Report to the Penrose Inquiry

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RE: Communication to Patients about Hepatitis 1974-1995.

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CURRICULUM VITAE

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QUALIFICATIONS:

MB ChB	1976 (Sheff).	MD	1990
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DATE APPOINTED: 1/12/94

Following General Medical Training posts in Sheffield and London Teaching Hospitals and MRCP I embarked on Higher National Training in Haematology in Sheffield Teaching Hospitals. This focused latterly on Thrombosis and Haemostasis in The University Dept of Haematology in the Royal Hallamshire Hospital, the main research interest of the Department. I became a Senior Lecturer in Haematology in The University Dept of Haematology, Liverpool University in May 1987. I have been a director of a Thrombosis and Haemostasis Centre since that time. I have published more than 60 papers in Thrombosis and Haemostasis. I have been involved as an expert witness since the early 1990s.

Introduction:

I have been asked to prepare a report to address the following questions: -

a. What was the risk of non-A, non-B hepatitis at each of the landmark years?
b. What was the state of knowledge about the severity of the illness at each of the landmark years?
c. What information was given to patients (or their parents) about the risk of non-A, non-B hepatitis and the severity of the condition before their treatment with blood or blood products.
d. What was my personal practice in relation to telling my patients the results of anti-HCV positive tests? Did my practice change over the period?
e. What could clinicians reasonably have been expected to tell their patients about the implications of hepatitis C; in the early days; and from 1995 onwards?
f. Would the information and practice differ between patients who had been treated before or not?
g. The tracing and testing of patients who might have been exposed to the virus through their treatment with blood or blood products: was there any guidance (e.g. from CMO or advisory bodies) for clinicians on testing for hepatitis C? What should clinicians have been telling patients about HCV testing?
h. When did HCV testing of patients with bleeding disorders start? Who carried out early tests? What type of test was used? Would all UK clinicians have had access to these early tests?

Relevant Personal Biographical Details:

1. I was the Haematology Houseman at Sheffield Royal Infirmary in the summer of 1977. As such, I managed some of the patients undergoing liver biopsy as part of the early investigation of non-A, non-B hepatitis, the results of which were published by Preston et al in 1978. This was essentially a research study and liver biopsies in such patients were not being carried out systematically elsewhere.

2. I administered the first dose of DDAVP used by that unit for the treatment of haemophilia, very shortly after this treatment was first described by Mannucci in a letter to the Lancet (43). I was therefore made aware of non-A, non-B hepatitis very early in my career because of the research interest of the department in which I worked.

3. When I returned to this department as a senior registrar in 1983, I examined a patient in clinic who had severe haemophilia A and who had undergone liver biopsy only three years before. He had a recent history of confusion and had developed physical signs of cirrhosis. This diagnosis was confirmed by a further liver biopsy. His previous liver biopsy showed chronic persistent hepatitis. At that time chronic persistent hepatitis was thought to be non-progressive, based on a series of liver biopsies reported by Chadwick et al in patients with chronic hepatitis B. I proposed that the natural history of non-A, non-B hepatitis might differ from chronic hepatitis B and suggested a series of liver biopsies to investigate this further. This was agreed and we completed the investigation over the next 18 months or so. We showed progressive liver disease in a significant proportion of patients, a surprising and alarming finding at that time. This was published in 1985 and 1987 and formed the basis for my MD thesis (1989).

4. I became a Senior Lecturer in Liverpool in May 1987 and have pursued other research interests since that time. I have, however, been continuously involved in the management of patients with bleeding disorders since 1983, as a Haemophilia Centre Director since 1987. I was one of the expert witnesses for the defence in the Hepatitis C class action in England earlier this decade. I have been custodian of the UK National Haemophilia Database since 2002 and am currently conducting a national hepatitis C lookback exercise to identify those patients at risk of chronic hepatitis C.

Hepatitis C testing and the risk from blood products and blood components prior to 01/09/1991

5. In the early 1970s, hepatitis B was thought to be the commonest cause of post-transfusion hepatitis. Screening of blood donations reduced this risk dramatically, however, and by the mid 1970s it became apparent that most patients with post-transfusion hepatitis had neither markers for hepatitis A nor for hepatitis B. They had so-called non-A, non-B hepatitis. This was a diagnosis of exclusion defined by abnormal liver function tests, absent markers for hepatitis A and B and the exclusion of other causes of elevated liver enzymes. The clinical significance of this condition was unknown in the mid 1970s. Patients with this condition who underwent liver biopsy generally had mild liver disease. It was considered a benign and non-progressive condition.

6. It is now known that at least 70% of patients who contracted acute non-A, non-B hepatitis developed a chronic carrier state and remained infectious for this agent. A significant proportion of these patients had normal liver function tests and lacked evidence of chronic liver disease. In the absence of a reliable specific test for the virus, it was not possible to identify infectious donors reliably or at all. All types of blood and blood products have subsequently been shown to transmit hepatitis C.

7. The causative virus for non-A, non-B hepatitis was eventually identified in 1988 (1). The first generation hepatitis C antibody test was developed soon afterwards, but lacked sensitivity, predictive value and a true confirmatory test and was therefore not adopted in the UK for screening of blood donations. A second generation test became available in 1991, and was adopted in the UK for universal screening of blood donations on 01/09/1991.

8. Prior to the adoption of hepatitis C antibody testing, various strategies for reducing the risk of transmission of non-A, non-B hepatitis had been considered. These include surrogate testing using liver function tests (ALT) and anti-HBc (HBcAb) testing. These are discussed in detail below. First one must consider the impact of self-exclusion of high-risk donors and anti-HIV testing on the risk of post-transfusion hepatitis B and hepatitis C infection since these three viruses have similar epidemiological risk factors. Excluding donors infected with or at risk of HIV even prior to the advent of HIV testing, markedly reduced the prevalence of hepatitis C and B in the donor population. This is also thought to have reduced the relative value but not the disadvantages of surrogate testing.

Donor Self-Exclusion and HIV Testing:

9. A pilot scheme of donor exclusion of donors thought to be at risk of HIV, using a donor self-exclusion questionnaire, started in North London in 1984 and was generally adopted for North London blood donors in 1985. In the rest of the country, starting in 1984/85, donors were given leaflets asking them not to donate blood if they fell into various risk groups defined in the leaflet. These risk groups were reviewed from time to time but included: - a history of intravenous drug abuse (ever in their life), homosexual sexual intercourse in the past five years, prostitution, and a history of blood product therapy in the donor or their spouse. Donors with tattoos and body piercing were not excluded. It is difficult to know to what extent these steps reduced the number of donors at risk of HIV, hepatitis B and hepatitis C, because HIV testing was introduced shortly after the donor self-exclusion leaflet, in late 1985. HIV testing involved testing for HIV antibody by ELISA technique.

