Witness Name: RICHARD KELLETT-CLARKE

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Dated: APRIL 2019

INFECTED BLOOD INQUIRY

WITN1323002

MEDICAL REPORT

ON

MR ROGER G Q CLARKE

D.O.B. GRO-C 1954

REPORT PREPARED FOR

MARSHALL & GALPIN
SOLICITORS
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BY

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DATED
9th April 2003

This report is prepared at the request of Marshall & Galpin, solicitors. In preparing this report I have access to:

1. Copies of reports from general practitioner
2. Copies of reports from Oxford Haemophilia Centre
3. Copies of reports from John Radcliffe Hospital, Oxford
4. Copies of reports from Queen Elizabeth Hospital, Birmingham.

BACKGROUND

Roger Clarke has a long history of haemophilia A which on laboratory grounds has been classified as severe. His original management was in Glasgow and his dominant early problems were recurrent haematuria. He was first seen in Oxford in 1980.

The first clinical mention of abnormal liver function tests was in June 1988. The abnormal liver function tests were discovered following a medical examination carried out in conjunction with an application for insurance. At this time he was also found to have an abnormality on a chest x-ray. In view of previous travel to the US a possible diagnosis of coccidiomycosis was entertained. Abnormal liver function tests were once again documented in February 1991 (Gamma GT 552 iu/l, AST 188 iu/l). Investigations were deferred, partly for social reasons. He underwent vaccination against hepatitis B during 1991. On the 14th January 1992 he was reviewed in clinic and was noted to be jaundiced. The jaundice was thought to have improved in February 1992 and he was not thought to be jaundiced in May 1992. However, in September 1992 he was less well. An ultrasound suggested the presence of hepatosplenomegaly in the absence of dilatation of the bile ducts. However, a 9 mm stone was noted in the distal common bile duct. As a consequence an ERCP was scheduled and carried out in September 1992. This was complicated by bleeding from a sphincterotomy (cut in sphincter at lower end of common bile duct). Following an unsuccessful attempt to manage this endoscopically he underwent a laparotomy on the 6th October 1992. At laparotomy the liver was described as normal in appearance. However, post-operatively he developed ascites which would normally be indicative of the presence of underlying cirrhosis. He was eventually fit for discharge around the 26th October 1992. The notes from that admission contain two references to him being hepatitis C negative.

A liver biopsy was performed during the laparotomy on the 6th October 1992. A number of findings were noted at that time. Firstly, some granulomas were seen and these raised the possibility of a sarcoid. Secondly, there was moderate fibrosis and some changes which could have been consistent with alcohol use although it was stated that this was not thought to be a problem clinically. In addition there were some changes that were thought to represent a response to the biliary problems immediately prior to the biopsy being taken. This biopsy was reviewed later by Dr Collier. On two separate occasions she states that the fibrosis was stage 3 out of 6 and

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on another occasion it was stage 2/3. There are two dominant systems for staging fibrosis with 4 being the upper limit in one and 6 being the upper limit in the other. Stages 4 and 6 in the respective systems represent cirrhosis. By either system, a diagnosis of cirrhosis was not established by the biopsy in 1992. These staging systems were not in use when the biopsy was initially reported.

The clinical diagnosis of sarcoidosis was first considered in January 1990, principally on the basis of the changes on chest x-ray.

He attended Dr Trowell's clinic on a number of occasions between 1993 and 1995. In June 1995 Dr Trowell states that no appointment was made but she will make plans to see him later in the year.

The first reference to hepatitis C positivity in the clinical notes was on the 27th May 1996.

He had a blood test performed in August 2000 which indicated persistently abnormal liver function tests. He was then referred to Dr Trowell but did not attend on the 19th September 2000. He was, however, seen in November 2000 and at that time an alpha-fetoprotein of 78 was noted. An ultrasound was requested but did not show any evidence of hepatoma. Subsequently, a CT scan was carried out and this identified an hepatocellular carcinoma which was estimated at 3 cms in its maximum diameter. He was subsequently referred to Birmingham where following a period of assessment he was placed on the waiting list for liver transplantation. This was carried out in March 2001. Subsequently he has been diagnosed has having a definite metastasis involving an orbit. He also has an abnormal radio-isotope scan of the ribs but these have not been definitely proven to be metastatic disease.

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Review of serial liver function tests between April 1980 and June 1996

These indicated that the liver function tests were almost normal until 1988. On three occasions prior to 1988 the transaminase (AST) was mildly elevated at between 44 iu/l and 58 iu/l (normal range up to 35). There was a distinct change in the liver function tests in June 1988 with an increase in the alkaline phosphatase and Gamma GT. The AST also increased but the order of magnitude of this increase was considerably less until January 1991. By that time there had been a further increase in the Gamma GT from 352 up to 522 and the alkaline phosphatase from 249 to 349. The bilirubin remained normal until January 1991 but increased to 28, subsequently 41 and then returned to the normal range which is less than 17. The platelet count and serum albumin were entirely normal throughout this period. There was a further deterioration in the liver function tests in January 1992 with an increase in bilirubin to 48 umol/l, alkaline phosphatase to 348 iu/, AST 166 iu/l and Gamma GT 507 iu/l. These subsequently improved, particularly with respect to the bilirubin (falling to 15 umol/l) and to a lesser extent a fall in the Gamma GT to 428 iu/l. The liver function

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tests significantly deteriorated following the ERCP and laparotomy in October 1992. However, the overall pattern between 1992 and 1996 was one of on-going fluctuation with a generally persistent elevation of the serum bilirubin. The serum albumin again remained totally normal throughout this period. The platelet count fell for the first time in May 1993 and has progressively decreased since then.

