Patient Name: David Black.

Date of Birth: 1st May 1937.

DATE OF DEATH: 31st October 2003.

David Black suffered with haemophilia and there was a positive family history with affected uncles. Almost inevitably, he was exposed to hepatitis C as a consequence of treatment received for his haemophilia. In my experience, his history is fairly typical of patients with haemophilia who have acquired hepatitis C at a fairly young age. After a long duration of infection, he developed severe liver damage with cirrhosis and portal hypertension. He underwent successful liver transplantation. At transplantation, it was discovered that his cirrhosis had been complicated by the development of liver cancer. He developed hepatitis C infection of his transplanted liver and this progressed to cirrhosis during the seven years after transplantation. I believe that the cause of death was hepatocellular carcinoma. Concerning the origin of the hepatocellular carcinoma there are two possibilities. It is possible that the hepatocellular carcinoma was recurrent disease. According to his medical records, the explanted liver had multiple areas of liver cancer. Under that circumstance, there is a significant risk for recurrence, but recurrence is usually seen before such a long post-transplant period has elapsed. An alternative explanation for the hepatocellular carcinoma is that it developed *de novo* in the transplanted liver. There are reports of primary hepatocellular carcinoma developing in the cirrhotic transplanted liver. However, reports are few and it is a most unusual complication. It is not possible from the available records to determine whether the liver cancer represented disease recurrence or *de novo* development.

The following is a brief summary of his clinical course as described in the available records (see list at end of report).

I can see that liver biochemistry was reported as abnormal in the mid '80s. That was prior to the so called "discovery" of hepatitis C virus. At that time it was known as chronic non-A, non-B hepatitis. It was recognized that this was common in patients with haemophilia.

His first possible complication of hepatitis C infection was gastrointestinal bleeding, which was experienced during a trip to the United States of America in 1987. He returned from the USA and underwent further treatment and investigation at Glasgow Royal Infirmary. Investigations there included upper gastrointestinal endoscopy, which identified oesophageal varices. Therefore, we can assume that cirrhosis was present in 1987. Typically, cirrhosis takes at least two decades to develop, so hepatitis C infection was probably

acquired in the 1960's. During the next few years, the patient suffered further episodes of bleeding, which were probably from the oesophageal varices. Therefore, he required repeated endoscopic therapy.

In 1994 he was referred to the local Gastroenterologist for consideration of hepatitis C antiviral therapy. At the time of that referral, the available treatment for hepatitis C simply comprised Interferon. This drug was given on three occasions per week for 6 or 12 months. The patient had already developed cirrhosis with evidence of decompensation. In all probability, antiviral therapy if given would have caused significant morbidity and was unlikely to cure the infection. It is recorded that the patient was not keen for treatment. That was a very reasonable decision.

During 1994 and 1995, there was further evidence of hepatic decompensation and the patient was referred to the Edinburgh Liver Transplant Unit. He underwent a period of assessment in Edinburgh in October 1995. It was concluded that transplantation was not yet necessary. However, the patient's condition deteriorated and he was reviewed in January 1996. Reassessment in March 1996 determined that he was suitable for transplantation and he was placed on the waiting list.

He underwent liver transplantation in April 1996. There were no early serious complications.

Liver transplantation does not cure hepatitis C infection. It simply replaces the severely damaged liver with a new liver. The new liver is inevitably infected by circulating hepatitis C virus. In most cases liver damage is experienced. The severity and rate of that damage varies quite considerably.

Abnormal liver function tests consistent with recurrent hepatitis C infection were noted in August 1996. A liver biopsy was performed in December 1998. The appearances were entirely consistent with recurrent hepatitis C virus infection. According to the records, the possibility of antiviral therapy was discussed with the patient on a number of occasions during 1999, 2000, 2001 and 2002. At that time, there were few published data to encourage the use of antiviral therapy for hepatitis C after transplantation. It was recognised that the results of Interferon treatment were poor with very few patients cured. In addition, it was recognised that Interferon was associated with significant side effects and that treatment could precipitate rejection of the transplanted liver. I assume that the pros and cons of treatment were discussed with the patient. The decision not to undertake antiviral therapy at that time was quite reasonable. The year 1997 saw the first reports of combination antiviral therapy for transplanted patients. Combination antiviral therapy includes the drugs Interferon and Ribavirin. Compared with Interferon alone, it appeared that the combination therapy was more likely to be successful. However, the addition of Ribavirin was associated with additional side effects, particularly anaemia. Between 1997 and 2002, the peer-reviewed medical literature included approximately 10 small reports that described the results of combination antiviral therapy. The average cure rate in those reports was less than 20%. Therefore, the results of treatment were still disappointing and