10. HIV testing re-enforced the effect of donor self-exclusion and, taken together, these steps reduced the number of high-risk donors giving blood. This is evidenced firstly by a considerable reduction in the number of donors testing positive for markers of past or present hepatitis B infection following the

introduction of donor self-exclusion and HIV testing. In North London, before 1984, the frequency of HbsAg in first-time donors was 0.2%. This fell to 0.07% over the next two to three years (2). Anti-HBc positivity in North London donors also fell from 1.8% to 0.6% between 1983/84 and 1985 (3).

11. It is difficult to quantify the effect of donor self-exclusion and HIV testing on the risk of non-A, non-B hepatitis because there were no reliable diagnostic criteria for non-A, non-B hepatitis in the early 1980s. The prevalence of chronic non-A, non-B hepatitis also varied geographically. The condition appears to have been commoner in the USA than in Northern Europe (4-6). Contemporary studies suggest that the prevalence of non-A, non-B hepatitis in Northern European blood donors was approximately 0.4-1.0% in the early 1980s (4, 5). In contrast, Contreras reported a much lower rate of infectivity of 0.085% per donor-unit amongst 387 UK patients transfused an average of 3 units of blood each in 1987 and tested using an hepatitis C antibody ELISA (7). This suggests an approximately tenfold reduction in the risk of post-transfusion hepatitis C, in the UK during the course of the 1980s, following the introduction of donor self-exclusion and HIV testing. In the USA, where the background risk was much higher, the introduction of HIV testing and donor self-exclusion resulted in a similar fall in the incidence of post-transfusion non-A, non-B hepatitis from 7-12% to less than 1% (8, 9).

Surrogate Testing:

12. Before a specific serological test for hepatitis C was developed, surrogate tests were investigated in the hope that such testing might reduce, but not eliminate, the risk of post-transfusion non-A, non-B hepatitis. Two tests were proposed: raised ALT levels and the presence of anti-HBc. Unfortunately, these tests failed to distinguish between donors clinically proven to be infectious or non-infectious for non-A, non-B hepatitis (10-13). The tests are non-specific and lack sensitivity. They identify some donors infectious for hepatitis C, miss others who are

infectious for hepatitis C and cause further donors, uninfected with hepatitis C to be rejected.

13. ***ALT-Testing:*** The rationale for ALT testing is that ALT testing of blood donations should reduce the risk of post-transfusion non-A, non-B hepatitis because non-A, non-B hepatitis is a common cause of an elevated ALT (6, 13). Unfortunately obesity and alcohol are also very common causes of elevated ALT and so the test is very non-specific. Furthermore, many patients infected with non-A, non-B hepatitis have normal ALT levels and would be missed by the test, but are nevertheless infectious for the virus. Two large US studies, the Transfusion Transmitted Disease (TTV) study (6) and the National Institute of Health (NIH) study (14), suggested that although 60-70% of donors with a high ALT level do not transmit non-A, non-B hepatitis, exclusion of donors with elevated ALT levels might prevent 30% of cases of non-A, non-B hepatitis (6-11). This was predicted to be achieved at the expense of a loss of about 3% of all donors, who are not infected with non-A, non-B hepatitis but have some other cause for an elevated ALT (9-11).

14. About half of the donors with elevated ALT were thought to have chronic non-A, non-B hepatitis and most of the rest were thought to have elevated ALT levels secondary to obesity or alcohol. The group of hospitals administered by the National Institute of Health in America introduced ALT testing in 1981. This appeared to have no effect on the incidence of post-transfusion non-A, non-B hepatitis in the three years that followed (8). Estimates of the likely efficacy of ALT testing were based upon historical controls [comparisons] and there was a widespread suspicion that the actual benefits might be smaller than predicted by the TTV and NIH studies (9-11). Several authorities called for further study and preferably a prospective randomised study to assess the efficacy of ALT testing (9-13). Despite this, and in the face of some resistance from the scientific community (8, 10), the American Association of Blood Banks made ALT and anti-HBc testing of all blood donations mandatory in 1986. In the absence of

persuasive evidence of the merits of this strategy, this should perhaps be regarded as a political rather than a scientific decision. Furthermore, the introduction of surrogate testing in the USA coincided with the introduction of donor exclusion and HIV testing and so the efficacy of these steps cannot now be individually and retrospectively determined. Between 4 and 6% of all blood donations were discarded in the USA because of positive surrogate testing.

15. ***Anti-HBc-testing:*** An unexpected finding of the TTV study was that there was an association between the presence in the donor of anti-hepatitis B core antibody (anti-HBc) and the risk of transmission of non-A, non-B hepatitis (15). It is not clear why anti-HBc is associated with a risk of non-A, non-B hepatitis, particularly since there is no significant association with other serological markers of hepatitis B infection (15). The NIH study (16) and several others confirmed these observations (17-21). Studies conducted before the introduction of donor self-exclusion and HIV testing, suggested that the incidence of non-A, non-B hepatitis was three times greater following the transfusion of anti-HBc +ve blood compared with recipients of anti-HBc-ve blood. (8, 11, 15, 16). Although 70-88% of anti-HBc +ve blood did not transmit non-A, non-B hepatitis it was estimated that anti-HBc testing might prevent about 30% of cases of non-A, non-B hepatitis at the cost of the loss of between 4 and 8% of non-infectious donors. Alter conducted a meta-analysis of these two studies from which he estimated that anti-HBc testing might eliminate as many as 28% of cases of non-A, non-B hepatitis (9).

16. Another surprising finding of the TTV study was that only 15% of patients with elevated ALT or anti-HBc were positive for both markers (15). This implied that the markers were identifying different populations at risk of transmitting non-A, non-B hepatitis and that the two markers combined might have greater predictive power than either on its own (11, 15).

17. Alter (1985) suggested that the efficacy of surrogate testing for non-A, non-B hepatitis was likely to be influenced by other steps taken to increase the safety of the blood supply e.g. HIV testing and donor self-exclusion (11). That is to say that since HIV testing and donor exclusion decrease the number of anti-HBc +ve donors by 66% (28) and non-A, non-B hepatitis infected donors who donated blood by 90% (4,5,7-9), the value of the surrogate test will be reduced commensurately. There were fewer donors infected with non-A, non-B hepatitis to screen out after these steps had been taken. At the same time, the proportion of false positives would be expected to increase, because donor self-exclusion would have little effect on the number of heavy drinkers and obese donors who donate blood.

