Witness Name: Prof. Geoffrey Dusheiko
Statement No: WITN3754048
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Dated: 20 January 2021

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PROFESSOR GEOFFREY DUSHEIKO

I, Professor Geoffrey Dusheiko, provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 6 August 2020 and will say as follows: -

Section 1: Introduction

1. **My name, address, date of birth and professional qualifications are as follows:**

   1.1. Geoffrey Mark Dusheiko, Liver Unit, Kings College Hospital London UK GRO-C GRO-C 1948 MB BCh (Wits) FCP(SA) FRCP FRCP (Edin).

2. **The positions I have held as a doctor, the organisations in which I have held these positions and my role and responsibilities in these positions are as follows:**

   2.1. Intern, Medicine Baragwanath Hospital, Johannesburg, 2 January 1973 to June 1973

   2.2. Intern, Surgery Baragwanath Hospital, Johannesburg, July 1973 to December 1973

2.3. Locum Tenens positions January 1974 to July 1974: Paediatric Ward Northwick Park Hospital, Middlesex, U.K; Dr H.B. Valman, General Practice, Johannesburg; A.E.C.I, Modderfontein

2.4. Sen. Intern Paediatrics, Johannesburg Childrens Hospital, July to December, 1974

2.5. Sen. Intern Cardiology, Johannesburg Hospital, January to June 1975

2.6. Registrar Medicine (Respiratory, Endocrine, Neurology, Coronary intensive care units, Haematology, General medicine), Johannesburg Hospital, July 1975 to July 1978

2.7. Research Fellow, Liver Unit, Johannesburg Hospital, July 1978 to July 1979

2.8. Visiting research associate, Liver Unit (South African Medical Research Council Fellow), Liver Diseases Section, National Institutes of Health Washington DC USA, August 1979 to July 1981

2.9. Senior Physician (Consultant), Hillbrow and Johannesburg Hospital, August 1981 to December 1983

2.10. Unit Head (Consultant and Ward Head), Hillbrow and Johannesburg Hospital, January 1984 to December 1987

2.11. Guest Researcher (Vice Chancellor's Research Award), Dept of Microbiology, University of Minnesota USA, September 1986 to March 1987

2.12. Senior Lecturer, Academic Dept Medicine, Royal Free Hospital School of Medicine, January 1988

2.13. Reader in Medicine, Royal Free Hospital School of Medicine, 1989

2.14. Professor of Medicine, Royal Free Hospital and University College School of Medicine 1996

2.15. Emeritus Professor of Medicine, University College London Medical School, January 2014

2.16. Consultant Hepatologist, Royal Free Hospital London, 2014-2016

2.17. Consultant Hepatologist, Liver Unit, Kings College Hospital London UK, 2016-to date

2.18. Interim Deputy Director, Blood safety, Hepatitis HIV and STI National Infection Service, Public Health England, March 2019 to December 2019

2.19. I am assisting Lewisham University Hospital during the Covid19 crisis

2.20. I have attached an up to date bibliography of my publications (annotated see below). [WITN3754049]

a. An outline of the medical training you undertook in South Africa and the focus of any research you undertook there

2.21. After qualifying in medicine in 1973, I trained in paediatrics and subsequently in internal medicine and Hepatology, as a registrar in medicine and research fellow in the Department of Medicine, University of the Witwatersrand in Johannesburg. I qualified as a specialist physician (Fellow of the College of Physicians of South Africa) in 1977.

2.22. I was first exposed to a research environment by Professor Michael Kew. I did not begin my research in hepatitis. In 1979 while a registrar, I was fortunate to be able to document the occurrence of a previously undescribed inherited metabolic disorder causing steatosis and hypoglycaemia in an adult, and to publish a description in the New England Journal of Medicine.

2.23. The indelible imprint of the morbidity and aftermath of chronic hepatitis B and hepatocellular carcinoma (HCC) that I first witnessed in South Africa has left me with a determination to see the morbidity of these disease diminished. The focus of my research was laboratory-based assessment of the immune response to hepatitis B. In 1979 I was awarded a South African

Medical Research Council Fellowship which enabled me to work for two years as a visiting associate in the Liver Unit of the National Institutes of Health in Bethesda, USA with Dr Jay Hoofnagle and Dr E Anthony Jones.

2.24. I returned to a post in Medicine and Hepatology in the University Department of Medicine. In January 1984, I was appointed head of one of the four wards at the Hillbrow (old Johannesburg General Hospital) administering 25 male and 25 female beds.

2.25. Upon my return to South Africa, I initiated together with research colleagues a series of studies elucidating the natural history and epidemiology of hepatitis B and HCC in an endemic area. Our studies documented, for example, the importance of horizontal spread of hepatitis B in African children and contrasted the epidemiology in Africans with that in Asia. We were able to document the molecular changes in hepatitis B viral replication in patients with advanced liver disease, and to demonstrate a changing epidemiology in patients migrating from rural to urban areas. These studies indicated the need for universal vaccination of South African patients although it took much effort (and a change of government) to persuade the Government of the time to initiate universal HBV vaccination.

2.26. In 1982 I recognised the possible antiviral potential of recombinant interferon alpha for chronic hepatitis B, devised a treatment strategy, within an ethically approved protocol, and documented that a proportion of patients with replicative chronic hepatitis B responded to interferon alpha. This study also showed that the efficacy of interferon alpha was restricted; I catalogued the exacerbation of hepatitis seemingly required for efficacy, the criteria favouring a response, and documented the loss of both HBeAg and HBsAg in patients with a response. The events accompanying the response pointed to the role of the immune response in reducing hepatitis B replication. I also documented the side effects of subcutaneous recombinant interferon. These studies were followed by further controlled trials, which have stood the test of time. These early studies were (with human insulin), the first therapeutic use of a recombinant human protein.

Fortunately, treatment for hepatitis B has been mostly supplanted by maintenance suppressive treatment with nucleoside analogues although interferon or oral interferon inducers (Toll-like receptor agonists) may yet be used in future finite curative regimens.

