Patient Name: Victor Tamburrini.

Date of Birth: 27th April 1957.

DATE OF DEATH: 17th November 2004.

This patient developed cirrhosis and liver failure which was due to the combined effects of hepatitis C virus infection and alcohol. It is not possible to dissect the relative contributions that each of these factors made. He developed liver failure and underwent liver transplantation at the Royal Edinburgh Infirmary on 26th October 2002. He suffered serious complications of the bile duct. This required repeated endoscopic treatment. In addition, there was recurrent hepatitis C infection. The combination of biliary disease and hepatitis C infection led to graft failure. He underwent re-transplantation on 4th February 2004. His second liver transplant was complicated by peritonitis which was secondary to a bile duct leak from the entero-enterostomy. Reflecting concerns that aggressive recurrent hepatitis C infection would be observed, this patient commenced antiviral therapy on 29th March 2004. Despite antiviral therapy, the hepatitis C virus titre remained very high and the liver biopsy two months after commencement of treatment showed aggressive damage from hepatitis C virus infection. Despite persistence with antiviral therapy, the patient developed failure of this second graft. In addition, his final illness was complicated by fever and leukopaenia. Some of his agonal problems may have been contributed to by his antiviral treatment. He died in the Royal Edinburgh Infirmary on 17th November 2004.

The following is a detailed chronological account of this man's illness. I will include a brief description of each relevant event.

In September 1984, he was admitted to the Glasgow Royal Infirmary with burns. As part of his treatment, he received intravenous human plasma. He made a good recovery from that injury. The batch number of the administered plasma was identified by Professor Isobel Walker, consultant haematologist at Glasgow Royal Infirmary, (document 7(h) at end of report), and the measures taken to guarantee the microbiological safety of this specific batch were reviewed by Professor Jean-Pierre Allain of the Cambridge Blood Centre (documents 7(e)(f)). He concludes that documented measures would have destroyed the hepatitis C virus, if present. Thus, I agree that it is extremely unlikely that hepatitis C was acquired as a consequence of administration of that plasma.

In July 1998, he was referred by his General Practitioner for management of gynaecomastia. The referral letter from the General Practitioner mentions alcohol excess and abnormal liver function tests. The patient was admitted to Glasgow Royal Infirmary and underwent mastectomy in December 1998. The medical

records describe a history of alcohol abuse and consumption of 25 to 30 units of alcohol per week. Liver function tests were checked at that time and were abnormal. The abnormality would be consistent with alcoholic liver damage. The results were also consistent with hepatitis C virus infection, and also were consistent with damage due to both alcohol and hepatitis C virus. His MCV at that time was 100 which is in keeping with alcohol excess. The mastectomy was complicated by haemorrhage and he required evacuation of the haematoma and blood transfusion. Once again, it is extremely unlikely that the blood components given at that time were responsible for the hepatitis C virus infection.

In January 1999, he was admitted to Glasgow Royal Infirmary with abdominal pain. The exact cause is unclear. Blood tests showed that his serum amylase had risen slightly. Therefore, a diagnosis of possible pancreatitis was made. Ultrasound demonstrated a stone in the gallbladder. Choledocholithiasis and excess alcohol consumption are important causes of acute pancreatitis. Either may have precipitated this episode of pancreatitis.

During 2001, he developed swelling of his lower limbs. He was referred to the Glasgow Royal Infirmary for further investigation. At that time, his recorded alcohol consumption was in excess of 20 units of alcohol per week. Blood tests performed at that time strongly suggested severe liver damage. The results would be consistent with cirrhosis and hepatic decompensation due to the effect of alcohol, due to hepatitis C, or due to the combination of the two. Once again the MCV was very high (111) which is consistent with significant alcohol consumption. Other important investigations performed at that time included his hepatitis C serology which showed that he was hepatitis C virus positive. This was first demonstrated in October 2001.

The patient was advised to abstain from alcohol. In December 2001, he admitted that he still consumed an occasional glass of wine. In January 2002, he claimed abstinence from alcohol (apart from a brief period of consumption of alcohol around Christmas time), and in June 2002 he claimed complete abstinence from alcohol.

As a consequence of the positive hepatitis C result, he was asked about previous intravenous drug use and it appears this was denied on a couple of occasions. Therefore, the source of his hepatitis C infection could not be stated at that time.

The Gastroenterologist at Glasgow Royal Infirmary (Dr Stanley) referred the patient to Dr Ken Simpson (Consultant Hepatologist at the Royal Edinburgh Infirmary Transplant Unit) and the patient was seen for assessment in February 2002. At that time, there was some concern that the patient had developed primary liver cancer. However, investigations including scans and laparoscopy were unable to identify any cancer. As part of his assessment for transplant suitability, the patient underwent psychiatric assessment. He admitted that he consumed between 50 and 100 units of alcohol per week for at least eight years.