18. The efficacy of these tests is greater when and where the prevalence of hepatitis C is high, because a relatively large number of infectious donors and a comparatively low number of non-infectious donors are rejected (see below). When the prevalence of infectious donors is very low, as is the case in Northern Europe, post donor exclusion and HIV testing some donors infected with hepatitis C are missed and many non-infectious donors are rejected. In the UK, for example, the prevalence of non-A, non-B hepatitis amongst blood donors was about one tenth that found in the USA in the early 1980s. This was reduced a further tenfold approximately by the introduction of HIV testing and donor self-exclusion. This suggests the possibility that had surrogate testing been introduced in the UK, in the late 1980s, it would have detected very approximately one hundredth the number of donors infected with non-A, non-B hepatitis suggested by the TTV and NIH studies. The introduction of a hepatitis C antibody test in 1990 permitted retrospective analysis of the efficacy of these surrogate markers (18-23). As expected, these studies showed greater efficacy for surrogate testing in countries with a high prevalence of hepatitis C compared with countries with a low prevalence. Blachman (Canada), in a randomised study conducted from 1988 to 1992, showed that surrogate testing reduced the risk of hepatitis C from 2% to 0.5% per donor-unit (18). Jullien (France) (1993) showed that the risk of hepatitis

C transmission fell from 0.4% per unit for unscreened blood to 0.34% per unit for ALT tested blood to 0.14% per unit for blood screened for both ALT and anti-HBc (19). Barrerra (Spain) (1991) suggested that ALT testing might reduce the risk of hepatitis C from 1.2% per unit to 0.8% and that anti-HBc testing would have a similar effect (20). The study of van der Poel (Holland), for example, suggested that ALT testing would have reduced the risk of hepatitis C from 0.7% per unit to 0.54% per unit (21). Given that the risk of hepatitis C transmission in London was a far lower 0.085% per unit (7), it is likely that the introduction of surrogate testing in the UK would have yielded very modest benefits.

19. Surrogate testing was not adopted in the UK and many other countries, partly because it was thought likely to reduce the risk of non-A, non-B hepatitis very modestly, after the introduction of donor self-exclusion and HIV testing, and partly because it led to the rejection of otherwise perfectly good blood donors. The rejection of such non-A, non-B hepatitis –ve donors would not only have reduced the blood supply but would also have caused significant distress to the donors themselves. Later procedures for dealing with patients who tested positive for anti-HCV give one some insight into the procedures likely to have been followed for dealing with donors who tested positive with a surrogate test. Practices varied from Transfusion Centre to Transfusion Centre. Some centres just wrote to the donor asking them to consult their GP (and to stop donating blood) and wrote more fully to the GP. The donor was expected to consult the GP and the GP was expected to deal with the problem and possibly refer the patient to a hepatologist for further investigation. Other centres recalled the patient, gave counselling, and arranged direct referral to a hepatologist for further investigation. Bearing in mind that non-A, non-B hepatitis was, until the early 1990s, a diagnosis of exclusion, these investigations would probably involve a liver biopsy. All of this would engender considerable anxiety in the donor/patient.

20. ***Hepatitis C Antibody Testing:*** The hepatitis C virus was finally identified in 1988 (13). A first generation test, an RIA based solely on the c-100-3 antigen of

hepatitis C was developed shortly thereafter (15). This "first generation" test missed 20-40% of infected patients (6, 13, 16-19) and was particularly insensitive in the early stages of the infection, leading to a long window-period. False positive tests were also a problem with the first generation ELISA test, which would have potentially caused much distress to donors falsely identified as having hepatitis C had it been adopted for screening of blood donations or of patients (20, 24).

21. These limitations were compounded by the absence of a true confirmatory test. A confirmatory test is generally one, which may be more time consuming than the screening test and possibly unsuited to mass screening, but which is more specific than the screening test. A confirmatory test should accurately identify the false positives and negatives thrown up by the screening test. The first "confirmatory test" was a recombinant immunoblot assay (RIBA I) (21). This test was also based on the c-100-3 antigen, like the screening test. The RIBA I was actually less sensitive than the ELISA and no more specific (20). It could therefore be argued to have been a supplementary assay but not a true confirmatory test.

22. ***Second Generation Testing:*** In 1991 a second generation ELISA anti-HCV antibody test became available. This test used not only the c-100-3 antigen, but also the c-22 antigen and c-33 antigen. This test had much improved predictive value, sensitivity and specificity (22, 23). Antibodies to c-22 and c-33 are detectable 30-90 days earlier than antibodies to c-100-3 antigen (48). This led to an increase in sensitivity and shortening of the window period by up to six weeks, compared to the first generation test (23, 25).

23. A further supplementary test, the RIBA II test, was also introduced in 1991. This test included the two c-33 and c-22 antigens as well as the c-100-3 antigen. Reactivity with at least two of the three bands was considered confirmatory; reactivity with one band considered indeterminate. This test showed improved sensitivity for the detection of patients with post-transfusion non-A, non-B

hepatitis and was able to distinguish infectious donors amongst those testing ELISA positive (24-26). A good correlation was found between the RIBA II and HVC RNA PCR testing.

24. The second generation anti-HCV ELISA and the RIBA II confirmatory test were adopted for screening of all blood donations, and became routine throughout the country starting on 01/09/1991. From my knowledge at the time I was aware that the availability of a reasonably reliable confirmatory test was an important prerequisite for the adoption of universal screening of blood donations for hepatitis C since false positives are still a problem with the second generation ELISA test.

25. The ELISA test may also miss patients incubating hepatitis C who are incubating the infection and who are infectious but do not yet test antibody positive (the window period). For that reason, hepatitis C screening of blood donations reduces the risk of post-transfusion hepatitis C considerably, but does not eliminate it. In Japan, in patients transfused 1-10 units of blood, the risk of post-transfusion hepatitis C was reduced from 4.9% to 1.9% by hepatitis C screening. The corresponding figures for patients transfused 11-20 units were 16.3% and 3.3% (27). The prevalence of hepatitis C is much lower in the UK than in Japan, but the same basic principal applies. Even now, the current leaflet for potential blood recipients from the National Blood Service, entitled "*Your questions about blood transfusion answered*" quotes a risk of hepatitis B or C transmission at 1 in 200,000 (28). The leaflet continues, comparing this risk with the 1 in 25,000 risk of dying whilst playing football and the 1 per 8000 chance of dying in a road traffic accident.

26. The first generation test was from the Chiron Corporation and was employed in a few centres with a research interest in hepatitis C (31,32) but was not widely distributed, used or employed for donor screening because it was unreliable, giving a significant proportion of false-negatives and some false-positives (31,32).

