infected with what became known as serum hepatitis from an infected batch of yellow fever vaccine in 1941 / 2. Twenty five years were to pass, however, before the causative agent could be identified as the hepatitis B virus and reliable tests for the virus were not widely available until the nineteen-seventies. Most of these episodes of hepatitis were mild, and although some deaths occurred, almost all patients appeared to make a complete recovery.

Until the end of the nineteen-sixties haemophilic patients appeared largely untouched by this side-effect of replacement therapy, partly because very little treatment was given by present day standards, and partly because the only available treatment came from single blood donations (eg plasma or cryoprecipitate).

Haemophilic patients were thus exposed to blood from very few donors. Isolated episodes of hepatitis B following treatment with cryoprecipitate or plasma were reported in 1969/70 but at this time only 11 per cent of haemophilic patients had biochemical evidence of chronic liver disease.

All this was to change following the introduction of factor VIII concentrate in the mid nineteen-seventies. 77 per cent of haemophilic patients were found to have biochemical evidence of chronic hepatitis by 1978.

Although thought to be caused by transfusion transmitted viruses, it was not immediately clear which virus was responsible for this liver disease. Although a high proportion of these patients had antibodies to the hepatitis B virus suggesting that they had been exposed to hepatitis B, few had a history of jaundice or had the chronic hepatitis B carrier state which is associated with chronic liver disease. It was argued that since haemophilic liver disease was not caused by hepatitis A (infectious hepatitis, not transmitted by transfusion) and not usually caused by hepatitis B that it should be attributed to the newly described non-A, non-B hepatitis (NANB).

ACUTE NON A, NON B HEPATITIS

Although the clinical concept of NANB was first described in 1974 the main causative agent, the hepatitis C, virus was not discovered until 1989. Infection in the general population is probably by contaminated food. Sexual transmission is unusual, and infected patients seldom infect members of their family. The infection seldom makes the patient jaundiced or sick and so most patients are unaware that they have contracted the infection unless blood samples are taken at frequent intervals to look for raised liver enzyme levels.

Despite this, and even if they make a complete recovery, infected patients frequently remain carriers of the hepatitis C virus for life and blood from such individuals will transmit the disease. Since almost 1 per cent of blood donors are carriers of this virus, and since factor VIII and IX concentrate are made on an industrial scale from plasma pools containing thousands of donations, it naturally follows that all factor VIII concentrate not subjected to a special viral inactivation step will be contaminated with hepatitis C.

With hindsight, it is not surprising that a study in 1983 found that all haemophilic patients developed NANB hepatitis after their first injection of factor VIII concentrate, and that there was no difference between American and UK brands in this respect.

HAEMOPHILIC LIVER DISEASE

Although we now know that, in the days before heat-treatment, all haemophilic patients treated with concentrate contracted NANB hepatitis, most did not become ill, and were unaware that they has been infected. Chronic hepatitis, as shown by abnormal liver function tests, developed in 70-80 per cent of individuals but these patients were also usually very well.

Early liver biopsy studies tended to confirm the general impression that haemophilic liver disease was a benign condition causing the patient no problems, and which should not give cause for concern. It was not until the mid eighties, well into the HIV era, that further liver biopsy studies whilst confirming some of the earlier findings showed that serious liver disease did occur in a significant minority of patients.

These studies showed that at least three quarters of haemophilic patients had very mild inflamation of the liver unlikely to progress or to cause problems. About 25 per cent of patients were found to have more severe inflamation of the liver. Although this improved in some patients it progressed in others resulting in cirrhosis of the liver in 15 per cent of patients, usually after many years.

Although probably more benign than some other forms of cirrhosis, cirrhosis following hepatitis C does carry a significant mortality.

PREVENTION

Increasing awareness of transfusion hepatitis during the nineteen-seventies led to the universal adoption of hepatitis B testing of all blood donations, and the closure of American skid-row blood banks. This greatly reduced the frequency of hepatitis B after transfusion, but had little impact on the prevalence of tranfusion hepatitis as a whole since it was usually caused by non A, non B hepatitis, The hepatitis C test is only now becoming widely available after the discovery of the virus in 1989, and all blood donations will be tested for this virus within the next few months.

All tests for antibodies to viruses suffer a common limitation called the "window period". This is the period during which an infected individual may be infected with a virus before the tests for the virus or

HAEMOPHILIA AND LIVER DISEASE

antibody to it become positive. For hepatitis B and C and HIV the window period lasts about three months. If an individual donates blood during this period the infection may be transmitted by that blood or blood even though the tests are negative.

For this reason testing of blood donations can very greatly reduce the transmission of blood-borne viruses but can never eliminate it entirely. This has long been recognised by the plasma fractionators who have been searching for an effective way to render factor VIII concentrate virologically safe since the early eighties.

Early attempts to heat-treat factor VIII concentrate to render it virologically safe were ineffective. Factor VIII was denatured and the end product would not dissolve. Factor VIII of greater purity than had previously been available had to be produced before the problem of loss of solubility following heat treatment could be overcome and before the factor VIII concentrate could be heated sufficiently to kill the viruses.

Indeed, although heat treated concentrates were widely adopted as safe from HIV in 1985, some batches of the concentrates available at this time still transmitted hepatitis B and C since these viruses were very much less sensitive to heat treatment than HIV.

Pasteurisation destroyed viruses effectly but also denatured 50 per cent of the factor VIII. A clinical trial of such a product began in Germany as early as 1981 but continued throughout the eighties and was published only in 1989. Supplies of this product became available much too late to have an impact on the HIV epidemic, are still in limited supply, and have only been licensed for use in this country for about 18 months. Pasteurisation and solvent/detergent treatment of concentrate has now largely replaced dry heating, and all concentrates currently licensed can be regarded as completely safe from hepatitis and HIV

TREATMENT

transmission. Haemophilic patients newly treated in the last three or four years no longer suffer this complication.

Although patients recently treated with concentrate will not become infected with hepatitis, most older patients with severe haemophilia will have been infected with hepatitis C at sometime in the past. Most of these patients will not require treatment, having only very mild liver disease, but a minority with more severe liver disease are at risk from clinical complications of liver disease, and in these patients some form of treatment would be desirable. The only form of treatment currently undergoing trial for such patients is alpha-interferon. This is given by self-administered subcutaneous injection three times a week, and in the doses effective in hepatitis C, has few side-effects.

Early results are extremely encouraging, but this form of treatment may have to be given for a year or more, or possibly intermittently over a period of years, to control the liver disease. The length of time for which interferon should be given, and the patients to whom it should be offered remain to be determined by clinical trial but at present this form of treatment would appear to offer the best option for patients with severe haemophilic disease. One disadvantage of such an approach is that the severity of liver disease can often only be reliably determined by liver biopsy.