2.27. I directed studies examining the effect of gene methylation on hepatitis B replication on the expression of hepatitis B virus in carriers with replicative and non-replicative infection. Together with Ann Bowcock, I documented the chromosomal integration sites of hepatitis B virus in PLC/PRF/ 5 (Alexander) HCC cells. In 1987 I was awarded the Vice Chancellor's Research Fellowship and spent six months in the Department of Microbiology at the University of Minnesota, Minneapolis USA, learning in-situ hybridisation. While at the University of Minnesota, I studied alpha fetoprotein messenger RNA expression by in-situ hybridisation in patients with HCC. These findings suggest that steady-state quantities of alpha fetoprotein RNA are increased in malignant hepatocytes, perhaps because there is an anomalous reversion increasing gene transcription.

b. An outline of your role and work in your postgraduate training with Professor Hoofnagle and the focus of your research in that post National Institutes of Health 1979-1981

2.28. In addition to research studies in the Liver Unit, I was responsible for the care of patients with liver disease admitted to the NIH Clinical Centre. Together with research colleagues in the Liver Unit, I studied the functional activity of B cells and synthesis of neutralising antibodies (anti-HBs) in patients with chronic hepatitis B. The data suggested that patients with chronic hepatitis have an impairment in B cell synthesis of neutralising antibodies, probably because of high dose antigen specific immunological tolerance. This work was published in the Journal of Clinical Investigation. (1) (B cell dysfunction remains a focus of current research in hepatitis B). (2) At the same time, I was fortunate to be involved in some of the landmark studies of the time of the natural history, molecular virology, serology and potential antiviral treatment of chronic hepatitis B, including

studies that documented the phenomena of spontaneous seroconversion to anti-HBe during the natural history of viral hepatitis, and which were widely cited.

c. A description of your role and responsibilities in relation to (i) clinical work with patients, and (ii) research at the Royal Free Hospital as a Professor of Medicine and as a Consultant with the Liver Unit at the Gastrointestinal and Liver Services Departments ("the Department")

2.29. In 1988 I was invited to join the Royal Free Hospital School of Medicine as a Senior Lecturer in the Academic Department of Medicine and was appointed Reader in the same department in 1989. My clinical commitments include those of Honorary Consultant to the National Health Service, a general medical service rotation and Hepatology Consultant in Hassal Liver Ward. For 17 years I had a full time general medical rotation commitment as well as responsibilities for in-patient and ambulatory hepatology care. My clinical commitments became more necessarily focused on my specialist interest in the care of patients with liver disease, particularly chronic hepatitis, cirrhosis, and HCC. I held a personal chair as Professor of Medicine (from 1996).

2.30. At the Royal free Hospital, I was approved for 6 NHS and 6 academic program activities based on clinical activity, training, departmental activity research and clinical trials. These activities include hepatology consultant Hassall Ward involving a regular on call commitment with single consultant responsibility. I delivered an attending (academic) liver service including on-call regular attendance at intramural clinical meetings, including x-ray, liver biopsy, and multidisciplinary HCC meetings

2.31. My viral hepatitis outpatient clinic recorded the highest clinic activity for the many consecutive years. We maintained a regular inflow of new referrals. My outpatient clinic was a large hepatology clinic. The outpatient clinic registered over 6500 patients. For many years, the service-maintained standards and quality of care in the face of underfunding for chronic hepatitis. Our safety record for complex antiviral treatment was high. We

took special note of the appropriate indications for treatment and the cost-effective use of antiviral therapy I provided an in-patient consultant service for patients with viral hepatitis and HCC.

2.32. I was responsible for research students (MD and PhD) supervision and mentoring and contributed to student examinations (internal and external), teaching of special study modules and regional teaching. I was actively involved in undergraduate and postgraduate teaching and examination and involved both in bedside teaching, outpatient instruction, seminars, special study modules, masterclasses, and Royal College of Physician Regional Teaching seminars. I was appointed as an external examiner of final year medical students Oxford University for 6 years and an examiner in Hong Kong for the Licentiate degree. I also provided an outpatient service to the Haemophilia Centre and have clinical interactions with the HIV and immunodeficiency clinics for patients with chronic viral hepatitis.

2.33. The mainstay of my work has been to improve the understanding of the pathogenesis, natural history, and antiviral treatment of chronic hepatitis. My research work has benefited from numerous collaborations with basic and clinical scientists, epidemiologists, virologists, clinical colleagues research fellows, and nurses, from whom I have learned a great deal. When I use the term "we" in the annotations to my publications and in this statement, I am referring to, and acknowledging, the contributions of numerous clinical and scientific colleagues (named on the publications) without whom, cross-platform research work could not have been done. The published results have led to insights into the geographical importance of disease, classification of genotyping of hepatitis C, and antiviral therapies which have improved the outcomes of chronic viral hepatitis.

2.34. My collaborative efforts have been directed at reducing the morbidity from chronic viral hepatitis: 1) I directed clinically applicable translational research from within antiviral, molecular, virological, epidemiological and natural history analyses to inform the treatment of chronic viral hepatitis and have been associated with several major advances in treatment. 2) These

efforts have engendered results that led to improved insights into chronic hepatitis and had a worldwide impact on the treatment of these diseases, changing practice and transforming the outcome both nationally and internationally. 3) I have been part of a group of individuals who formed a driving force behind national/international efforts to educate clinicians in the treatment of viral hepatitis, and to provide consensus guidelines for the care of these diseases. Some of these efforts have been directed by national organisations such as the British Association for the Study of the Liver, British Liver Trust and the HCV trust. 4) I was accorded emeritus Professor status upon my retirement from University College London in 2013 and granted a further two-year contract at the Royal free. Upon my retirement from the Royal free Hospital in 2016, I was invited to participate as a part-time hepatology consultant at Kings College Hospital London and I continue to provide appropriate input into NHS medicine to maintain a busy ambulatory clinical load, and research mentoring within Kings College Hospital. Lewisham University Hospital have asked for my assistance during the Covid-19 pandemic.

2.35. I have provided national and international advice on new antiviral agents. I acted as a principal investigator on several studies examining new treatments for hepatitis B and C, to shorten the translational research time and to extend advances in therapy for persistent viral hepatitis, cirrhosis and decompensated cirrhosis. These efforts were published in high impact journals including The New England journal of Medicine, The Lancet, Journal of Experimental Medicine, Gastroenterology, Proceedings of the National Academy of Sciences, The Lancet, Journal of Hepatology and Hepatology, Nature Reviews Disease Primers, among others. I have played a significant role in the writing of National and International guidelines including successive EASL guidelines for hepatitis B and C.

2.36. Given the epidemiology of viral hepatitis I maintained a professional commitment to the welfare of disadvantaged groups of patients and minorities. I acted as an expert adviser to NICE for hepatitis treatments. I have played a role in the training of hepatology specialists across the

network and explored the extension of the service within a managed network to people with injecting drug use, rehabilitated drug users, and prisoners. The clinic provided care to ethnic minorities with high rates of hepatitis B and C.