27. The second generation test was validated and widely introduced in late 1991 and early 1992 (33, 34) and the first hepatitis C test for most patients generally dates from 1992 or 1993 for that reason.

28. Many patients have gained the false impression that they contracted hepatitis C in 1992 or 1993 because that is the date of their first specific hepatitis C test. It is usually possible to establish that their hepatitis C dates from an earlier time either on the basis of their treatment history or on the basis of earlier abnormal liver function tests. Some patients, particularly those with mild haemophilia who are treated infrequently and who have defaulted from follow-up may be first tested later than 1992/93 and only after tracing. In general, no harm will have come from this delay in diagnosis, because the rate of progression of hepatitis C is slow. Furthermore, treatment with alpha-interferon as a single agent was successful in only about 10% of this group (35, 36) in the late 1990s, and was only licensed for this condition in late 1995. Before Interferon was licensed for the treatment of hepatitis C, Health Authorities were resistant to funding it and so it was not widely used for this indication outside clinical trials until 1996.

Calculation of risk of hepatitis C transmission from blood product and blood component therapy

29. Patients treated with pooled blood products prior to the introduction of viral attenuation in 1985-87, will have been infected with hepatitis C. The precise cuttoff of risk for pooled blood products is a complex issue since the early attempts at viral attenuation, whilst effective in eliminating HIV, were not completely effective in eliminating the risk of hepatitis C transmission. The prevalence of hepatitis C in the donor population during the 1970s and early 1980s was not known with certainty but was subsequently estimated to have been approximately 0.4-1.0% (37-41). Pooled blood products were manufactured from plasma pools of between 20,000 and 100,000 plasma donations. Transmission of hepatitis C from these products prior to the introduction of viral attenuation is

now, therefore, recognised to have been inevitable (42). There was no difference at all in the infectivity for hepatitis C of different brands sourced from the UK, mainland Europe or the USA (42).

30. The risk of transmission of hepatitis C from the administration of single-donor blood products depends on the number of units transfused, the year in which the donations were collected and the prevalence of hepatitis C in the relevant donor population at that time. The background prevalence of hepatitis C in the donor population varied geographically and with time. The prevalence was considered relatively high in the USA and in Southern Europe but relatively low in Northern Europe: the UK, France and Holland.

31. The prevalence *amongst the blood donor population* also fell substantially throughout the western world as a result of the introduction of donor selection questionnaires in late 1983 and early 1984 and the introduction of universal testing of blood donors for HIV during 1985. Although the objective of these measures was to reduce and then eliminate the risk of HIV transmission, the risk factors for hepatitis B, hepatitis C and HIV are similar and so donor questionnaires and HIV testing also reduced the risk of hepatitis B and C transmission. Contreras (7) reported that "*The implementation of self-exclusion of donors at risk of HIV infection in 1983 and anti-HIV screening in 1985 has been associated with a reduction in the prevalence of anti-HBc in the North London Transfusion Centre donor population from 1.8% in 1983-4 to 0.6% in 1985*". There are no corresponding figures for the effect of donor selection on the prevalence of hepatitis C amongst the donor population, but one would expect a reduction of similar degree.

32. Early assessments of the incidence of hepatitis C using the first generation hepatitis C antibody test and dating from 1990 and 1991 are unreliable, since this test had a very high false negative rate (22-26).

33. For these reasons I rely, in the following sections, on estimates of the risk of hepatitis C conducted during the first half of the 1980s.

34. In the early 1980s the hepatitis C virus had not been described although the disease that it caused was recognised, and was known as non-A, non-B hepatitis. Since the hepatitis C virus had not yet been identified, there was no specific test for non-A, non-B hepatitis and the diagnosis was one of exclusion. That is to say, if the patient developed elevated transaminases and other causes, including alcohol, hepatitis B and hepatitis A, were excluded, then a diagnosis of non-A, non-B hepatitis could be made.

35. Studies that assessed the risk of transmission of non-A, non-B hepatitis from blood and blood products prior to the advent of the hepatitis C antibody test did so by monitoring patients liver function tests (LFTs) following transfusion. Heart surgery patients were usually chosen for such studies because they required transfusions of several pints of blood and so fewer patients were required to assess the infectious risk attributable to a single donor-unit (37-41). In reaching an estimate of risk, patients with other causes of liver disease would be excluded from the analysis as far as was possible. These studies have several weaknesses. Abnormal LFTs are not specific for non-A, non-B hepatitis and reliance on this indicator could lead to a small overestimation of the risk of non-A, non-B hepatitis. In theory, later studies dating from the late 1980s and early 1990s in which patients were tested for hepatitis C antibody would get around this problem. From the medico-legal point of view the interpretation of such data is complicated by the need to estimate the impact of donor selection introduced in the mid 1980s. Furthermore, the first generation hepatitis C test had relatively low sensitivity and probably missed over 30% of patients.

36. A problem with several of these studies is that LFTs were not tested with sufficient frequency, so that some cases of non-A, non-B hepatitis were probably missed. When virally attenuated concentrates became available in 1985 and 1986, it was established that clinical trials to establish the viral safety of these products

37. The risk of non-A non-B hepatitis transmission in the early 1980s was estimated to be 0.4% per donation, mainly based on Collins and Bassendine (40). The attraction of this particular study is that it was contemporary and it was conducted in the UK. This study showed that six (2.4%) of 248 patients developed acute non-A, non-B hepatitis after a mean of approximately six units of blood each. From this, one may derive a risk of 0.4% per unit of blood transfused (2.4% divided by six). LFTs were measured intensively in this study until death or discharge from hospital but were generally not tested again until six months post-operatively. The investigators would therefore have stopped regular testing just before most patients with non-A, non-B hepatitis developed abnormal LFTs and may therefore have seriously underestimated the risk. The authors tested LFTs once more six months post-operatively to assess the prevalence of chronic hepatitis C. They found only a single patient with abnormal LFTs. This is an implausibly low number, given that only 15% of patients infected with hepatitis C clear the virus and between 50% and 85% have biochemical evidence of chronic hepatitis. Patients with hepatitis C commonly have intermittently abnormal LFTs and so many patients with chronic non-A, non-B hepatitis may remain undetected by a single LFT test at six months. I suggest, therefore, that the Collins and Bassendine estimate of the risk of chronic non-A, non-B hepatitis (0.4% of patients) is probably an underestimate and that their estimate of the risk of contracting post-transfusional acute non-A, non-B hepatitis (0.4% per blood donation) is also, almost certainly an underestimate (40).