CONCLUSION

For newly diagnosed haemophilic patients, haemophilic liver disease is of historical interest only since current licensed concentrates are virologically safe. For older patients, it is usually not an active concern since most will have recovered or will have mild liver disease. A minority of patients are at risk from more serious problems and may require treatment with alph-interferon however, even though the role of such treatment is still under investigation. Certainly, it is one of the functions of every haemophilia centre to monitor all patients for evidence of chronic liver disease and the clinical problems that can result from this.

MANY THANKS

Chris Bishop, Managing Director of Armour Pharmaceutical Company, presents General Secretary David Watters with a cheque for £10,000 towards the costs of producing The Bulletin during 1991.

NEW FAST PRENATAL TESTS

It was reported in 'GP News' recently that a new rapid test for prenatal diagnosis of haemophilia was on the way. This test has been developed at Guy's Hospital paediatric research unit. It is claimed that any NHS genetics laboratory could perform the procedure in two days — provided that it knew the mutation causing the disorder in the patients.

We hope to be able to carry a fuller article on this in a future edition of The Bulletin.

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Royal Liverpool University Hospital

GRO-D

Your Ref: Our Ref: CRMH/LAN If telephoning please ask for:

7 October 1991

Professor L Klenerman
Orthopaedic Department
RLUH

John please help

No reference to date received / passed

Dear Professor Klenerman

Re: William Murphy, GRO-C Liverpool GRO-C

Diagnosis: Severe Haemophilia
HIV seronegative
Arthritis of the left knee

This gentleman was on the waiting list for left knee replacement. Unfortunately his operation had to be cancelled at the last minute. For some reason the letter cancelling the operation had been delayed and he only heard as he was about to set out for hospital. He became upset and so I suspect refused the alternative date that was given to him.

I saw him for review on 30/9/91. He is increasingly disabled with his left knee and can hardly walk. The pain is quite severe and keeps him awake at night. I am sure he justifies knee replacement and is now again very anxious to go through with the operation. I would be most grateful if he could be listed again for surgery. There are no haematological problems other than his haemophilia, so the whole thing should be very straightforward and the patient accepts the usual risks which have been explained to him in detail both by yourself and us. If you have got a date for him, I would be grateful if you could let me know.

With best wishes.

Yours sincerely

TCH for gno 10/12/91

GRO-C

Charles Hay
Consultant Haematologist,
Director, Mersey Regional Haem. Centre

cc. Mr Walsh
Orthopaedic Surgeon
RLUH

Dr M S Feld
GRO-C
Liverpool GRO-C

Occasional Survey

PROGRESSIVE LIVER DISEASE IN HAEMOPHILIA: AN UNDERSTATED PROBLEM?

C. R. M. HAY F. E. PRESTON
D. R. TRIGER J. C. E. UNDERWOOD

University Departments of Haematology, Medicine, and Pathology, Royal Hallamshire Hospital, Sheffield

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 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

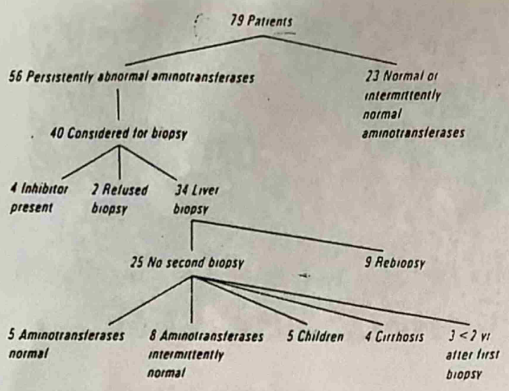

Fig 1—Factors in the decision to carry out liver biopsies.

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	71·4
3	CPH	CAH	33	56	653·6
4	CPH	CAH	22	27	687·4
5	CPH	Cirrhosis	67	58	291·8
6	CPH	Cirrhosis	48	69	34·5
7	CAH	CPH	26	93	501·1
8	CAH	Cirrhosis	36	31	29·4
9	CAH	Cirrhosis	55	48	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 haemophiliic 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

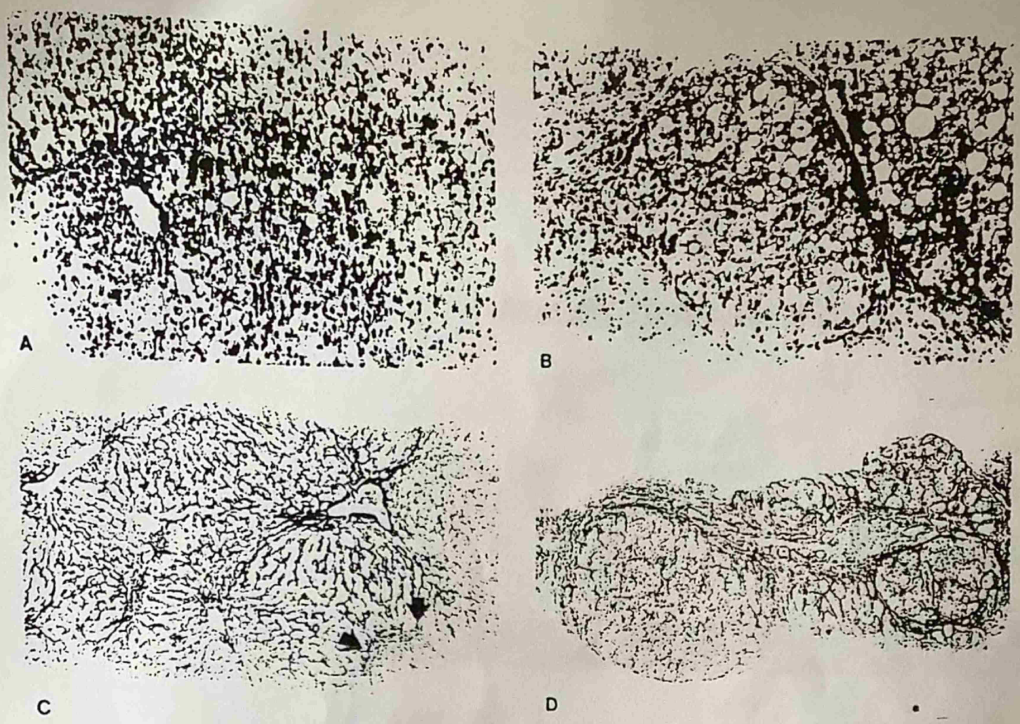

Fig 2—Serial liver biopsies showing progression from CPH or mild CAH to micronodular cirrhosis.

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 [illegible] 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.

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

Correspondence should be addressed to D. R. T., Department of Medicine, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

REFERENCES

1. Mannucci PM, Colombo M, Rizzetto M. Non-progressive course of non-A non-B chronic hepatitis in multitransfused hemophiliacs. *Blood* 1982; **60**: 655–58.

References continued at foot of next page

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AL LIVERPOOL UNIVERSITY HOSPITAL - CHEMICAL PATHOLOGY - TEL: 051 - 706 423

16/1/92

HEPATITIS? (Yes/No)

RY OF VIRAL HEPATITIS? (Yes/No)

her infections

RELEVANT CLINICAL DETAILS

Liver failure
Haemophilia

GRO-C: R Je

ure of M.O.