It is stated in the records that there was no history of intravenous drug use. His assessment concluded that liver transplantation was indicated though a period of abstinence from alcohol was required. The patient was seen during this period by Nurse Audrey Ewing who is a Community Psychiatric Nurse working for the Community Alcohol Service. In the correspondence, there is a letter by Nurse Ewing dated 10th April 2002. The letter states in reference to the patient that "he admitted to some experimental drug use in his teens but denied any current use". The letter does not specifically mention intravenous drug use. Nevertheless, it is possible that the patient was exposed to hepatitis C virus infection at about that time.

The patient underwent liver transplantation on 26th October 2002. The patient had post-operative complications including renal impairment (this resolved without the need for dialysis) and sepsis secondary to a leak from the bile duct anastomosis. This was confirmed at ERCP. The ERCP was complicated by pancreatitis. The patient was reviewed in the Outpatient Clinic on a regular basis. On 17th March, it was noted that the patient was jaundiced. Ultrasound examination and ERCP showed that the bile duct was dilated beyond an anastomotic stricture. This required placement of an endoscopic stent. The bilirubin fell slowly which suggested that the endoscopic stent was providing biliary drainage. The ERCP was repeated on 11th September 2003. This showed that the anastomotic stricture persisted. The stent which had been placed six months earlier was not visible. Additional investigations performed at about that time included magnetic resonance angiography. The MR angiogram was described by one clinician as showing some arterial stenosis. Another physician claimed that the MRA showed tortuosity of the hepatic artery but without stricture. The bile duct was re-examined by MRCP in December 2003. Apparently, this showed narrowing at the bile duct anastomosis but without dilatation of the donor bile duct or intrahepatic ducts. Liver biopsy was performed at about that time and showed established graft cirrhosis with evidence of recurrent and active hepatitis C infection. Poor liver function persisted. It was decided that the patient should be re-grafted and this happened on 4th February 2004. It is interesting that the surgeon found a dilated and thickened donor bile duct. Also there was portal vein thrombosis. The appearance of the donor bile duct suggests that biliary complications (in addition to the recurrent hepatitis C infection) probably contributed to the development of cirrhosis and graft failure. Unfortunately, the patient developed biliary peritonitis secondary to a leaking entero-enterostomy. He made an eventual recovery from that admission.

At the end of March 2004, the patient was admitted for liver biopsy. The exact reason for liver biopsy is uncertain. The liver function tests were abnormal at that time but there was no obvious trend for deterioration. The liver biopsy showed no evidence of rejection or of significant hepatitis C recurrence. The caring clinicians were concerned that the patient was susceptible to aggressive hepatitis C recurrence. Therefore, antiviral therapy with a combination of Interferon and Ribavirin was commenced on 29th March. The hepatitis C virus level was

measured on a number of occasions during his antiviral therapy. Despite antiviral therapy, the hepatitis C virus level remained extremely high and there was no obvious improvement during antiviral therapy. Indeed liver biopsy was repeated on 1st June 2004. This is reported as consistent with aggressive hepatitis C recurrence. The appearances were those of "fibrosing cholestatic hepatitis" which is an aggressive type of hepatitis C generally seen in patients who are immunosuppressed. Antiviral therapy was continued and required the additional use of erythropoietin and other haematologic growth factors. Liver biopsy was repeated in September 2004. The histological appearances sound much improved from those observed in early June. Nevertheless, the patient's condition deteriorated. During October and November 2004, he suffered fever and leukopaenia. Eventually, there was ascites and confusion. He died at the Royal Edinburgh Infirmary on 17th November.

I have been asked to consider four important questions.

What was the underlying cause of the original liver disease? In my opinion, both hepatitis C virus infection and alcohol caused cirrhosis and subsequent hepatic decompensation. It is not possible to determine the relative contributions of hepatitis virus infection and alcohol to his liver damage. The duration of his hepatitis C infection is unknown. It is possible that he was infected with hepatitis C at a young age when he was involved with experimental drug use. It is also possible that he was infected at a much later date. I do not believe that blood products were the cause of his hepatitis C infection. At times in his life, his alcohol intake was excessive and certainly sufficient to cause liver damage. His reported (or at least documented) alcohol consumption varies quite significantly. Perhaps the most expert assessment would have been undertaken during his psychological assessment for liver transplantation. That assessment stated that he consumed 50 to 100 units of alcohol per week for eight years.
He underwent liver biopsy in August 2002. The liver biopsy showed that he had a micronodular cirrhosis and that the changes were consistent with chronic hepatitis virus infection. At that time, there were no particular signs of alcoholic liver damage. This observation is not surprising and does not exclude alcohol as a significant cause of his liver damage. It seems likely that he was abstinent from alcohol during all of 2002 and that his alcohol consumption during the last quarter of 2001 was not excessive. I believe that the histological changes associated with alcoholic liver damage could have resolved during his period of abstinence. Indeed the hepatologists in Edinburgh would have been encouraged by the histological appearances which would have reassured them that there was no significant recent alcohol intake. In summary, I believe that hepatitis C and alcohol contributed to his liver disease.