side effects were significant. Therefore, many Transplant Units were reluctant to consider antiviral therapy for their liver transplanted patients. Nevertheless, it is clear from the records that the possibility of antiviral therapy was discussed with the patient on a number of occasions between 1997 and 2000.

In April 2002, liver biopsy showed that the patient had developed quite significant fibrosis, though not clearly cirrhosis of the graft. These results were discussed with the patient and it was decided that he should embark on antiviral therapy. He commenced antiviral treatment on 9th December 2002. Unfortunately, he experienced severe anaemia as a consequence of the Ribavirin therapy and treatment was abandoned. He required blood transfusion.

In May 2003, it was planned that liver biopsy would be repeated. The patient was admitted for liver biopsy. Ultrasound examination raised the possibility of liver cancer. According to the records, this was not confirmed by CT scan. The patient's condition appeared to be deteriorating. Therefore, he was admitted for liver biopsy in June 2003 and this demonstrated the evidence of hepatocellular carcinoma.

I think that the development of multifocal liver cancer was the cause of hepatic decompensation and fairly rapid clinical deterioration. Sadly, the patient died in hospice care on 31st October 2003.

In my opinion, the patient almost certainly acquired hepatitis C infection as a consequence of treatment with blood products for his haemophilia. After decades of infection, he developed cirrhosis and then liver failure complicated by liver cancer. Liver transplantation was the appropriate treatment and he underwent transplantation in April 1996. Antiviral therapy if given successfully during the early years after transplantation may have prevented the development of graft cirrhosis. If his hepatocellular carcinoma represented *de novo* cancer in the graft, then the prevention of cirrhosis by antiviral therapy may have prevented the development of cancer. If, however, the hepatocellular carcinoma represented a recurrence of his original disease, then antiviral therapy may have had no impact on the timing and consequences of the development of hepatocellular carcinoma in the graft.

It is clear from the medical records that the issue of antiviral therapy was discussed with the patient on a number of occasions. It seems likely that the pros and cons of treatment were discussed with the patient. The eventual decision to treat the hepatitis C with Interferon and Ribavirin was justified. He experienced the unfortunate side effect of severe anaemia requiring transfusion and treatment cessation. At about that time, multifocal liver cancer was growing in the transplanted liver and liver cancer was the eventual cause of death.

I have no concerns at all about the treatment given. From the time that he developed complications of liver disease, his medical management in Glasgow and Edinburgh seems entirely appropriate.

In preparation of this report I have referred to the following documents.

1. Principal Glasgow Royal Infirmary records (1980 – 1989)
2. Principal Glasgow Royal Infirmary records (1990 – 1995)
3 Principal Glasgow Royal Infirmary records (1996 – 2003)
4. File described as "Copy Edinburgh Royal Infirmary Records No 1 (numbered 1 – 284) but which appear to be mainly copies of GRI rather than ERI records
5. File - "Edinburgh Royal Infirmary (2) p 1-345 consisting of copy ERI records
6. Principal GP records (1948 – 2004)
7. Folder of copy GP records – Copy GP records No 1 (numbered 1 – 64)
8. Folder of miscellaneous material:
   (a) Draft chronology of key events being worked up by Inquiry team
   (b) Copy death certificate
   (c) Post Mortem report by Dr T MacLeod dated 3 November 2003
   (d) Central Scotland Police – sudden death report
   (e) Letter from NHS National Services (Scotland) dated 22 December 2004.

Yours sincerely

Dr David Mutimer

Consultant Hepatologist