SPECIMEN

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MURPHY
WILLIAM
GRO-C 1934 M
GRO-C

REQUEST

SMAC + Gluc

H LABELS TO BOTH COPIES

Unit 4Y

Date of Birth Hay

74 M/F

WARD 4A

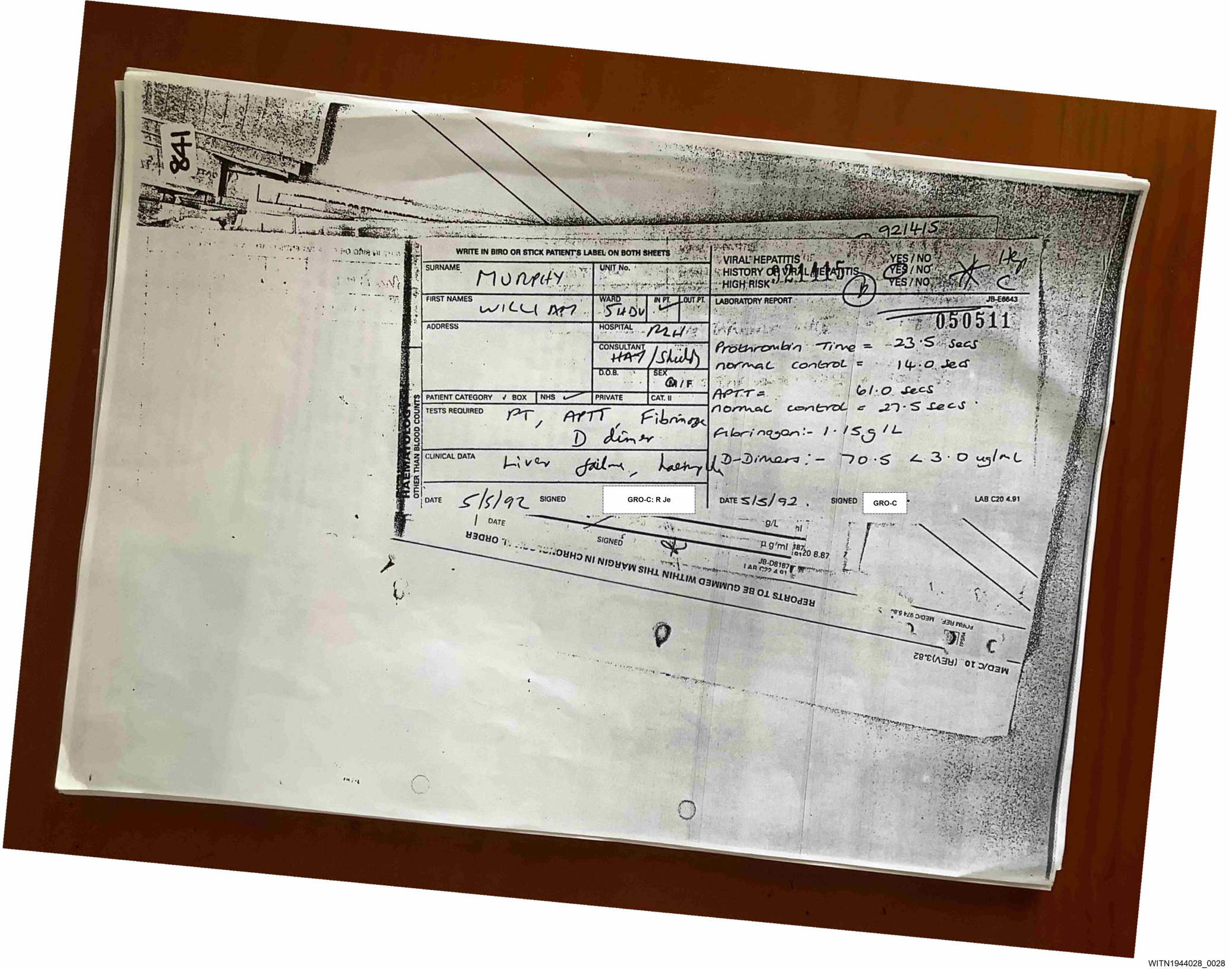
s appropriate NHS ☑ PRIVATE ☐ CATEGORY 2 ☐ IN-PATIENT ☑ OUT-PATIENT ☐ DAY HOSPITAL ☐

LABORATORY USE ONLY

Plasma ALT	27	U/L
Plasma Alk Phosphatase	101	U/L
Plasma Urea	2.0	mmol/L
Plasma Creatinine	62	umol/L
POTASSIUM	3.5	mmol/l
BILIRUBIN	59	umol/l
GLUCOSE	5.7	mmol/l

Signature GRO-C

CLINICAL CHEMISTRY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WRITE IN BIRO OR STICK PATIENT'S LABEL ON BOTH SHEETS
SURNAME
MURPHY
UNIT No.
FIRST NAMES
WILLIAM
WARD
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IN PT.
OUT PT.
ADDRESS
HOSPITAL
RAH
CONSULTANT
HAT / Shiu
D.O.B.
SEX
M / F
PATIENT CATEGORY ✓ BOX
NHS
PRIVATE
CAT. II
TESTS REQUIRED
PT, APTT Fibrinogen
D dimer
CLINICAL DATA
Liver failure, haemoptysis
DATE 5/5/92
SIGNED
GRO-C: R Je
HAEMATOLOGY
OTHER THAN BLOOD COUNTS
VIRAL HEPATITIS
HISTORY OF VIRAL HEPATITIS
HIGH RISK
YES / NO
YES / NO
YES / NO
LABORATORY REPORT
JB-E6643
050511
Prothrombin Time = 23.5 secs
normal control = 14.0 secs
APTT = 61.0 secs
normal control = 27.5 secs
Fibrinogen:- 1.15 g/L
D-Dimers:- 70.5 < 3.0 ug/mL
DATE 5/5/92
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LAB C22 4.91
LAB C20 8.87
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MED/C 10 (REV)3.82

Hepatitis

the facts

TREATMENTS

There are differing approaches to the treatment and management of hepatitis C in people with haemophilia across the country. The following information is not intended to identify right or wrong practice, but rather inform those affected by HCV of the differences and to make people aware of issues surrounding various treatments.

INTERFERON

WHAT IS INTERFERON?

Interferon is a substance made by the body in response to a viral infection. Its role is to destroy viruses which are infecting the body. When interferon is given for treatment of hepatitis C, much higher doses than those produced by the body are used and the aim is to eliminate the virus from the body. However, interferon does not repair any liver damage that has already occurred.

Three types of interferon are licensed in the UK, produced by different manufacturers. Viraferon (the same as Intron) is made by Schering Plough, Roferon by Roche and Wellferon by Wellcome. Most of the trials in hepatitis C have been performed with Intron and Roferon, and there is no evidence that there is any difference between them in terms of response.