I note from the flow charts and summary sheets that the hepatitis C antibody test was said to be positive in January 1991. These flow charts suggest that the hepatitis C antibody and hepatitis C RNA were positive in January 1992 (latter unlikely to be accurate). Further positive hepatitis C tests are indicated in March 1993 and January 1996. I have not been able to find the notes that verify these results.

COMMENT

Mr Clarke has chronic hepatitis C infection which led to progressive liver disease and the development of cirrhosis. The cirrhosis in turn put him at risk of developing hepatocellular carcinoma which was diagnosed in December 2000. The indication for liver transplantation was the presence of an hepatocellular carcinoma rather than liver failure. Following the transplant he has developed evidence of metastatic disease.

The liver function tests were first found to be significantly abnormal in 1988. The abnormalities documented prior to then were very subtle. Initially no specific diagnosis was suggested for the abnormal liver function tests. Subsequently however, the possibility of sarcoidosis was considered in view of the changes on the serial chest x-rays. The liver function tests would be compatible with this diagnosis. At that time the dominant abnormality in the liver function profile was an elevated Gamma GT. This is often due to alcohol or fatty liver, but on rare occasions may reflect granulomatous liver disease or other diffuse infiltrations of the liver. His alcohol history has been consistently recorded as low and there is no evidence that this was ever considered to be an unreliable history. Some granulomas were seen on the liver biopsy in 1992 and these were considered to be compatible with a diagnosis of sarcoidosis.

Diagnostic tests for hepatitis C became available around 1990/1991. There was some variation in the introduction of the tests on a geographical basis. There were also some problems with the earlier tests which yielded unacceptably high levels of false positives. However, from 1991 onwards the testing was considered to be reliable when supported by secondary investigations.

There are two issues to be considered with regard to the delay in establishing a clinical diagnosis of hepatitis C. The first relates to failure to communicate the three possible positive tests between 1991 and 1993 to the clinician monitoring his liver disease. I cannot comment on that any further at present because of the absence of these reports from the records that are available to me. The second relates to Dr Trowell's failure to request hepatitis C testing on clinical grounds. It is

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understandable that one may wish to avoid a liver biopsy in the management of abnormal liver function tests in the setting of haemophilia. However, in that setting one would expect that a clinician would perform a comprehensive set of non-invasive investigations. Screening for hepatitis C would be a standard part of that testing and this is even more pertinent in patients at risk, including haemophiliacs.

There are definite implications for failure to make a diagnosis of hepatitis C during the period 1992 to 1996. The liver biopsy in 1992 did not establish a diagnosis of cirrhosis. This is critical as the response rate to the treatment available at that time fell dramatically in patients with cirrhosis. The liver biopsy is generally taken as the gold standard in evaluating the presence or absence of cirrhosis. In that context, however, it is a little curious that he developed ascites following the laparotomy which is a characteristic of somebody with cirrhosis. Acknowledging that caveat, it would appear that there was an opportunity to treat this man with anti-viral therapy in the pre-cirrhotic stage. The conventional treatment at that time was interferon and response rates were less than 10% in patients with cirrhosis and up to 30% in patients without cirrhosis. The platelet count at that time was normal and would not have represented a difficulty with regard to therapy. However, by 1995 the platelet count had fallen to 79 and 54. These levels would certainly have proven problematic to anti-viral therapy, either then or on future occasions. Consequently, I conclude that it is unlikely that he would have had the opportunity to have treatment with the later anti-viral regimens including interferon and ribavirin or pegylated interferon with or without ribavirin.

I will now consider the scenario where the patient was treated with anti-viral therapy between 1992 and 1995 and had a sustained response. In this setting our current understanding is that these patients may well not have progressed to cirrhosis. If progression to cirrhosis was avoided, the risk of developing hepatocellular carcinoma would have been extremely low.

If the patient had been offered anti-viral therapy at that time but had not responded then there is no indication that the subsequent clinical course would have been altered. There are a small amount of data, principally from Japan, that anti-viral therapy decreases the risk of developing hepatocellular carcinoma. However, this experience has not been reproduced in the West.

Once the diagnosis of cirrhosis is made, it is now common practice to regularly screen patients for hepatocellular carcinoma. This is carried out independent of other symptoms of their liver disease. The standard practice is to carry out an alpha-fetoprotein (blood test) and ultrasound at intervals of 4 – 6 months. There is no evidence that Mr Clarke's clinical condition was adversely affected by the absence of such surveillance. When he was reviewed in November 2000 the alpha-fetoprotein was 78 and the ultrasound did not identify an hepatocellular carcinoma. An alpha-fetoprotein of 78 in the setting of hepatitis C is not strongly indicative of hepatocellular carcinoma. Although it is above the upper limit of normal (which

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range between 10 and 20 in most laboratories) levels like these are very commonly seen in patients with hepatitis C in the absence of hepatocellular carcinoma. The levels that are considered to be strongly suggestive of hepatocellular carcinoma are in the range of 200 to 500. Most practitioners would have accepted an alpha-fetoprotein of 78 and a negative ultrasound as satisfactory with regard to screening for hepatocellular carcinoma. It was fortuitous, however, that he had a CT scan which demonstrated an hepatocellular carcinoma estimated at 3 cms. The pathway to subsequent transplantation was quite quick and it is difficult to see how this could have been organised more rapidly.

Chemo-embolisation is commonly performed to stabilise tumour growth while patients wait for transplantation. However, this does not appear to be a relevant issue in this case as the patient was very rapidly transplanted once he was listed. Adjuvant chemotherapy is sometimes offered to patients following transplant where the tumour exceeds the protocol dimensions, as in this case, once the liver is examined histologically after removal. This does not appear to have been considered in this case. However, many programmes do not do this because of the lack of convincing data supporting its efficacy.

If you require further clarification, please do not hesitate to contact me.

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