2.37. Other leadership roles have included offices within learned societies, invited lectures visiting professorships local, national and international posts including WHO technical consultation on hepatitis C (1998-2003); specialist editor GUT (2004-2006) Editorial Board Hepatology, Editorial Board Journal of Viral Hepatitis; Journal of Viral Eradication; I am currently the Viral Hepatitis Editor for Alimentary Pharmacology and Therapeutics. I acted as an adviser to the British Liver Trust and was the educational counsellor in the Governing Council of EASL, (2005-2009) devising the annual postgraduate courses, and EASL Schools for training of hepatologists. These provided for the training of younger hepatologists from across Europe and elsewhere. I have participated in the Department of Health Skipton Fund, National Institute of Clinical Excellence (For the Royal College of Physicians) and advised Haemophilia Societies. I have acted as a Medical adviser to the Thalassaemia Society and as a clinical advisor to the Scottish National Blood Transfusion Service. I have recently been asked (November 2020) to become a member of the Paediatric Working Group on Viral Hepatitis convened by the WHO.

2.38. I have provided a service to the Department of Health for the care of hepatitis B positive healthcare workers. I am a frequent reviewer of grants including the Wellcome Trust, Medical Research Council, NHS executive, Research and Development World Health Organisation, the NIH cooperative grant panel from 2000-2005 INSERM, Korean Science agency, and am a reviewer on the Scientific Advisory Board for the Translational and Clinical Research Flagship program for the National Medical Research Council of Singapore; the German Research Foundation; I am on the Scientific Advisory Board for the TherVacB study funded by the EU; and others. I was the 2000 visiting Professor, University of Western Australia 2004, visiting Prof University of St Louis 2011, visiting lecturer Melbourne

and Sydney 2012- 2013 and am listed on Who's Who in the world. I have been invited to act as a nominator for the Japan prize and for the Lasker award (2005). Over the course of my career, I have been invited to deliver several named lectures locally and internationally including Humphrey Davy Rolleston Lecture Royal College of Physicians, Bushell Lecturer Australian Society of Gastroenterology and faculty meetings of AASLD EASL, AASLD Single Topic, APASLD, IASLD.

2.39. I have acted as a member of numerous drug safety monitoring boards including those for Gilead Sciences, Human Genome Sciences, Janssen, Glaxo Wellcome, Enanta, Roche, Aligos, and still act as chairman of several monitoring boards including those investigating treatments for non-alcoholic fatty liver disease and new curative therapies for chronic hepatitis B.

2.40. I have advised several public facing civil society and patient groups including the Thalassemia International Federation, Mainliners, HCV Action, the Hepatitis C Trust, Positive Action, British Liver Trust, as a supporter of the NOHep movement and interacted with the World Hepatitis Alliance and the EASL Foundation. [WITN3754050]

d. A full and up to date bibliography of your publications

2.41. I have attached a publication list exported from the UCL research publications site [WITN3754049] with brief annotations My Hirsch index is 72 and my published work has been cited 28,779 times. My publications include over 1,250 co-authors, whom I gratefully acknowledge.

3. Please set out your membership, past or present, of any committees, associations, parties, societies, or groups relevant to the Inquiry's Terms of Reference, including the dates of your membership and the nature of your involvement.

3.1. I have served on NICE panels, (USA) National Institutes of Health Hepatitis Consensus panels, EASL guidelines committees, World Health Organisation advisory boards, the Skipton Fund, (2014-2017) NHS EIBSS

(2018) and have advised the Thalassemia International Federation, UK Thalassemia Society and several Haemophilia Societies in the past, and still do.

3.2. At a National level, I advised a working party on liver disease in haemophilia, the British Liver Trust Medical Advisory Board, and am a member and have been a faculty speaker for the British Association for the Study of the Liver, and British Society of Gastroenterology. I am a Fellow of the Royal College of Physicians of London and Edinburgh. I have been called as an expert witness in a High court judgement on a patent dispute in diagnostic testing for hepatitis C.

3.3. I have served as a faculty speaker on the European Working Party on Chronic Hepatitis, the European Association for the Study of Liver Disease, the American Association for the Study of Liver Disease, the Asian Pacific Association for the Study of Liver Disease, the African Association for the Study of the Liver, the International Association for the Study of the Liver, and the European Hepatitis Group (Eurohep).

3.4. I have written hepatitis B guidelines for the WHO and have served on WHO advisory groups

4. Please confirm whether you have provided evidence to, or have been involved in, any other inquiries, investigations, criminal or civil litigation in relation to the human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement and copies of any statements or reports that you provided, save for those that are already provided to you with this request.

4.1. I have given evidence for claimants before the Irish Tribunal of Inquiry into the Blood Transfusion Service Board. I have given evidence in a patent dispute between Chiron versus Murex/Organon, and the Hammersmith hospital transmission of hepatitis B 1990. The latter inquiry led to a

recommendation that the Department of Health should review its guidelines on hepatitis B; appropriate procedures to prevent harm to patients from infected hepatitis B and C medical and dental staff undertaking exposure prone procedures have resulted and have been modified over time. The advent of antiviral therapy has allowed individuals receiving antiviral therapy to return to work under updated guidance. [WITN3754051]; [WITN3754052]; [WITN3754053]

5. **In respect of your witness statement dated 11 February 2000 produced for the case of A. and Others v. The National Blood Authority, reported as [2001] 3 ALL ER ("the Hepatitis Litigation") [NHBT0086710] please confirm whether the contents of that statement are true and accurate. If there are matters contained within that statement that you wish to correct or clarify, please indicate this (and please expand on this in your answer to any specific question below, if you feel that the subject matter relates to a specific topic and is best explained in that context).**

5.1. The contents of that statement are true and accurate. I acted as a witness for the claimants. My detailed witness statement provided context to indicate the level of awareness of transfusion transmitted NANB hepatitis, and measures to contain transmission, including diagnostic testing. The statement includes a detailed background and a chronology of the discovery of hepatitis C.