WHO SHOULD BE TREATED WITH INTERFERON?

All patients should have access to treatment after discussions with a Liver Specialist to determine if it is appropriate and to explain potential side effects. Any patient who is hepatitis C PCR positive and has abnormal liver function tests should have the option of interferon discussed with them. Some Centres would consider treatment for patients who are PCR positive but who have normal liver function tests, although this is controversial.

IS A LIVER BIOPSY NECESSARY BEFORE STARTING INTERFERON TREATMENT?

Although most people without haemophilia have a liver biopsy before starting interferon this is not essential in haemophilia. Some Centres treat people with haemophilia without a liver biopsy but others perform a liver biopsy and offer interferon only to those affected with more advanced disease. See the 'Liver Biopsy' factsheet for more detailed information on liver biopsies.

HOW IS INTERFERON TREATMENT GIVEN?

Treatment is given by injection using a syringe and needle containing a small amount of fluid. The needle is inserted just under the skin of the stomach or the outside of the thighs. The injections are usually given three times a week (Mondays, Wednesdays, Fridays). After training from health care professionals, most patients are able to give their own injections at home.

HOW IS THE RESPONSE TO INTERFERON MONITORED?

Response is monitored by measurement of the ALT (alanine aminotransferase) which reflects the degree of inflammation in the liver. An ALT test is performed from a blood test. Response is also monitored by PCR (polymerase chain reaction test) for hepatitis C which is a very sensitive technique that detects the presence of the virus in the blood.

HOW LONG SHOULD TREATMENT BE FOR?

For patients who fail to clear the virus after twelve weeks most doctors would either stop treatment, increase the dose of interferon, or offer the chance of trying the combination of interferon and ribavirin. For responders (ie. normal ALT and negative PCR), treatment is continued with the same dose of interferon for twelve months.

Different hospitals may offer different advice according to their treatment protocol as no single protocol is clearly superior.

WHAT ARE THE SIDE-EFFECTS OF INTERFERON AND WHAT CAN I DO ABOUT THEM?
The most common side-effect is flu-like symptoms (muscle aches, fever, headache, tiredness, feeling generally unwell) that affect almost everybody who takes the drug. Patients who experience this should take two paracetamol one hour prior to the interferon treatment. It also helps if the interferon is taken last thing at night. These symptoms often subside after a fortnight as the body adjusts to the interferon. However, a small number of people are unable to complete a course of interferon treatment as the symptoms are too uncomfortable.

Numerous other rarer side-effects have been reported. These include hair loss, depression, nervousness, reduction in the white cell and platelet counts and thyroid abnormalities. It is advisable to avoid interferon treatment if you are susceptible to depression.

Patients with cirrhosis are more likely to have side-effects, but if you do experience any side-effects it does not mean you have cirrhosis.

WHAT ARE THE CHANCES OF INTERFERON BEING SUCCESSFUL IN ELIMINATING THE VIRUS?
In people without haemophilia around 20% of all patients treated become long-term responders, ie, clear the virus and remain virus-free once interferon has been stopped. The results in haemophilia are not as good. Although 50% respond whilst receiving treatment, once the interferon is stopped only around 10% remain complete responders.

ARE SOME PATIENTS MORE LIKELY TO RESPOND?
Yes. Patients with hepatitis C genotypes 2 or 3 and patients with a lower level of viraemia (the amount of hepatitis C virus in the blood) respond best. A genotype is a group of organisms with the same genetic make-up. There are six main genotypes in hepatitis C and 80 subtypes. Most people with haemophilia in the UK, however, are infected with genotype 1 which does not respond very well to interferon.

It is also considered that the earlier interferon treatment starts in the course of infection, the more likely it is to produce a sustained response. Patients with advanced liver disease are known to respond poorly.

WHAT ARE THE LONG-TERM EFFECTS OF INTERFERON?
Interferon has been used for hepatitis C for around ten years. Patients who are complete responders at one year after the discontinuation of treatment are likely to remain so long-term. Some studies suggest that even in people who receive interferon and do not respond (in terms of clearing the virus) the chances of developing liver cancer in the long-term are reduced.

I AM HIV POSITIVE. SHOULD I BE TREATED WITH INTERFERON?
HIV positive patients respond less well but in general, provided your CD4 count is stable and more than 400, most doctors would consider interferon treatment.

I HAVE VON WILLEBRAND'S DISEASE/I AM A HAEMOPHILIA CARRIER. WHAT ARE THE IMPLICATIONS FOR ME?
Your liver disease is likely to behave in an identical manner to that of people with haemophilia as it was acquired through the same route. Interferon should be offered as above.

I HAVE ADVANCED LIVER FAILURE. CAN I BE TREATED WITH INTERFERON?
No. Interferon has little role in advanced liver failure and it is likely to make you feel worse. You should discuss the possibility of a liver transplant with your centre and your liver specialist.

RIBAVIRIN

WHAT IS RIBAVIRIN?
This is an antiviral drug that has been available for many years to treat a virus (respiratory syncytial virus) that causes chest infections in children. More recently it has been shown to have activity against hepatitis C.

It is available from Schering Plough but currently can only be obtained, in the UK, for patients that are entered into clinical trials. For people with haemophilia a liver biopsy is not required before receiving ribavirin.

WHAT DOES THE TREATMENT INVOLVE?
Ribavirin is a tablet that has to be taken daily. The dose depends on the persons weight, but is usually 5 or 6 tablets daily. On its own, however, it reduces but does not clear the virus, so now most trials use ribavirin in combination with interferon (viraferon).

WHAT ARE THE SIDE-EFFECTS OF RIBAVIRIN?
Ribavirin is generally well tolerated. The most common side-effects are an anaemia that is usually mild and reversible, itching, increased cough and muscle pains. Rare side-effects include gout, depression, nervousness, difficulty in sleeping and dizziness.

WHAT ARE THE RESULTS OF THE COMBINATION THERAPY SO FAR?
Results so far are preliminary, but suggest that the chances of response are better than interferon alone. The trials, however, have been very small and caution must be exercised in their interpretation.

LIVER TRANSPLANTATION

WHEN IS A LIVER TRANSPLANT CONSIDERED?
Once there is advanced liver failure. Your doctor will discuss this with you if it is present. Features of liver failure include swelling of the abdomen due to fluid (ascites), dilated veins (varices) in the gullet (oesophagus) which can rupture and cause vomiting of blood, or confusion (encephalopathy). In general a transplant will be considered if a person is expected to survive for less than one year.

HOW EASY IS IT TO GET A TRANSPLANT?
People with haemophilia have access to liver transplantation in exactly the same way as non-haemophiliacs. Because tissue matching only depends on blood group it is actually much easier to get a liver transplant than a kidney transplant.

There are seven liver transplant centres in the UK and two of them have experience in transplanting people with haemophilia.