38. Cossart et al (41), in Australia, found 18 cases of post transfusion hepatitis following 842 cardiac surgical procedures (from which a risk of 4 cases per 1000 units transfused (0.4%) is derived). Four cases of post transfusion hepatitis were caused by other viruses, giving a residual risk of hepatitis C of 0.31%. Samples for LFTs were taken at 2, 4, 8, 12 and 16 weeks. Although more closely monitored than the Collins study, some patients will have been missed by omission of tests at 10 and 14 weeks and so the study is also likely to underestimate the risk of hepatitis C to some degree.

39. Aach et al (37) reported the US transfusion-transmitted virus study which prospectively followed 1513 transfusion recipients and reported an "attack rate" of non-A, non-B hepatitis of 10%. Follow-up was scrupulous, with sampling every seven days for two weeks and then at 4, 6, 8, 10, 12, 15, 18, 21, 24, and 40 weeks. The authors are unlikely to have significantly underestimated the number of patients who contracted hepatitis C. 165 patients who were followed for <21 weeks were excluded. The patients received a mean of 3.7 units of blood. 156 (11.6%) patients developed hepatitis C. This suggests a risk of hepatitis C of approximately 3.1% per unit transfused (11.6 divided by 3.7).

40. Aymard et al (39), in France, followed 64 patients after cardiac surgery. This study was probably conducted mainly in 1984 and 1985. It is a comparatively small but well conducted study. Patients were sampled every two weeks for five months and so case ascertainment is likely to be complete. Four (6.25%) patients developed hepatitis C after a mean transfusion of 4.2 units of single-donor blood products. This give a risk of hepatitis C of 1.48% per unit transfused. This may be slightly lower than the risk, which pertained in 1983 since the study was probably conducted partly during the period in which donor screening for HIV was introduced.

41. Though methodologically weak, the attraction of these studies is that they were contemporary. By the time hepatitis C testing had become available HIV testing

and donor selection had greatly reduced the risk of transmission of hepatitis B and C by blood transfusion.

42. Contemporary estimates of hepatitis C risk from single donor blood products varied considerably from 0.31% to 3.1%. Those with higher estimates, from both sides of the Atlantic, tested more regularly and almost certainly had more complete case ascertainment (40). The Collins and Bassendine report was particularly flawed in this respect. On this basis I would suggest that the risk of contracting hepatitis C in the UK around 1982-84 was probably significantly in excess of 0.4%, probably somewhere between the Bassendine and the Aymard estimates. This would place the risk during 1983-4 at between 0.6% and 1% per unit of single-donor blood product transfused, say 0.75%.

43. The following table estimates the cumulative risk at different levels of risk and with different numbers of units of single-donor blood products transfused at that time. The principle used to derive this table may be illustrated by the following example. If the risk of developing hepatitis C following a single unit of cryoprecipitate is 0.75% (or 0.0075) then the chance of remaining *uninfected* after a single unit of cryoprecipitate is 99.25% (or 0.9925). The risk of remaining *uninfected* after the second unit of cryoprecipitate would be 99.25% (or 0.9925) of this residual risk i.e. 99.25% of 99.25% (or 0.9925 X 0.9925) = 98.5% (or 0.985). The risk of hepatitis C transmission would be 99.25% of this residual risk i.e. 0.9925 X 0.985, and so on and so on. The risk of becoming infected is clearly the reciprocal of the risk of remaining uninfected and this value is used in the table. It is mathematically incorrect to merely multiply the risk from one unit by the number of units transfused (which gives a much higher estimate of risk).

44. In practical terms, rather than doing multiple calculations, one uses a scientific calculator to raise the risk of non-infection with a single unit by the power of the number of units transfused as in the following example where the [keystrokes] are indicated:-

Example: 0.75% risk, 133 units of cryoprecipitate.

Risk of remaining uninfected 99.25% or 0.9925

0.9925 [X^y] 133 [=] 0.3674 ie the risk of remaining uninfected is 36.74%

Therefore the risk of infection in this case would be approximately 63%

Table: Risk of hepatitis C transmission according to the % risk per unit and the number of units transfused

% Risk/unit	0.3%	0.4%	0.5%	0.6%	**0.75%**	1.0%
No. units infused						
40 units	11%	15%	19%	21%	**24%**	33%
100 units	26%	33%	39.5%	43%	**53%**	63%
133 units	33%	42%	49%	55%	**63%**	74%
200 units	45%	55%	63%	70%	**78%**	87%
219 units	48%	58%	66%	73%	**81%**	89%
250 units	53%	63%	72%	78%	**85%**	92%
300 units	59%	70%	78%	84%	**90%**	96%
440 units	73%	83%	89%	93%	**96%**	**99%**

What was the state of knowledge of non-A, non-B hepatitis amongst Haematologists during this period

45. Non-A, non B hepatitis was first described in 1974 (17) and first reported by Mannucci in the Journal of Clinical Pathology in 1975. Early studies of the prevalence of abnormal liver function tests in patients with haemophilia during the second half of the 1970s suggested that between 35% and 85% of patients with haemophilia were infected with non-A, non-B hepatitis (44-. Concentrates for the treatment of haemophilia A had largely replaced cryoprecipitate in the early 1970s. This condition was thought probably attributable to an unknown

virus, but this was not known for sure and some speculated that some chemical contaminant in the concentrate could be causing the problem.

46. Early liver biopsy series (44-48) all found evidence only of very mild liver disease - mostly chronic persistent hepatitis - and the latter two groups very much emphasised the non-progressive and benign nature of chronic persistent hepatitis. With the wisdom of hindsight one can see that these biopsy series were conducted early in the natural history of the condition since the patients had mostly only contracted hepatitis C in the late 1960s and early 1970s, when cryoprecipitate and then concentrate was introduced. Since the condition is usually non-progressive or slowly progressive. These findings were very influential at the time, and until the mid 1980s non-A, non B hepatitis was considered benign and non progressive. When I embarked on a series of liver biopsies in this patient group in 1984, one London Professor of Haematology (still practicing) rebuked me saying "What are you doing all these biopsies for? It's just a biochemical curiosity!" His view was not unusual.

47. The Sheffield liver biopsy series completed in early 1985 showed progressive liver disease in a significant minority of patients (49). When I presented our findings to the AGM of the British Society of Haematology in April 1985 in advance of publication in the Lancet, the results were greeted with alarm and incredulity. When the results were published they initially excited a lively series of letters from Mannucci who still maintained that the condition was non-progressive (50-51). There was initial widespread reluctance to accept that non-A, non-B hepatitis was progressive in a significant minority of patients. Later that year, however, our findings were confirmed in the USA by Aledort et al and then others (52,53) and gradually there was acceptance that the condition was much less benign than had previously been supposed.