5.2. I point out that in his summation the judge Mr Justice Burton stated: "The Claimant's Factual Witness Prof Dusheiko was described as a factual witness but to all intents and purposes, as he did not play a personal role in any of the events to which primary attention has been directed (save that he attended at the authors symposium in Rome, as did Dr Gunson and Dr Barbara), he was really an expert witness." Justice Burton found for the claimants. [PRSE0003333]

6. **The Inquiry understands that you took up a role as a Senior Lecturer in the Academic Department of Medicine at the Royal Free Hospital School of Medicine in 1988, and thereafter progressed to the role of Reader in 1989 and Professor in 1996. Please provide, in outline introductory terms (you are asked to give a detailed account on more particular points in subsequent questions):**

6.1. I have been engaged in studies of the natural history, epidemiology, pathology, clinical features, molecular virology, treatment, public health aspects, health impact and economics of chronic viral hepatitis since 1979. In order to condense the research to narrative chronology I have annotated my research publications indicating the major findings and conclusions. (See Q6a) [WITN3754049]. As pointed out above, my research endeavours would not have been possible without the input from numerous other clinicians, scientists, technologists and nurses, and the willingness of patients to participate in research.

6.2. I was able to utilise the opportunities afforded to straddle broad fields of research and was able to bridge clinical aspects and the contemporary molecular virology of viral hepatitis to undertake research that was of clinical and public health importance. My clinical studies were ultimately designed to alter the progression and morbidity of chronic viral hepatitis.

a. **A narrative chronology of your developing research focus over the course of your career, explaining your contribution to each topic area, and any major findings or conclusions that were drawn from this work; and**

b. **The extent to which your work in the Department at the Royal Free has been clinical, the nature of your engagement with patients, and the broad nature of their illnesses. If this has changed or developed over time, please explain how and why.**

6.3. In response to question 6a I have provide a list of publications referred to above, [WITN3754049] to summarise my research and publications. Selected publications have been annotated with the relevance of the

findings, the conclusions that were drawn from our work and the importance for future management of patients with chronic viral hepatitis (in blue italics)

6.4. I am a clinical scientist and have had, since graduation, close contact and engagement with both inpatient and outpatient care, with a large clinical load. I am trained in acute general medicine and hepatology and continued general medical inpatient care on acute medical take for 17 years from 1988. I have very limited training in transplant hepatology and no training in luminal gastrointestinal endoscopy.

Section 2: Your research about hepatitis

7. The Inquiry understands that you have conducted research or clinical trials and/or published articles in relation to each of the following topics that are relevant to the Inquiry's Terms of Reference. In respect of the topics listed below at a. to g., please answer the questions listed at (i) to (ix).

Topics of research

a. The diagnosis and nature of different types of hepatitis.

Please consider, in particular, your articles:

'Hospital Diagnosis of HCV', presented at the NANBH Ortho Symposium held in Rome on 8 February 1990 [NHBT0005060_007];

7.1. The symposium addressed the recent discovery of hepatitis C and the development of diagnostic tests. I addressed the diagnosis of NANB hepatitis (not hepatitis C) in this precis, providing current definitions of NANB hepatitis prior to the discovery of hepatitis C. Hitherto, the diagnosis of NANB hepatitis had depended upon the finding of an increase in serum aminotransferases and the exclusion of other causes of liver disease. A diagnosis of NANB hepatitis would be reinforced by a history of blood

transfusion or percutaneous exposure. Histological findings could be helpful.

7.2. I then went on to provide the crucial change in context after 1989 and the discovery of hepatitis C, and the development of diagnostic tests: Serological patterns of seroconversion to anti-HCV in acute resolving and chronic hepatitis C had been determined in small cohorts of patients with post-transfusion hepatitis and in chimpanzees with experimentally induced hepatitis C. In some cases, a prolonged interval between the peak in serum ALT concentrations and seroconversion could be observed. Hepatitis C RNA could be detected in the acute phase of the illness prior to seroconversion to antibody to hepatitis C. I wrote that antibody may persist for up to 25 years but may disappear in those who have resolving disease. I commented on the fact that some serologic difficulties can be encountered in making the diagnosis of active hepatitis C, due to the lack of a serological test for HCV antigens, and on the general unavailability of hepatitis C RNA to confirm viraemia.

Your article 'Acute viral hepatitis' Medicine International Journal, November 1990 [DHSC0002541_068]

7.3. I reported that in 1988, the molecular cloning of an RNA virus responsible for most cases of non-A non-B hepatitis had been published. This manuscript reviewed current clinical knowledge of Non-A, Non-B hepatitis (hepatitis C). I wrote that in countries in which hepatitis B virus testing is routine, post-transfusion non-A non-B hepatitis accounts for 90-95% of cases of post-transfusion hepatitis. I also reported on other risk groups including those on haemodialysis, renal transplant recipients, haemophiliacs, patients with thalassaemia, those with hypogammaglobulinaemia, bone marrow and liver transplant recipients, healthcare workers, intravenous drug users, male homosexuals, and possibly those who acquire the disease as a result of perinatal transmission.

7.4. Anti-HCV testing provided a specific diagnosis. Good diagnostic concordance had been found in well-defined cases of post-transfusion non-A non-B and in blood donors known to have transmitted non-A non-B hepatitis. I described the characteristics of the virus. I also reported that a commercial enzyme immunoassay test for HCV "is currently being used by clinical investigators and blood banks worldwide to diagnose hepatitis C".

Your article summarising the proceedings at the Second International Symposium on HCV, held in Los Angeles on 8 – 9 November 1990 [NHBT0057988_001]

7.5. Article 4 is an educational summary providing a precis of the Second International symposium on hepatitis C held in November 1990 in the United States. The virology of HCV was updated at this meeting. The structural organisation of the genome had been further elucidated. Proteins encoded by regions of the genome were identified. Advances had been made in the serological diagnosis of hepatitis C virus infection: antibodies to the C22 and C33 proteins, (a structural and non-structural protein respectively), appeared earlier than antibodies to C-100-3, shortening the period to seroconversion. Detection of HCV RNA by polymerase chain reaction was dependent upon the primers used. Alter had reported that perhaps 20% of those with chronic infection may develop chronic active hepatitis and cirrhosis. Some patients developed cirrhosis within 4 to 5 years, but others showed an indolent course and remain healthy for many years. However, the development of HCC and cirrhosis following chronic NANB hepatitis /hepatitis C had been documented, although the interval between transfusion and HCC was usually prolonged.

7.6. The proportion of patients who had been infected via transfusions in the United States had declined from previous years, and other sources of community acquired infection were important. The incidence of transfusion-associated non-A non-B infections in the United States decreased before the institution of surrogate testing by blood banks, and had been temporally associated with donor selection and self-exclusion.