WHAT IS THE SUCCESS RATE?
Around 80% of patients who have a liver transplant are alive five years later. The quality of life following a transplant is, in general, very good.

WHAT ARE THE RISKS INVOLVED FOR A PERSON WITH HAEMOPHILIA?
Immediately before the operation people with haemophilia are treated with clotting factor concentrates to correct the bleeding disorder and they require extra factor during the operation. Once the operation is over, however, there are no extra risks to a person with haemophilia.

HOW MANY LIVER TRANSPLANTS HAVE BEEN DONE ON PEOPLE WITH HAEMOPHILIA?
In the UK, at least ten people with haemophilia have had transplants and the figure world-wide is more than forty. Because it is no longer a novel procedure, cases are not reported in the literature so it is more difficult to know the exact figures.

DOES THE LIVER TRANSPLANT GET RID OF HAEMOPHILIA AND HEPATITIS C?
Because the liver manufactures factor VIII and IX, patients who have a transplant are cured of their haemophilia. The new liver invariably gets re-infected with hepatitis C, but it is too early to know how this will affect these patients in the future.

OTHER MEDICAL TREATMENTS

HCV affects millions of people world-wide and a lot of research is currently being carried out on this disease. A number of new treatments are undergoing early trials and no doubt new agents and new methods of delivering current treatments will become available in the near future so that the chances of clearing the virus will be increased.

For information on complementary therapies, please see the Complementary Therapies Factsheet.

We are grateful to Dr Mike Makris from The Royal Hallamshire Hospital, Sheffield for his help in producing this factsheet.
November 1996

1425

MNH.EM. 1020860T

8th June, 1994,

Dr. I.T. Gilmore,
Consultant Physician/
Gastroenterologist,
Link Unit 5Z,
R.L.U.H.

Dear Dr. Gilmore,

RE: Mr. William Murphy: dob dob GRO-C 1934
GRO-C Liverpool GRO-C

I would be very grateful if you could see this patient of Professor Sir Robert Shields'. He is a haemophiliac who has subsequently developed cirrhosis due to Hepatitis-C and subsequently developed portal hypertension and oesophageal varices. His oesophageal varices have been obliterated by sclerotherapy.

His current problem is tense ascites, which is making his umbilical hernia uncomfortable. We have resisted operating on his hernia because of his thrombocytopenia, haemophilia and portal hypertension. Indeed, he recently had a left inguinal hernia repair and despite platelets and factor VIII, he is left with a large haematoma in the left scrotum, which is slowly resolving.

At the moment he is on Fruseride and Amiloride for his ascites.

I would be very grateful if you could offer any other medical management to make him more comfortable. I would appreciate it if you could see him fairly soon in your clinic, because of his discomfort.

Many thanks,

Yours sincerely,

MR. MARK N. HARTLEY,
SENIOR SURGICAL REGISTRAR.

5112

Royal Liverpool University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 051-706 2000 FAX: 051-706 5806

Your Ref: D Our Ref: MNH.EM. 1020860T If telephoning please ask for:

8th June, 1994,

Dr. I.T. Gilmore,
Consultant Physician/
Gastroenterologist,
Link Unit 5Z,
R.L.U.H.

Next Monday
1/7
29/6/94
(note I saw him @ CMRH - his hospital arrangement discussed)

Dear Dr. Gilmore,

RE: Mr. William Murphy: dob dob GRO-C 1934
GRO-C Liverpool GRO-C

I would be very grateful if you could see this patient of Professor Sir Robert Shields'. He is a haemophiliac who has subsequently developed cirrhosis due to Hepatitis-C and subsequently developed portal hypertension and oesophageal varices. His oesophageal varices have been obliterated by sclerotherapy.

8/7
3PM
IH

His current problem is tense ascites, which is making his umbilical hernia uncomfortable. We have resisted operating on his hernia because of his thrombocytopenia, haemophilia and portal hypertension. Indeed, he recently had a left inguinal hernia repair and despite platelets and factor VIII, he is left with a large haematoma in the left scrotum, which is slowly resolving.

At the moment he is on Frusemide and Amiloride for his ascites.

I would be very grateful if you could offer any other medical management to make him more comfortable. I would appreciate it if you could see him fairly soon in your clinic, because of his discomfort.

Many thanks,

Yours sincerely,

GRO-C

MR. MARK N. HARTLEY,
SENIOR SURGICAL REGISTRAR.

DATE

Blood Levels of Iron.

AFP · 92[illegible] on 18/7/94

8/8/94 Bosendine

NMR scan → small cirrhotic liver
+ portal hypertension
+ 6-7 cm lesion on edge
of (L) lobe – probably
going through capsule.

Discussed c̄ Dr Gilmore → (would 5.X) more
– he will discuss
findings with him
– we will simply say
we have finished assessment
+ will let him know outcome

NRB.

p.m. Bosendine

COR has informed pt + wife of Δ.

I ... suggested that surgery (transplant / resection) was probably not now an option and that Dr. Gilmore will discuss Rx options including 1.) chemotherapy
2.) intrahepatic alcohol.

Mr Murphy asked if transplant would be reconsidered if HCC shrank – I said it could be but not to hold out too much hope as may still not be accepted onto programme.

Please arrange to copy NMR scans to send to Dr. Gilmore in Liverpool

NKB

FREEMAN GROUP OF HOSPITALS

MEDICAL

R4B

IN-PATIENT SHEET No. .....
or
OUT-PATIENT SHEET No. .....

..... HOSPITAL

CONSULTANT

.....

REFERRED BY

.....

SURNAME (Block Letters) Murphy

FIRST NAME(S) Lorraine -

HOSPITAL NUMBER

AGE

DATE

22/8/22 TRANSPLANT MEETING -

- ? CR -

- ? HCC -

- unlikely to be suitable -

- await if dramatic response to ADRIAMYCIN

GRO-C

Discussed w Dr Gilmore.

For t+p/l c Adriamycin if good response to pre op dose of Adriamycin

GRO-C: MT

POTTS PRINTERS LIMITED

FGH /50

PROF M F BASSENDINE - EXT 26208

MFB/DA/0301316T 19 August 1994

Dr I T Gilmore
Consultant Physician and Gastroenterologist
Royal Liverpool Hospital
Prescot Street
LIVERPOOL
L7 8XP

Dear Dr Gilmore

WILLIAM MURPHY DATE OF BIRTH GRO-C 34
GRO-C LIVERPOOL GRO-C

DIAGNOSIS
1. Haemophilia A
2. Cirrhosis secondary to chronic hepatitis C with portal hypertension
3. Hepatocellular carcinoma

Thank you very much for asking us to assist with this charming 59 year old man for liver transplantation. As discussed on the phone we were all optimistic that he would be an ideal candidate, as transplant would not only cure his liver disease, but also his haemophilia. As part of his work up he had an NMR scan (copy enclosed), which confirmed a small shrunken liver with splenomegaly and ascites, but unfortunately also revealed a lesion of approximately 7cm in the left lobe possibly penetrating the capsule. On review of his Liverpool medical records we unearthed an alpha-fetoprotein protein from blood taken on 15th of July of 9280, confirming that he has developed a hepatocellular carcinoma, on the background of his hepatitis C cirrhosis.