Specific Questions Raised by the Penrose Inquiry:-

48. The risk of contracting hepatitis C from clotting factor concentrate approached 100% at all times prior to the introduction of viral attenuation. This was not known at the time (see above). It was appreciated that the risk from concentrate was greater than from plasma components but it was not recognised that the risk approached 100% until late 1983 (42, 54).

49. The risk of contracting hepatitis C from blood components in 1974 through until about 1983 is not known precisely but is thought to be 0.5-0.75% per donor unit infused. Many patients with haemophilia were infected from cryoprecipitate long before concentrates were introduced. After the widespread introduction of donor exclusion on the basis of lifestyle, the evidence suggested that the risk of hepatitis C transmission reduced tenfold, even before the introduction of hepatitis C testing on 01/09/1991. This estimate is based on the effect on HIV risk and the prevalence of hepatitis C in the donor population when testing was introduced compared to the admittedly much softer estimates of Bassendine and Collins in the early 1980s.

50. What was the state of knowledge in the landmark years? Haematologists began to become aware of non-A, non-B hepatitis in 1975 when it was first reported in the rather obscure J Clin Path. Interest and awareness grew over the next two to three years. Initially, there was very little known about the severity and natural history of non-A, non-B hepatitis. A very varied prevalence of biochemical abnormality was reported and small liver biopsy series suggested a benign non-progressive condition. This view held sway, with many different groups reporting similar findings until 1985. In 1985 it became apparent that a proportion of patients were developing severe progressive liver disease. It was still felt that the majority of patients would have non-progressive or very slowly progressive disease and this has proved to be the case, by and large.

51. A further step in our understanding of the natural history of HCV came with the advent of testing in 1991/92. At that point, it was realised that most patients with "cryptogenic cirrhosis", i.e. cirrhosis of unknown cause, did in fact have chronic hepatitis C. The link with hepatocellular carcinoma was also recognised though the first case reported to the National Haemophilia Database occurred in 1995.

52. What information was given to patients? In the mid to late 1970s, very little would have been said to patients because little was known and the extent of the problem (in terms of proportion of patients affected) did not become apparent until 1978. Even then, and for some time thereafter, the condition was not thought to be a clinical concern. Many, perhaps the majority of centres, did not monitor liver function tests systematically in patients with bleeding disorders until about 1980. From the late 1970s onwards, most regularly reviewed patients would have had liver function tests conducted and I would expect most of those affected to have been told that they had non-A, non-B hepatitis but that it was probably nothing to worry about.

53. In the **late 1970s and early 1980s** patients should have been told what was known about this type of hepatitis at that time. This would include: -
    a. Patients were generally asymptomatic
    b. That it was benign and non-progressive
    c. There was no test
    d. It was thought not to be readily transmissible
    e. There was no treatment at that time
    f. Patients should minimise alcohol intake

    Most patients would have been reassured, quite reasonably given the state of knowledge at that time. Many of these conversations will have been forgotten and may not have been documented.

54. In the early 1980s, the principal concern of haemophilia-treaters and of patients was AIDS and most counselling with patients around that time was completely

dominated by this condition. Here was a condition that rapidly led to illness and then death for which there was no test or treatment. This overshadowed hepatitis, which was considered benign and of little concern at the time to the extent that patients were not counselled to the same degree about non-A, non-B hepatitis as they had been in the immediately preceding period. If they were counselled about hepatitis in the context of a consultation also about AIDS they would often "deny" hepatitis C and deny that it had been discussed. Denial is a common psychological defence mechanism. I have found that patients commonly deny that they have been counselled about hepatitis C even when such counselling has been documented in the notes.

55. The extent to which HIV overshadowed hepatitis C during the early 1980s is also reflected in the guidance offered by UKHCDO at that time. The use of cryoprecipitate was reviewed in the UKHCDO Reference centre gGuidance of 24/06/83. This guidance is interesting because it is primarily concerned with the transmission of HIV, and no distinction at all is drawn between cryoprecipitate and freeze-dried NHS factor VIII concentrate. It reads:-

"For treatment of children and mildly affected patients or patients unexposed to imported concentrates many directors already reserve supplies of NHS concentrates (cryoprecipitate and freeze-dried) and it would be circumspect to continue this policy."

56. This indicates that the prevailing preoccupation of 1983 was the avoidance of HIV through the use of UK blood products in preference to those from abroad. There is nothing in this strategy that would have reduced the risk of hepatitis C transmission because there is no suggestion that cryoprecipitate should be used in preference to UK factor VIII concentrates.

57. The use of cryoprecipitate and plasma was again reviewed in relation to AIDS but not hepatitis in the UKHCDO Guidance of 14/12/84. The relevant passage reads:-

"3.) For haemophilia A needing blood products

(a) "Virgin"[previously untreated] patients, those not previously exposed to concentrate, and children use cryoprecipitate or heated NHS factor VIII (if available).

(b) Severe and moderate haemophiliacs previously treated with factor VIII use heat treated NHS factor VIII, if available or heat-treated US commercial.

4) Haemophilia B

(a) Mild Christmas Fresh-frozen plasma if possible (otherwise NHS factor IX).

(b) "virgin" patients and those not previously exposed to concentrate use fresh frozen plasma (or NHS factor IX concentrate if essential).

c.) Severe and moderate Christmas disease previously exposed to factor IX concentrate continue to use NHS factor IX."

58. This guidance was almost immediately overtaken by events, because convincing evidence emerged that the HIV virus was heat-labile and heat-treated concentrates became the preferred treatment in 1985, even though it was recognised that at least some batches of some of these products still transmitted non-A, non-B hepatitis.

59. Although it was recognised in 1985 and 1986 that non-A, non-B hepatitis was more severe than thought, this coincided with the advent of HIV testing and a rising death-rate from HIV and, soon after, the start of treatment with AZT. Patients would and should have been counselled about hepatitis but the whole issue was commonly overshadowed both in the patient and the clinician's mind by the more immediate problem of HIV. To give the Inquiry some idea, clinical consultations and clinic visits increased fivefold during this period and many additional staff were employed to deal with the problem of HIV. Many patients in my experience appear to have genuinely no recollection of documented conversations about liver disease that took place during that time.