7.7. I reported that Esteban of Barcelona had used second-generation tests to detect antibody to C22 and C33. In Japan HCC and cirrhosis were common in patients who gave a history of blood transfusion; 68% of patients with HCC had no hepatitis B markers.

7.8. The evidence for and against sexual and maternal infant transmission was still debatable. Roggendorf reported the results of a study in East Germany in which 2000 woman had been given anti-D immunoglobulin contaminated by non-A non-B. Sixty percent of the woman developed non-A non-B hepatitis. Chronic hepatitis developed in 53% of those with acute disease. None of their children were anti-C100-3 positive. Interferon (beta) had been recently used to treat acute hepatitis C. Efficacy was reported. After three months 75% of the treated patients had normal ALT compared to only 20% of untreated control patients. Twelve months after the onset serum ALTs were normal in 40% of treated but only 20% of untreated patients.

7.9. Hoofnagle reported that in the small number of patients studied at the NIH serum HCV RNA disappeared from serum after treatment of chronic hepatitis C, but HCV RNA disappearance did not preclude later relapse.

7.10. Several posters reported the finding of limited agreement between the first-generation ELISA assays and supplemental tests. False positives remained a problem in this group. The meeting consensus suggested at the time that donor screening would have some impact upon post-transfusion hepatitis, but post transfusion hepatitis represented a relatively small part of the total disease burden, and in order to control the disease all modes and sources of transmission needed to be further understood.

Viral hepatitis: part 1, Hospital Update, March 1992 [NHBT0000090_011]

7.11. This article summarised current knowledge of acute and chronic hepatitis for clinicians. A section reported the discover of hepatitis C virus to include a description of antibodies to hepatitis C antigens: The original cloned antigen (5-1-1) which was recombinantly expressed from a non-structural

region of the HCV genome was sub-cloned into yeast to express a protein termed C 100-3.

7.12. In the first generation of commercial assays a C100-3 peptide was used to capture antibody in serum of patients. Anti-C100-3 antibody developed one to three months after the onset in clinical illness but in some patients would not be detected for up to one year. I wrote that the first generation of antibody test to HCV had been superseded by second generation assays which detected antibodies to anti-C100-3 and other recombinant antigens, including C22 and C33. The second-generation assays were more sensitive and seroconversion more frequent. Antibodies to HCV were present in 85-95% of well documented cases of chronic post-transfusion non-A non-B hepatitis. However, in random blood donors in northern Europe the specificity of the test was lower and required verification by supplemental recombinant assays. Newer assays to detect antibodies to HCV peptides were in development. Detection of HCV RNA was the only direct test for active HCV infection and was at the time often the only means of diagnosing acute hepatitis C because of delayed seroconversion to antibodies to HCV; however, detection of HCV RNA was only available in reference centres only.

Improved diagnosis of chronic hepatitis C by detection of Antibody to Multiple Epitopes: Confirmation by Antibody Synthetic Oligopeptides', Journal of Medical Virology on 3 April 1992 [NHBT0000116_093]

7.13. In this study we tested serum samples from 226 patients for antibody to hepatitis C using first- and second-generation assays. Ninety of 117 sera (77%) from patients with suspected chronic NANB hepatitis were positive in the second-generation assay compared with 72/117 (61%) positive for C100-3. HCV RNA was detected in 60% of the anti-HCV positive sera. Thus, sensitivity was increased when antibodies to additional recombinant structural and non-structural antigens were tested by a second-generation assay. It was thought likely that the increased sensitivity was due in part to

the presence of antibodies to HCV core epitopes. These data had implications for the universal identification of infected blood donors.

'Genetic diversity of hepatitis C virus: implications for pathogenesis, treatment, and prevention', The Lancet, 4 March 1995 [HSOC0026680]

7.14. The Royal Free Hospital cooperated with The Lancet to present and subsequently publish an educational clinical "Grand Round". The up-to-date seminar illustrated, by a clinical case history, the clinical disease, a discussion of the virology and sequence variation (genotypes), genetic diversity, RNA quantitation and the pathology of hepatitis C, and prospects for a vaccine against hepatitis C. I reported that "only 15-25% of patients treated with interferon alpha show sustained responses. Patients with type 1 infection seem to be less sensitive to interferon treatment than are patients with type 2 or 3" (as was the case with the illustrative reported patient).

Chronic Hepatitis C Virus Infection in Haemophilic Patients: Clinical Significance of Viral Genotype" Thrombosis and Haemostasis, August 1995. [HSOC0026883]

7.15. These studies documented genotype distribution in a group of patients with haemophilia. We found higher levels of HCV RNA in patients with type 1 infection compared to genotype 2 or 3 infection, but these data could be related to differences in hybridization efficiency. We also observed a clear difference in response to interferon alpha between genotype 1 versus genotype 2 and 3. We wrote "genotype is emerging as an important independent predictive factor in treatment response in non-haemophiliac patients. However, this study highlights the dilemma in treatment of HCV infection with interferon. Patients who are least likely to respond are those for whom treatment is particularly indicated. Progression to cirrhosis, hepatic decompensation, and HCC are significant risks in HCV RNA - positive patients. Age, duration of infection, high alcohol intake and HIV coinfection was thought to be important determinants of progression." "There is clearly a need to assess alternative forms of treatment particularly

for patients with type I infection. Possibilities include high-dose interferon combination therapy with interferon and ribavirin. It would seem prudent to regard or HCV RNA - positive patients at risk of complications and to monitor them at regular intervals for evidence of progression."

Please also consider the correspondence you shared in April to May 1995 with F. E. Preston, Dr Christine Lee, Christopher Ludlam and Mr. G. Barker regarding possible trigger points for individuals infected with Hepatitis C. [HSOC0003733]

7.16. I was asked for an opinion regarding "possible trigger points" for (haemophiliac) individuals infected with hepatitis C. Trigger point was a poorly defined description: the inference being what would trigger an intervention? The suggestion to use endpoints of decompensated cirrhosis (ascites, oesophageal varices and encephalopathy) was clearly not suitable, as these are signs of advanced liver disease and liver failure.