Contd./....

PROF M F BASSENDINE - EXT 26208

MFB/DA/0301316T 19 August 1994

Mr Murphy and his wife have been told that he has developed a growth within his liver and that this alters our decision to recommend transplantation and probably other surgery. They know that on their return to Liverpool treatment options will be discussed with you and the ones that I have mentioned are of chemotherapy and/or intra-hepatic injection of alcohol, directly into the growth. Mr Murphy and his wife asked whether a transplant would be reconsidered if the tumour shrank and I indicated that we would happily re-discuss this with you, but emphasised that he should not hold out too much hope for this as in the past I had had patients turned down at the assessment meeting despite some improvement in the growth however, it may be that we will shortly adopt a protocol using intra-venous Adriamycin pre-operatively, during the anhepatic phase and post-operatively as good results have been obtained in tumours of this size using this regime in the States. Certainly if his alpha-fetoprotein falls reflecting repsonse to medical therapy I would be very keen to re-discuss this option with you.

King regards

Yours sincerely

M F Bassendine
Professor of Hepatology/Consultant Physician

ENC

1061

MURPHY

[redacted] Surname

[redacted] Surname

MURPH

[redacted] Surname

[redacted] Surname

[redacted]

ROYAL LIVERPOOL UNIVERSITY HOSPITAL — CLINICAL CHEMISTRY — TEL: 051-706 4230

Surname	Forename(s)	Unit/District Number	Cons/GP	Ward/Clinic	Destination
MURPHY	WILLIAM	1020860T	CRMH	5X	5X

Clinical Data	M/F	D.o.B.	Address
HAEMOPHILIAC	M	GRO-C /34	WARD 5X RLUH

Specimen Date / Time	AFP ug/l < 7	bHCG IU/L	AcPhos Total IU/l	AcPhos Prost IU/L					Comment
15/07/94	9280*								

Comments (only applicable to highlighted results)

Lab No.	Date/Time Received	Report Date	Authorised
94.4604848.Q	18/07/94 09:27	25/07/94	JR

or analysis
/sis
ıitable for analysis
[D], inappropriate
-], insufficient [I])

Comm

MLO C1213

Lab N
94.

FRH F12	PROF M F BASSENDINE MED

Clinical details:
LIVER TX ASSESSMENT

Specimen type: Serum

AFP = >100000ug/L

Spec Date/Time: 17/08/94 MO: AGARWAL Lab No: 614506

REPORT DATE		
23/08/94	12:37	CRP,FERRITIN,AFP,CU,MG,CAERULOPLASMIN

FH 213

August '94

Liver Transplant Assessment

Name: Hilary Murray

Bloods:

Hb	10.0	Na+	136	Ferritin:	104
WCC	5.9	K+	3.2	Iron	
Hct	29.5	Urea	4.8	%Satn	
MCV	99.9	Creatinine	83	TransF:	
Plt	56	Tot. Protein	73		
PT	19	Albumin	32	IgG	
KCT	83	Tot.Calcium	2.09	IgA	
Fib.	1.7	Phosphate	1.00	IgM	
Fac.V	777	Bilirubin	40	Caerul	0.34
B12	1000	Alk.Phos.	124	CRP	6
Folate	8.3	ALT	87		
RCFol	705	Amylase	14	TSH	
		Glucose	5.2		
		AlphaFP *	>100,000 *	Mg	0.69
		Alpha1-AT		Zn	

Fac VIII : 1.57.

AutoAb:

Cu :

Choles : 3.9

B-2-M :

TGs :

BLOOD GROUP: A Positive

Antibodies?

CMV IgG :

Blood Film: nad.

373

ULTRASOUND DEPARTMENT. Royal Liverpool University Hospital RPI No. 00027137
Casesheet number 1020860T
MURPHY, WILLIAM GRO-C 1934 MALE
GRO-C Liverpool, GRO-C

Report to : WARD 5X
Clinician : DR I.T GILMORE
Reported by : GRO-D , SENIOR REGISTRAR
Clinical History : HAEMOPHILIA FOR LIVER TRANSPLANT.

ULTRASOUND LIVER 20.07.94

THE LIVER IS MARKED SHRUNKEN AND HAS A VERY NODULAR OUTLINE. THERE IS A VERY WELL-DEFINED ROUND MASS (6.5 CM DIAMETER) IN THE LEFT LOBE OF THE LIVER. THIS HAS NO CHARACTERISTIC APPEARANCES AND IT IS NOT POSSIBLE TO DIFFERENTIATE BETWEEN A REGENERATIVE NODULE AND TUMOUR.
THE PORTAL VEIN CALIBRE IS NORMAL AND NORMAL FLOW WAS DEMONSTRATED INT HE PORTAL VEIN, THE MAIN PORTAL VEIN BRANCHES AND THE MIDDLE AND LEFT HEPATIC VEINS. THE RIGHT HEPATIC VEIN WAS NOT SEEN.
THERE IS A LARGE AMOUNT OF ASCITES. THE SPLEEN IS ENLARGED (16 CM).
INCIDENTALLY, THERE IS A 3 CM SEPTATED CYST AT THE UPPER POLE OF THE RIGHT KIDNEY. NORMAL APPEARANCES OF THE LEFT KIDNEY.

U.LI
(DFW//DW 94061700) ULTRASOUND

20 Jul 94

10th

9th

8th

7th

6th

5th

REQUEST FOR RADIOLOGICAL OPINION

FREEMAN GROUP OF HOSPITALS

Attach one patient label to this space on each page, and send one extra

Surname MURPHY M/S/W

First names WILLIAM M/F

Address GRO-C

GRO-C

GRO-C

Harlow Healthcare 091-455 4286 C0158/d16/179-80

Ward/Clinic/G.P. 12

Consultant MRS

NHS PP | CAT II | O/SEAS VISITOR

L.M.P. .....

IS PATIENT PREGNANT?

YES/NO Clinician | YES/NO Radiographer

Hospital No.	Date of birth	Previous X-ray Hospital	Year	WALK/CHAIR/TROLLEY DRIP/PORTABLE
	7/11/34.			