What was his ultimate cause of death? The final cause of death is difficult to ascertain. The contributing factors were aggressive hepatitis C recurrence and antiviral therapy. The antiviral therapy appears fully justified. The Physicians were concerned that aggressive hepatitis C recurrence would lead to early graft

damage and graft failure. The use of erythropoietin and growth factors enabled the continued administration of antiviral therapy despite suppression of the bone marrow. Suppression of the bone marrow including the leucocytes may have contributed to infection. As the patient died, there was a complicated picture of marrow suppression, possible infection and serious liver damage. Ultimately, the patient died as a consequence of liver disease which was secondary to hepatitis C virus infection and alcohol. That required liver transplantation which was complicated by recurrent hepatitis C infection. That contributed to the need for re-grafting. Antiviral treatment was given to prevent damage to the second graft. Damage occurred despite antiviral treatment. The patient died as a consequence of hepatitis virus infection and the required antiviral therapy.

Was his treatment and management appropriate? This man clearly had significant liver damage prior to the diagnosis of hepatitis C virus infection in October 2001. His medical attendants assumed that the abnormal liver function tests were due to the consumption of alcohol. The hospital admission with possible pancreatitis was also in favor of an alcoholic aetiology for the abnormal liver function tests. In general, alcohol-induced pancreatitis is only seen in patients with quite high levels of alcohol consumption. I cannot determine from the medical files if attempts were made to engage the patient with services that might modify his alcohol consumption. That would have been appropriate. Eventually, he developed overt liver failure. It was appropriate that he was screened for viral hepatitis. That confirmed hepatitis C infection. His subsequent management seems entirely appropriate. He was advised to abstain from alcohol and largely achieved that. He underwent appropriate psychological assessment. He was placed on the liver transplant waiting list and underwent liver transplantation. All of that seems quite appropriate. He had significant complications after transplantation. Those complications principally involved damage to the bile duct. This is a recognized complication after liver transplantation and attempts to investigate and manage with the biliary problems seem entirely appropriate. It is possible, however, that inadequate drainage of the bile duct contributed to liver damage and the development of cirrhosis. It was quite reasonable to attribute the rapid development of cirrhosis to the hepatitis C infection. Certainly it would have made a significant contribution. It is recognized that re-transplantation for aggressive hepatitis C infection can be associated with aggressive recurrence in the second transplanted liver. Therefore, it was quite reasonable and appropriate to plan for early antiviral therapy after re-transplantation. It was appropriate that antiviral therapy was deferred pending resolution of the early post-operative complications. Indeed antiviral therapy was commenced six weeks after re-transplantation at a time when liver graft function was good and biopsy confirmed that little damage had been experienced. Despite antiviral therapy, it appears that there was very aggressive hepatitis C recurrence with development of significant liver damage by June 2003. Under that circumstance, it was quite reasonable to persist with antiviral therapy. Unfortunately, antiviral therapy can have quite significant haematologic side effects. The patient would have been susceptible to infection. Susceptibility to

infection would have been a consequence of liver dysfunction and bone marrow suppression. In summary, I believe that this man's treatment and management were appropriate.

What was the likely source of the HCV? I cannot be certain. It may be relevant that the patient admitted to some experimental drug use at a young age. The letter from the Community Psychiatric Nurse does not specifically mention intravenous drug use. However, the patient may have been exposed to hepatitis C at that time. It is extremely unlikely that he acquired hepatitis C as a consequence of blood components administered for medical treatment during hospital admissions in 1984 and in 1998.

I have examined the following documents to enable preparation of this medical report.

1. Edinburgh Royal Infirmary – Volume 1 – Investigations 2002 - 2004
2. Edinburgh Royal Infirmary – Volume 2 – Investigations 2004
3. Edinburgh Royal Infirmary – Volume 1 – Correspondence
4. Edinburgh Royal Infirmary – Nursing Notes
5. Glasgow Royal Infirmary records file
6. File of documents from the SNBTS (comprising correspondence in relation to the previous Crown Office investigation into this man's death).
7. Folder of miscellaneous material
   (a) Summary of GP records (principal records destroyed)
   (b) Glasgow Royal Infirmary copy haematology records from 1984
   (c) Death certificate
   (d) Report by Dr Andrew Bathgate dated 19 August 2008
   (e) Report (1) by Professor J-P Allain dated 23 October 2008
   (f) Report (2) by Professor J-P Allain dated 8 February 2009
   (g) Police Report
   (h) Letter from Professor Isobel Walker, Dept of Haematology GRI to Procurator Fiscal, Glasgow dated 11 March 2008
   (i) Letter from Dr Myrtle Peterkin, SNBTS to Procurator-Fiscal, Glasgow dated 15 April 2008
   (j) Letter from Richard L Soutar SNBTS to Procurator-Fiscal Glasgow dated 10 June 2008

Yours sincerely

Dr David Mutimer
Consultant Hepatologist