7.17. It is necessary to treat far earlier to prevent cirrhosis and reduce the risk of hepatic decompensation. I wrote "one of the great difficulties with hepatitis C is predicting, at one point in time, which patients with mild or moderate chronic hepatitis will in fact progress. Histologically, if there is fibrosis then it is likely that the patient is showing a progressive course and fibrosis is generally regarded as irreversible. Unfortunately, with haemophiliacs, biopsy is not readily accessible, and this is a less useful marker. There are no good serum markers which correlate with fibrosis…The other indices as you point out in the letter are all evidence of decompensation and occur late in the disease. These are not useful trigger points"

7.18. It would be some years before we had more useful non-invasive markers of hepatic fibrosis to indicate progression, in particular transient elastography (Fibroscan).[1]

b. **Aetiology of different types of hepatitis.**

Please consider, in particular, your articles:

Immunoglobulin and the prevention of post-transfusional hepatitis' presented at the Third International Symposium on HCV in Strasbourg from 16 - 17 September 1991 [NHBT0000016_009 p. 5]

7.19. The study retrospectively analysed stored sera, factor concentrates and immunoglobulins for the presence of anti-HCV antibody in these factions to assess the possible efficacy of immunoglobulin prophylaxis. Not surprisingly this retrospective analysis found antibodies to hepatitis C to be present in immunoglobulin, but we stated that no conclusion could be drawn regarding the role of neutralising antibodies as prophylaxis against hepatitis C.

Hepatitis B viral expression in renal transplant recipients - a fourteen year follow up', American Association for the Study of Liver Diseases. Ord Annual Meeting, Chicago, November, 1982

7.20. This paper was published as a full paper in Hepatology in 1983. We followed 83 immunosuppressed renal transplant patients for a period of 2 to 15 years. Several patterns of expression of hepatitis B were observed in these patients which we documented. Reactivation of hepatitis B replication or continued high levels of HBV replication was common in renal transplant patients. However anti-HBe positive patients were not always susceptible to reactivation despite immunosuppression. Anti-HBs appeared to confer protection against hepatitis B despite immunosuppression.

The 1990 International Symposium on Viral Hepatitis and Liver Disease, Contemporary Issues and Future Prospects, 'Clinical Course and Histological Correlations in Serum Hepatitis Virus (HCV) Antibody Positive Post-Transfusion Hepatitis: The Royal Free Hospital Experience', 4 - 8 April 1990 [NHBT0000016_025 p. 31]

7.21. The study examined the clinical course of 24 patients with hepatitis C positive post-transfusion hepatitis and correlated the findings with liver biopsy appearances. The liver histology in this cohort showed either resolving hepatitis mild chronic active hepatitis, chronic active hepatitis, active cirrhosis or inactive cirrhosis. Most biopsies showed periportal and lobular inflammation with lymphoid follicles characteristic of hepatitis C liver disease. The clinical course remained stable and continued unchanged for a mean of 13.9 years (range 1-27 years). The study pointed to an indolent course in some patients, whereas cirrhosis could occur in others. However, this early study included only a small number of patients. Later, we published a more comprehensive picture of hepatic histological changes in chronic hepatitis C (3).

Your Symposium Poster for the Virology Workshop at the Third International Symposium on HCV held from 16 - 17 September 1991 in Strasbourg, France 'HCV Seroprevalence In HIV-Infected Haemophilic Patients' [NHBT0000016_006 p. 7]

7.22. We documented HCV seroprevalence in patients with haemophilia who were also infected with HIV. Sera from 125 haemophiliacs were analysed. All had received unsterilized clotting factor in the past. Comparisons were made between an anti-C100-3 (Abbott HCV EIA first-generation) and the Abbott HCV EIA supplemental essay in which HCV core protein was incorporated. This abstract documented that in haemophiliac patients, approximately one quarter did not have antibodies detectable by the first-generation C-100-3 assay; second generation tests incorporating antigens derived from the core, NS3 and NS4 regions of the HCV genome improved diagnostic sensitivity in patients.

Your article 'Epidemiology and transmission of hepatitis C infection' European Journal of Gastroenterology and Hepatology 1991, Vol 3 No 8 [NHBT0000102_027]

7.23. In this paper I pointed out that most of the sero-epidemiologic studies of hepatitis C carried out so far had been based on the prevalence of anti-C100-3. Seroconversion could be delayed in the acute phase of the disease. However the presence of detectable anti-C100-3 antibody seemed to reflect active replication of hepatitis C. I tabulated the prevalence of anti-C100-3 antibody in blood donors; I pointed out that in retrospective studies in blood donors who had been implicated in the transmission of post-transfusion NANB hepatitis, anti-C100-3 was a marker of infectivity as would be expected from a non-neutralising antibody that is induced more frequently in chronic than acute self-limiting infections. I also referenced the responsibilities that would fall on Transfusion Services. I pointed out that haemophiliacs could also be HCV PCR RNA - positive without detectable anti-C 100-3 antibody and referenced the statements. The advent of serologic testing had shown that most community- acquired NANB was caused by the same virus (hepatitis C) responsible for post-transfusion NANB hepatitis, albeit acquired via a different source.

7.24. This comprehensive review also examined modes of transmission and the infectivity of HCV as well as sexual transmission, intrafamilial spread, and maternal infant transmission, categorised transmission of hepatitis C and the correlation of transmission with the presence anti-C100-3 antibody in donors.

c. **Prevalence and progression**

Please consider, in particular, your articles:

The progression of HCV-associated liver disease in a cohort of haemophilic patients' in the British Journal of Haematology, 10 March 1994 [DHSC0032212_092]

7.25. In this manuscript (Telfer et al) retrospectively studied clinical data on all patients with congenital coagulation disorders registered at the Royal free Hospital who had been treated with clotting factor concentrates and who were positive for hepatitis C. Patients who were anti-HCV positive by enzyme immunoassay but negative or indeterminate by RIBA were included. The clinical characteristics were described. 255 patients (68.5%) were HCV seropositive. The median duration of follow-up since exposure to concentrate was 15 years but ranged from 3.5-28 years. The median time from first concentrate exposure to hepatic decompensation in the 11 patients who had decompensated was 16.5 years (range 7.7-22 years). The risk of progression to liver failure estimated by the Kaplan-Meier analysis was 1.7% at 10 years after exposure to concentrate and 10.8% (95% confidence interval 3.8-17.8%) 20 years after exposure to concentrate. The relative hazard of developing liver failure after HIV co-infection was significantly increased. The hazard was also increased for those with haemophilia A, those with higher use of concentrate and in older patients.