Relevant Clinical Information

for LIVER TRANSPLANT ASSESSMENT. Sev Haemophilia A. Therefore NIL angiography. urgent

Suggested Examination MR ABDO

Printed surname of Doctor completing request GRO-C

Date 2/12/94 Signature GRO-C

Date Rec.	Appt.	Complete	Radiographer	RM	Films	Contrast Media	Dose	By.
	9am		AH	MR				

REPORT

MR ABDOMEN: Axial and coronal proton density and T2 weighted spinecho, axial T1 weighted spinecho, coronal oblique dynamic gadolinium enhanced FLASH. There is marked ascites which results in some motion artefact. The spleen is enlarged. The liver is small with an irregular contour inferiorly. From the lateral segment of the left lobe a mass is seen to arise. This is isointense or of increased signal intensity compared to normal liver on T1 weighted scan and slightly hyperintense on T2 weighted scans with central areas consistent with regions of necrosis. This mass measured approximately 7cm in diameter. On the immediate post injection scan it is hyperintense compared to normal liver and becomes hypointense on later images with a thin hyperintense rim. It abutts the surface of the liver. The stomach is displaced posteriorly and inferiorly by the mass. The SMA and hepatic artery are identified and are patent as is the SMV, portal vein, right and left

XR

ALL PREVIOUS FILMS MUST ACCOMPANY THE PATIENT

FH/17

rahepatic portal veins and the splenic vein at the confluence with the SMV (the splenic vein more distally is not included in the dynamic imaging block). The IVC is patent. Hepatic veins are narrow and difficult to identify, but do appear patent.
SUMMARY: Small shrunken liver with marked ascites. 7cm mass inferiorly in the left lobe of the liver likely to represent a hepatoma. The major vascular structures are patent.

MRI C BAUDOUIN/PB 18H t

DATE	CLINICAL NOTES (Each entry must be signed)
[illegible]	[illegible]
	[illegible] ... No protocol available
	[illegible]
	[signature]
5/6/92	Still awaiting protocol ? [illegible] [illegible] which way [illegible] levels need to be increased but [illegible] away today. GRO-C
8/6/92	D/W Dr Hay, Consultant Haematologist, who is not at all happy for this man to have a fuller liver w/u and considers it essential to restrict investigations to OGD & scleros + anything else vital. Clearly prognostic indicator assessment is not vital; cannot do OGD & scleros now ∴ readmit 28/6/92 for same 30/6/92. Fully explained and apologised to Mr Murphy [signature]

DISCHARGE SUMMARY IN CS

DATE

22/5/92 + Stable –

Dx FBC –

Rx – 1 further dose of 8 x 575u Monoclate this am. & then home.

Home on tranexamic acid 500mg qds further 7d.
Ranitidine 150mg b.d.

To return 7/6/92 for repeat sclerotherapy.

GRO-C

22.5.92 8x575 u/per vial monoclate given Hay pt NO problems Home Rx given.
C Marsden CNP.

WCC Hb 4·3
Hb 11·6 –
Platelets ??
22/5/92 12⁰⁵ MS.

2/6/92 Discharge Summary:-

- 58yr ♂ haemophilia / Hep C. / oesophageal varices
- patient under jt care of Dr Hay / Prof Shields
- admitted for full formal liver working 8/6/92
- in view of extreme risk / extreme cost / limited likely benefit of work up as NEW Dr Hay cancelled
- discharged same day
- TCI / OPD - Scheduled. 29/6/92. for 30th

GRO-C

1433

Royal Liverpool University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 051-706 2000 FAX: 051-706 5806

Your Ref: 1058/061/080

Our Ref: CRMH/TAA

If telephoning please ask for:
TEL: 051-706 4322
FAX: 051-706 5810

19th August 1994

GRO-D
Department of Haematology
Royal Hallamshire Hospital
Glossop Road
Sheffield
S10 2JF

Dear GRO-D

RE: William Murphy
GRO-C Liverpool GRO-C

Diagnosis - Severe Haemophilia
Hepatitis C
Decompensated cirrhosis of the liver
Oesophageal varices
Hepatocellular carcinoma

I am just writing to you about this patient for information. Mr Murphy is one of 3 haemophilic brothers the other 2 of whom were HIV positive and died of AIDS. Mr William Murphy has been known to have cirrhosis for some time, and we have been injecting his varices quite successfully for the last 18 months. His ascites has developed over the last year, and was quite easy to control until very recently. Alpha-fetoproteins have been negative and an ascitic tap showed no abnormalities suggestive of underlying carcinoma. We have been considering hepatic transplantation with our hepatologists for 2 or 3 months in view of his deteriorating quality of life, and my general feeling that his prognosis was poor, and they had been dragging their feet a bit. He was admitted with his first episode of hepatic encephalopathy only 10 days ago and his ascites was even more difficult to keep under control, at which point (I was on holiday), they finally sent him up to Newcastle for urgent assessment for liver transplant. They have just sent him back and tell us that he has hepatocellular carcinoma. We are planning cytoreductive chemotherapy, following which they will reconsider him for transplantation. I am sure this is a complication we will see more of, but since the numbers are currently low I felt I should let you know.

It is ironic that I received this bad news whilst going through Mike Makris' thesis!

With best wishes.

Yours sincerely

GRO-C

Charles Hay
SENIOR LECTURER IN HAEMATOLOGY
DIRECTOR OF MERSEY REGION HAEMOPHILIA CENTRE

pc Dr P Giangrande
Oxford Haemophilia Centre
The Churchill Hospital
Oxford
OX3 7LJ

PAGE 1 COPY

BEING A HAEMOPHILIAC HAS LED TO SEVERAL OTHER PROBLEMS WITH MY HEALTH. OVER THE YEARS SINCE CHILDHOOD, I HAVE HAD INNUMERABLE BLEEDS INTO MY JOINTS WHICH IN TURN HAVE LED TO MY JOINTS BEING ARTHRITIC AND PAINFUL AND I AM UNABLE TO USE MY ARMS FOR MANY EVERYDAY THINGS LIKE COOKING, PREPARING VEGETABLES, OPENING CANS. SOMETIMES IT IS EVEN DIFFICULT AND PAINFUL TO WRITE.

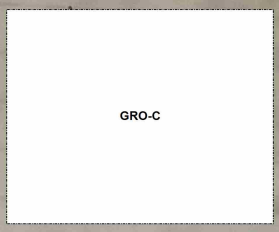
IN 1978 DUE TO THE USE OF CONTAMINATED BLOOD PRODUCTS TO CONTROL BLEEDING I CONTRACTED HEPATITIS. IN 1981 THE USE OF BLOOD PRODUCTS DURING A STAY IN HOSPITAL AGAIN RESULTED IN HEPATITIS WHICH HAS NOW CAUSED CIRRHOSIS OF THE LIVER. IN 1991 IT WAS NECESSARY TO HAVE A KNEE REPLACEMENT AND THIS PROVED DIFFICULT DUE TO EXCESSIVE BLEEDING INTO THE JOINT LEAVING IT SOMEWHAT LESS FLEXIBLE THAN ANTICIPATED. APPARENTLY THE BLEEDING WAS EXCESSIVE DUE TO REDUCED LIVER FUNCTION. THIS HAS ALSO LEFT ME WITH VARICES AND RESULTED IN SEVERAL FAIRLY SEVERE BOUTS OF INTERNAL BLEEDING AND STAYS IN HOSPITAL. I NOW HAVE TO MAINTAIN A SALT FREE DIET.