60. In the **mid 1980s**, most affected patients will have been told: -
    a. That they had non-A, non-B hepatitis,
    b. But since hepatitis was still considered non-progressive they would have been told that it was benign and non-progressive in most patients
    c. That a minority, perhaps 20%, developed cirrhosis eventually
    d. That it was generally asymptomatic.
    e. That it was slowly progressive if it did progress
    f. That there was no test or treatment
    g. But we needed to monitor the liver disease systematically
    h. That they should minimise alcohol intake

    These conversations would have been short and not very memorable. They would have been told that the condition was usually asymptomatic and that if progressive, it was likely to be only slowly so. They would have been told that a minority, perhaps 20% would eventually develop cirrhosis and they would have been advised to moderate their alcohol intake. They would have been advised that it was not very infectious and that unless they also had HIV, condoms were not required. Spouses were generally not tested at that time.

61. Between 1985 and 1995, 2/3rds of the HIV cohort died. In 1994/95 15% of the UK cohort died in a single year. Most of them had accumulated several AIDS-defining illnesses before they eventually succumbed. The following year that, quite dramatically, stopped because of the introduction of HAART. These events completely overshadowed everything else that was going on.

62. Most patients were tested for hepatitis C for the first time using a second generation test in 1992/93. Only research centres had access to and used first generation tests. There was no immediate clinical urgency to test, because there was no treatment and most patients with abnormal liver function tests would have been informed of this already. There was no central guidance on testing. The second generation test became commercially available in early 2002 and was fully available to all centres during the course of that year. Haemophilia centre staff

would have conducted the tests in the context of routine review. Milder bleeders are reviewed less frequently and so may have been tested after a delay in some cases.

63. It was my practice in Liverpool and Manchester to inform patients that I was testing them for hepatitis C and to go over (again) an outline of hepatitis C. Consent and counselling was, and is, not the norm prior to hepatitis C testing and hepatologists would, and do, routinely test for hepatitis C as part of an investigation for abnormal liver function test without discussing the test specifically with the patient. They may tell them they are testing for hepatitis viruses.

64. Some patients have complained, many years after the event, that they were tested "without their permission". In some cases they may, indeed, have been tested without being specifically informed and in other cases it is documented that they were informed both that they were being tested and of the result. The idea that a hepatitis C test should engender prolonged pre-test counselling derives from the practice adopted after 1985 by most centres of counselling prior to HIV testing. The implications of a +ve HIV test could be perceived as a death sentence, led to loss of insurance, marriage breakdown, and even in some cases suicide. There is no comparison between this and hepatitis C testing. For that reason, there has never been a specific consent process attached to hepatitis C testing even though it would be normal practice to inform the patient that they were being tested and to inform them of the result.

65. In our centre, we informed them we were testing them for hepatitis C, discussed the result with them when available and wrote to the GP and documented the discussion.

66. Initially, only an antibody test was available in 1992. We could therefore tell those with a positive antibody test and abnormal LFTs that they probably had chronic hepatitis C. With the advent of hepatitis C antigen testing we could confirm chronic hepatitis C and identify carriers with normal LFTs. We also

offered testing to spouses, whilst reassuring them that the risk of transmission was relatively low. The take-up rate for this was low, especially since most of the men attended clinic alone.

67. In 1995/96 Interferon started to be used to treat chronic hepatitis C and we started to discuss this with patients. There was no clinical urgency to start treatment , the response rate we quoted at that time was low (25% quoted based on early literature but a lower response rate of 10% actually experienced) and many patients were and continue to be put off by side effects. Many patients still refuse treatment. These discussions were often delayed in patients co-infected with HIV, partly because their response-rate was even lower, partly because they had enough on their plate and partly waiting for improvements in treatment, which did come. All these patients have been offered anti-HCV treatment for many years now and current combination therapy is much more effective than the treatment used in the late 1990s.

68. From the early 1990s it was becoming apparent that we were seeing more severe liver disease, particularly in patients co-infected with HIV. There was a transient increase in deaths from liver disease and 3/4 of those patients were co-infected with HIV and also had AIDS. Hepatitis C progressed more rapidly in the immunosuppressed patient. Conversations about liver disease became more frequent and adopted a higher profile. We would tell them: -
    a. That the condition was benign and non-progressive in most patients
    b. That there was eventual progression to cirrhosis in up to 30% of patients
    c. That HIV was a co-factor for hepatitis C progression as was alcohol
    d. That there was a small risk of liver cancer
    e. That there was treatment available with interferon but the treatment lasted six months and response-rate was only 25%
    f. That we needed to monitor the liver disease systematically

    Patients were regularly screened by ultrasound and alpha fetoprotein from the late 1980s and closer working relationships, and some joint clinics, were established

with hepatologists from the late 1980s and early 1990s. Severe liver disease was jointly managed with hepatologists from the very beginning. During and since the late 1980s and early 1990s patients were repeatedly offered treatment for hepatitis C and would have been told how bad (or good) their own liver disease was and what their biochemistry and ultrasound showed at their clinic visits.

69. Would information and clinical management differ between patients who had or had not been exposed to blood products?

    a. Patients who had never been treated with blood products would have been known to have no higher risk of hepatitis C than the general population and would be reassured and not tested.
    b. The way in which management varied according to previous exposure differed with time clinical circumstances and treatment history and I have detailed this in the appendix (below).
    c. Patients who had only been treated with blood components would be and should have been told that they were at less risk of contracting hepatitis C but should all have been tested at the first opportunity after the second generation hepatitis C antibody test became widely available.

70.

APPENDIX: The Changing Standard of Clinical Care with time.

The most appropriate treatment depends on the severity of the haemophilia, the clinical circumstances, the patient's past treatment history and the state of knowledge and opinion at the time of the treatment. Previous blood product therapy may also have been taken into account in some cases of infrequently treated mild haemophilia. For simplicity, I have therefore divided the following section according to the severity of the bleeding disorder.

Severe and Moderate-Severity Haemophilia A and all degrees of severity of Haemophilia B:

For patients with severe and moderate-severity haemophilia, the accepted standard of care would have been as follows: - Cryoprecipitate would have been used for all bleeds in haemophilia A between the mid 1960s and the early 1970s. After that time, factor VIII concentrate would usually have been used for the treatment of all bleeds. This concentrate would not have been virally attenuated until 1985. Due to the unavailability of UK virally attenuated concentrates until the autumn of 1985, many centres continued to use non-virally attenuated concentrate until that autumn. This use of untreated UK concentrate during 1985 fell within the UKHCDO guidelines issued on 14/12/84 and quoted in paragraph 57. These guidelines were drawn up to reduce the risk of HIV transmission.

All patients with haemophilia B would have been treated with UK factor IX concentrate from the early 1970s. This was virally attenuated from the autumn of 1985.