7.26. Thus, this study clarified some of the uncertainty regarding the risk of progression of NANB hepatitis, in patients with haemophilia. (4) The study provided strong evidence that HIV co-infection accelerated the progression of hepatitis C and our finding of an association of older age with HCV progression was consistent with other reports. We concluded that there was significant morbidity and mortality associated with hepatitis C virus infection which was likely to increase in the coming decades. We stated that anti-viral therapy should be considered.

The natural course of chronic hepatitis C: implications for clinical practice Journal of Viral Hepatitis, 1998, 5 (Suppl 1), 9-12 [NHBT0000117_048]

7.27. This paper reviewed the spectrum of disease in hepatitis C which ranged from mild hepatitis to cirrhosis and HCC. I pointed out that the disease was complex and predictions about the long-term prognosis for individual patients "remain difficult." I also gave the consensus view that it was generally accepted that 10 to 20% of patients with chronic hepatitis C will develop cirrhosis within 10 years of first infection: "Identifying the group at greatest risk remains a primary challenge for clinician. Older age of infection, duration of infection degree of liver inflammation at first biopsy and cofactors such as alcohol abuse all appear to be predictors of a poorer prognosis."

7.28. In this editorial I indicated that one of the difficulties of studying the natural history had been the bias that occurs in studying different populations. General population studies had been the most useful, but the most difficult to carry out. A clinic-based population could involve selection bias since the latter patients will often have been referred because of symptomatic or discernible disease. "There is a desperate need for better non-invasive methods of measuring fibrosis in the progression of fibrosis which may not be too far off".

7.29. Following an untreated at-risk patient group for a prolonged period of time would not be ethically justifiable. The review provided an estimate based on published evidence of risk factors for progression after the acquisition of hepatitis C. I cite a number of relevant references (5-10). To conclude the editorial, I posted a number of unresolved questions including: what proportion of patients have a severe outcome, what is the proportion of patients with minimal morbidity, to what extent does spontaneous recovery from chronic hepatitis C occur, is there a change in the rate of progression with age, does the rate of progression during the first 20 years indicate the likelihood of progression during the second 20 years? "Each of these questions remains unanswered."

The natural history of HCV in cohort of haemophilic patients infected between 1961 and 1985', 22 June 2000 [PRSE0002936]

7.30. A later analysis of the clinical and treatment records of 310 patients treated with blood product before 1985 was published by Yee et al, which firmly established the risk of morbidity and mortality among haemophilia patients in the UK. Seventy two percent were alive by September 1999, 8% had died of liver -related death and 20% had died from other, predominantly HIV related causes. Yee documented that Kaplan-Meier progression rates to death 25 years after exposure to HCV were 47% for death from any cause, and 19% for liver related deaths, (95% confidence intervals 10-27) respectively. The adjusted relative hazard of death for individuals co-infected with HIV compared for those infected with HCV at different age groups was compared. (The risk was elevated). The adjusted relative hazard for genotype 1 was 2.7. We commented in the discussion "clearly the challenge is to provide treatment to delay progression or "cure" patients. Unfortunately, a large number have poor prognostic factors for successful eradication: male sex, high viral load, long period of infection, gentotype I HCV and HIV coinfection. Nevertheless, a minority of these patients responded to alpha-interferon alone or combination therapy, with response rates similar to those recently reported.

The natural history and antiviral treatment of Hepatitis C' (2002) Haemophilia, vol 8, p. 322-239 [DHSC0038538_078]

7.31. In this review we updated findings of the natural history and anti-viral treatment of hepatitis C in haemophilia. We reported recent data to suggest that the combination of standard interferon alpha and ribavirin doubled the effectiveness of interferon alone and was the current standard of care for the treatment of chronic hepatitis C. We also reported that the duration of therapy depends upon genotype: patients with genotype 2 or 3 should have six months therapy while those with genotype 1 should have one year of therapy. We commented that pegylated interferon was an emerging therapy. We also commented on the difference in the natural history

reported from prospective studies of blood transfusion recipients versus retrospective studies which tended to include patients with established liver disease. We reviewed the indications and aims of treatment. The review points to the decision to treat being a complex issue which "must take into account numerous variables including the age of the patient, the general state of health, the risk of cirrhosis, the likelihood of response to treatment, other medical conditions that may decrease life expectancy and any contraindications to the use of interferon alpha and ribavirin".

7.32. We cite the NIH consensus document on hepatitis C management which had concluded "treatment is recommended for the group of patients with chronic hepatitis C who are at the greatest risk for progression to cirrhosis. These patients are characterised by specifically elevated ALT, positive HCV RNA and a liver biopsy with either portal bridging fibrosis and at least moderate degrees of inflammation and necrosis". We cited that the merits of treating viraemic patients who had minimal histologic disease is uncertain. We also stated that the EASL international consensus conference on hepatitis C [PRSE0002940] recently concluded that HCV RNA - positive patients need not necessarily be considered for liver biopsy or treatment. However, a proportion of viraemic patients with normal ALT may have active and progressive liver disease.[2] The review provided several updated references comparing the efficacy of standard interferons and pegylated interferon with or without ribavirin in genotype 1 versus genotype 2 and 3 patients: treatment responses had improved to 76% of patients with genotype 2 and 3 treated with pegylated interferon and ribavirin and to 46% in patients with genotype 1 treated with the same regimen. (11-15)

Please consider the evidence you gave in the Hepatitis Litigation, where (i) you are reported to have estimated the risk of an individual with hepatitis C developing cirrhosis at 20% - 30% over 20 - 30 years [DHSC0011771 p. 82 (p 370 of the judgment)] , and (ii) in your statement at paragraph you said, "Patients who have acquired hepatitis C as a result of blood transfusions appear to be at greater risk of the development of severe liver disease compared to patients who did not acquire the disease by this route" [NHBT0086710]