AS A RESULT OF THE STIFFNESS IN MY KNEE AND BEING UNABLE TO BEND PROPERLY I NOW HAVE A HERNIA FOR WHICH MY DOCTORS ARE RELUCTANT TO OPERATE DUE TO THE PROBLEMS OF CONTROLLING THE BLEEDING. MY HEALTH HAS DETERIORATED NOTICEABLY IN THE PAST 18-MONTHS — 2 YRS AND I NOW HAVE TO GO TO BED

Page 2 COPY

FAMILY FREQUENTLY DURING THE DAY AS I
BECOME TIRED VERY EASILY BECAUSE OF MY
LIVER PROBLEMS

L. MURPHY 14/1/94



J151

Royal Liverpool University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 051-706 2000 FAX: 051-706 5806

Your Ref: Our Ref: If telephoning please ask for:

22 December 1993

To Whom It May Concern

Re: William Murphy Dob: GRO-C 34
GRO-C Liverpool GRO-C

Diagnosis

Severe Haemophilia
Severe Haemophilic Arthropathy
Cirrhosis of the Liver (secondary to hepatitis C from Factor VIII Concentrate)

I write in support of Mr Murphy's application for the higher rate of disability living allowance. His general health has deteriorated over the last couple of years, as a consequence partly of his haemophilia and partly of the cirrhosis, which has developed as a complication of the treatment of haemophilia and he has required several hospital admissions for bleeding of oesophageal varices.

Apart from his poor general health, he has found it increasingly difficult to undertake normal every day tasks because of his severe arthropathy, caused by bleeding into the joints over the years and affecting his shoulders, elbows, knees and ankles. We have replaced his left knee but the other joints we cannot replace. He is finding it increasingly difficult to put on his socks, fasten his buttons, comb his hair and to attend to other personal needs.

Yours sincerely

GRO-C

Charles Hay
Consultant Haematologist

HAEMATOLOGY DIRECTORATE

Royal Liverpool University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 051-706 2000 FAX: 051-706 5806

Your Ref: Our Ref: LS/MEB If telephoning please ask for:

15th December 1993 SOCIAL WORK EXT 2840

Disability Living Allowance
Warbreck House
Warbreck Hill
Blackpool
FY2 0YE

Dear Sir/Madam

Re: Mr William Murphy - d.o.b. GRO-C 34

National Insurance No: GRO-C

I write on behalf of the above-named gentleman who has been in receipt of the lower rate of D.L.A. care component since 1992.

Mr Murphy has numerous health difficulties, exacerbated by haemophilia, a blood clotting disorder which causes painful internal bleeding into the joints of the body. Over the past 6 months, Mr Murphy's joints have deterioated significantly and his ability to attend to his personal care needs has been reduced substantially as a result.

Over recent months, Mr Murphy has come to rely upon his wife to assist him with many routine daily tasks ie. washing, combing his hair, putting on socks, fastening buttons etc. He requires constant assistance with many other personal care needs and in my opinion, should be considered for transfer to the higher rate of D.L.A. care component.

I should be extremely grateful if Mr Murphy's case could be reviewed with a view to transfer to the higher rate. If you require any further information, please do not hesitate to contact me on: GRO-C

Many thanks for your assistance in this matter. I look forward to receiving your reply.

Yours sincerely

GRO-C

Mrs Linda Smith
SOCIAL WORKER

Royal Liverpool
University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 051-706 2000 FAX: 051-706 5806

Your Ref: Our Ref: If telephoning please ask for:

9 September 1994

Dear Mrs Murphy,

I was very sorry to hear about your husband's death - please accept my sincere condolences. It was particularly disappointing that his hopes were raised by a transplant possibility but that was not to be. I have let my colleagues in Newcastle know.

He was a splendid, courageous patient and it was a privilege to look after him.

Yours sincerely

GRO-C: Ian Gilmore

DR I. GILMORE.

PS Do not hesitate to phone my Secretary if it would help you to talk about any aspect of his illness.

1437

Royal Liverpool University Hospital

PRESCOT STREET LIVERPOOL L7 8XP TEL: 0151-706 2000 FAX: 0151-706 5806

Your Ref: Our Ref: ITG/PL If telephoning please ask for:

20 October 1994

PRIVATE & CONFIDENTIAL

Dr. C. Hay,
Senior Lecturer,
University Department of
Haematology,
Duncan Building,
RLUHT.

Dear Charles,

Re: William Murphy (deceased)
GRO-C Liverpool GRO-C

I thought I would write to let you know that Mr. Murphy's relatives came to see me for a general talk about his illness (you will remember that he was a haemophiliac with HCV infection and a terminal hepatoma). They had specific concerns about whether earlier referral for transplantation would have resulted in a better outcome and whether screening for hepatoma could have been helpful. I explained the difficulties in timing transplantation and that there had been a hepatological input from Professor Shields, before I got involved in mid-1994.

The other issue they wanted to raise with me was a general one. They have already written to Virginia Bottomly about the lack of compensation to haemophiliacs who contract HCV in contrast to that made for HIV. I think they are also trying to take this up through the Haemophilia Society. I did not feel qualified to comment on this aspect and did not know the background. However, I thought I should mention it in case they contact you. As they seem committed to these general issues, I made the point that the decision in timing of liver transplantation would have been very much easier had we a centre in Liverpool, and I think they have taken this on board.

What difference did it make that we did not have a T/P centre in Liverpool, to the time of a T/P. It would appear that if you live near a T/P Hosp. you get better care. Dr Gilmore is answering an question as to why & considers a T/P pointed that this should have been done much earlier. He has said that he got Dr Lucas to take.

Kind regards,

Yours sincerely,

GRO-C

I.T. Gilmore
Consultant Physician & Gastroenterologist

The University of Liverpool

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21st November 1994

Mrs M Murphy
GRO-C
Liverpool
GRO-C

Dear Mrs Murphy

I was much saddened when I heard of your husband's death, particularly when I heard of the distressing circumstances which surrounded it.

I am glad that we were finally able to discuss this face to face, although I am sure you would agree that it would have been much better had we been able to talk some weeks ago, when I know that both Alison and Linda Smith told you that I wished to talk to you.

I know that I should have written at the time, and can only apologise for that, but I knew that both Alison and Linda Smith were visiting you, and since I had asked both of them to arrange a meeting, I was a little saddened when you did not take up the offer.

You clearly have many unresolved questions in your mind in relation to Bill's illness and his management. I doubt that we were able to deal with all of those fully during the chat we had in Coventry. I would be only too happy to discuss things further either with you or with your son, either here or in Manchester. I realise it would be far more convenient for you to see me here, but bear in mind that I leave at the end of the month. Should you wish to see me, please give Tracy a ring on GRO-C to make an appointment.

With best wishes.

Yours sincerely

GRO-C

Charles Hay
SENIOR LECTURER IN HAEMATOLOGY
DIRECTOR OF MERSEY REGION HAEMOPHILIA CENTRE