The treatment of such a patient could only be judged to fall below this standard if the patient was able to demonstrate that they had contracted hepatitis C from untreated pooled blood products administered after 1985. Such patients would have normal liver function tests prior to this date and/or would have no history of treatment with pooled blood products prior to the beginning of 1986. That is to say, that they would have to be able to demonstrate that on the balance of probabilities they had not contracted hepatitis C prior to 1986. The literature would suggest that a high proportion of patients contracted hepatitis C between 1973 and 1977 (10, 37).

Similar considerations apply to patients with severe haemophilia B (Christmas disease, factor IX deficiency) of all degrees of severity because there was no reasonably haemostatically effective alternative to factor IX concentrate.

Mild Haemophilia A: factor VIII baseline <0.15 IU/ml:

It would be acceptable for patients with mild haemophilia A and a factor VIII baseline <0.1-0.15 IU/ml (10-15%) to have been treated in the same way as patients with severe haemophilia A because their response to DDAVP would have been inadequate to cover even minor procedures.

Mild Haemophilia A: factor VIII baseline >0.15 IU/ml:

For patients with mild haemophilia A and a factor VIII baseline greater than 0.15 IU/ml (>15%), acceptable treatment would have varied according to the clinical circumstances, the previous treatment history and the state of knowledge at the time of the treatment.

For the treatment of such a patient to be judged to have fallen below the accepted standard it would have to be demonstrated that the patient had contracted hepatitis C from blood products administered in clinical circumstances and at a time when a safer alternative was available, was the generally accepted treatment for such a patient and would have been haemostatically adequate for the type of episode treated. It would also be necessary to demonstrate that the liver function tests were normal prior to the treatment episode in question and/or that there was no previous history of treatment with non-virally attenuated factor VIII concentrate. The clinical circumstances and acceptable treatment options may have to be evaluated case by case, but some general principles follow:-

1.) BEFORE THE EARLY 1970s:

Plasma or cryoprecipitate would have been used for all bleeding episodes in this group of patients.

2.) EARLY 1970s UNTIL 1982/83:

It would have been acceptable and normal practice to have used factor VIII concentrate for all bleeding episodes and procedures, however minor. During this period it was not fully appreciated that hepatitis C invariably followed the first administration of all blood products or that hepatitis C was potentially serious and

progressive. Furthermore, the use of DDAVP was not fully established, even for minor procedures.

3.) 1982/83 ONWARDS (minor procedures):

DDAVP would usually have been used in this group to treat minor bleeding episodes such as dental extraction from 1982/83 onwards, since the haemostatic response would have been adequate and the use of DDAVP was widely accepted as the treatment of choice for this group of patients by this time. It would not be generally acceptable to use concentrate in such a patient for a minor procedure such as dental extraction after 1982/83 if there was no previous history of significant previous treatment with cryoprecipitate or concentrate unless the response to DDAVP was likely to be inadequate. It could be argued that concentrate would have been acceptable during this period for even minor procedures if the patient had previously been treated with pooled blood products or large amounts of cryoprecipitate or if there was earlier evidence of hepatitis C.

4.) 1984/85 SURGERY:

From 1984/85 it would have been reasonable to consider the use of DDAVP for some minor invasive surgery in patients with very mild haemophilia A and a baseline factor VIII of about 0.3-0.35, particularly if they had been documented to have a good response. Even in these patients, life-threatening bleeding and major surgery would usually have been treated preferentially with concentrate.

The treatment of more invasive surgery requiring the maintenance of normal factor VIII levels for five to seven days was a problem since the response to DDAVP in patients towards the bottom of the factor VIII range 0.15-0.5 IU/ml will be inadequate for invasive surgery and is unlikely to be sustained throughout the post-operative period. "Invasive surgery" includes procedures as apparently minor as vasectomy, herniorrhaphy and tonsillectomy and certainly the treatment of significant gastrointestinal bleeding, laparotomy, the treatment of trauma and more major surgery. The use of DDAVP to prevent bleeding after invasive surgery was not common until the mid 1980s in any case (22-24). The control or prevention of

bleeding was the primary concern when treating patients undergoing surgery or with major trauma and was generally achieved more easily and reliably using factor VIII concentrate.

Von Willebrand's Disease:

1.) TYPE III AND II VON WILLEBRAND'S DISEASE:

All bleeding episodes in patients with type III (severe) and type II (functional defect) von Willebrand's disease would have been treated with cryoprecipitate until the mid to late 1970s. Although the use of cryoprecipitate persisted longer in von Willebrand's disease than in haemophilia, factor VIII concentrates largely superseded cryoprecipitate for this group in the mid 1970s.

2.) MILD TYPE I VON WILLEBRAND'S DISEASE:

Mild type I von Willebrand's disease would have been treated with cryoprecipitate or concentrate, as for more severe von Willebrand's disease, until the early 1980s, when DDAVP became widely established for the treatment of minor procedures such as dental extraction. DDAVP was not widely used for invasive surgery until the mid 1980s. From that point on, and in the absence of specific contraindications, DDAVP would have been the treatment of choice for all minor bleeding episodes. It would also have been considered for surgery but concentrate would often have been used for invasive surgery throughout the 1980s.

3.) MODERATE OR SEVERE TYPE I VON WILLEBRAND'S DISEASE:

More severe type I von Willebrand's disease (VW activity <0.15 IU/ml) would have been treated with DDAVP for minor episodes but the response would have been inadequate for major surgery. These surgical episodes would have to have been treated with cryoprecipitate until the mid 1970s, after which concentrates would usually have been used.

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Declaration:

1. I understand that my overriding duty is to assist the Inquiry on matters within my expertise and that this duty overrides any obligation to any other party. I confirm that I have complied with that duty and will continue to do so.
2. I have mentioned all matters which I regard as relevant to the opinion that I have expressed. All the matters which I have expressed an opinion lie within my field of expertise. I have drawn to the attention of the Inquiry all matters of which I am aware which might affect my opinion. I have indicated the source of factual information wherever I have no personal knowledge. I have not included anything in this report which has been suggested to me by anyone without forming my own, independent, view of the matter.
3. Where, in my view, there is a range of reasonable opinion, I have indicated the extent of that range in my report. At the time of signing of this report, I consider it to be complete and accurate. I will notify those instructing me if, for any reason, I subsequently consider that the report requires any correction or qualification. I understand that this report will be evidence that I will give under oath, subject to any correction or qualification I may make before swearing to its veracity.
4. I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge are confirmed to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Dr Charles RM Hay MD FRCP FRCPath 31/12/11

Consultant Haematologist,

Honorary Senior Lecturer in Medicine.