7.33. I cited an accepted estimate of progression. It was difficult to obtain a consensus. [3] The subject is extensively covered in more detail in the reviews cited above, and the figure is supported by several authors. (17, 18). Poynard suggested that the median rate of fibrosis progression per year was 0.133 fibrosis units (95% CI 0.125-0.143). In his analysis, three independent factors were associated with an increased rate of fibrosis progression: age at infection older than 40 years, daily alcohol consumption of 50 g or more, and male sex. (8) Seeff summarised differences in outcome between prospective studies of transfusion associated non-A non-B hepatitis, retrospective-perspective studies of chronic non-A non-B and type C hepatitis and factors that might promote progression of HCV -related chronic liver disease. (5) In 1998 he suggested a circumspect viewpoint. (16) There was evidence to suggest that indeed patients who had acquired hepatitis C because of blood transfusions appear to be at greater risk compared to community-acquired hepatitis C. (19, 20). (21) Estimates of the progression of post transfusion hepatitis and community acquired disease varied and estimates were subject to bias and ascertainment. (22, 23) (reviewed by Seeff et al and covered in the reviews referenced above). In the light of the evidence to date, I inferred that the natural history was influenced by several host and viral factors. (4). In 1998 Poynard et al suggested that the published randomised controlled trials of interferon and preliminary results with a combination of interferon and ribavirin indicated that treatment improves the natural history of hepatitis C. (24)

d. **General management of hepatitis, available treatments, including Interferon, and questions of cost-effectiveness**

Please consider, in particular:

'Clinical consequences, prevention and treatment of non-A, non-B hepatitis: new discoveries about old diseases' (date and publication unknown) [NHBT0000097_008];

7.34. (This manuscript appeared in Current Medical Literature: Infectious diseases. 3: 5-11 1989, predating the publication of the discovery of hepatitis C). The manuscript gives a full exposition of what was known of NANB hepatitis at the time and references most statements.

7.35. I indicated "that the virus has come to be known as non-A non-B virus - a suitably enigmatic name. NANB hepatitis is an important cause of progressive liver disease. Despite the failure to identify the causative agent a great deal has been learnt of the epidemiology, pathology associated disease and even the treatment of in a NANB hepatitis"

7.36. I also wrote "although NANB hepatitis may not be commonly transmitted by blood transfusion in the UK, several groups are nonetheless at risk because of their dependence upon the blood supply, their occupation, their lifestyle or the reservoir of non-A non-B in their particular community. These groups include patients on haemodialysis, renal transplant recipients, haemophiliacs, thalassemics, hypogammaglobulinaemics, bone marrow and liver transplant recipients, healthcare workers, intravenous drug abusers, male homosexuals, and possibly those who acquire the disease as a result of perinatal transmission" and referenced the statements. "The clinical spectrum of NANB hepatitis ranges from acute disease with complete recovery, to acute fulminant hepatitis, relapsing hepatitis, chronic infection without apparent hepatitis, chronic active hepatitis, cirrhosis and HCC." I included sections on chronic NANB hepatitis and summarised what was known of the natural history, HCC, prevention and testing. I stated "the

exclusion of paid commercial blood donors has reduced the incidence of post-transfusion NANB hepatitis in the USA and is proving the single most important measure. The use of autologous blood and affinity-purified, or wet heated and particularly genetically engineered factor VIII preparations will limit the occurrence of new cases of NANB hepatitis in haemophiliacs" I also included a section on surrogate testing including donor ALT and anti-HBc testing. The review was up-to-date: I wrote "a preliminary report of alpha interferon treatment of NANB hepatitis by Hoofnagle and colleagues drew attention to the fact that in 8 of 10 patients with NANB hepatitis serum aminotransferases returned to normal within a few weeks of treatment with histological improvement in some. However, in all cases in whom interferon was stopped after 4 months of treatment, a relapse, judged by a rise in serum aminotransferases occurred." "A sizeable number of patients with presumed NANB hepatitis of now been entered into prospective controlled trials of alpha-interferon in the USA and the UK; overall efficacy, optimal doses, duration of therapy, relapse rate and the long-term benefits of treatment will soon be better defined".

7.37. I included a section on new developments including the identification of the NANB agent: "in March 1988 Houghton and colleagues of Chiron Corporation San Francisco reported the molecular cloning of an RNA virus after extraction of nucleic acid and cDNA cloning from an infected chimpanzee "From the expressed protein an enzyme immunoassay for NANB antibody has been developed, and good concordance has been found in "pedigree" cases of post-transfusion NANB. The finding likely represents an important breakthrough in the search for one of the major NANB agents which now will rightfully take its place as hepatitis C and heralds a timely advance in the prevention and treatment of a disease affecting millions worldwide."

'Response, Relapse, Re-Treatment and Viraemia in patients with chronic hepatitis c treated with alpha 2b interferon, a phase III study' presented at the Third International Symposium on HCV in Strasbourg from 16 - 17 September 1991 [NHBT0000016_009 p 3];

7.38. I presented the theoretical model of the costs and possible cost effectiveness of treating chronic hepatitis C with alpha-interferon. The study was done in cooperation with Dr Jennifer Roberts. The full paper was subsequently published in the journal Hepatology. (25)

Cost Effectiveness Study: Interferon Therapy in Chronic Hepatitis C', slides presented at the European Commission Seminar on Hepatitis C in Luxembourg on 14 February 1994 [NHBT0041690_012]

7.39. These data were subsequently published as a full paper in Hepatology. (25) The study was done in cooperation with Dr Jennifer Roberts, health economist at the London School of Hygiene and Tropical Medicine and a PhD student.

7.40. The assumptions made in the study were a response rate of 25%; sustained response to therapy would confer benefit, and that only 20% of patients with decompensated cirrhosis would be transplanted. The cost per Quality Adjusted Life Years (QALY) compared favourably with other health sector interventions. Economic appraisals were important for payers to assess value for money.

Recombinant leucocyte interferon treatment of chronic hepatitis B', International Meeting Viral Hepatitis, San Francisco, March 1984;

7.41. No paper was included. I would be grateful if the paper could be attached. We reported the results of our experience of treatment of hepatitis B in full papers. [WITN3754098; WITN3754099] (26-28)

'Review article: the management of hepatitis A, B, D and non-A non B', Alimentary, Pharmacology & Therapeutics (1989) 3, 1-20, dated 28 October 1988 [NHBT0083765]

7.42. This review provided an up-to-date overview of viral hepatitis including NANB hepatitis. Reference was made to the recent discovery of hepatitis C and recent preliminary results of interferon treatment at the National Institutes of Health in Bethesda, USA

Your report about the cost effectiveness of treatments delivered at the European Commission's Seminar on Hepatitis C in Luxembourg on 14 February 1994 [NHBT0041690_001 p. 44 – 48]

7.43. This meeting introduced hepatitis C to the European commission.

7.44. European experts invited to attend an EU Commission seminar provided a background to the problem, diagnosis and epidemiology and treatment of hepatitis C. I was asked to discuss cost effectiveness of interferon treatment of chronic hepatitis C. Delegates from the United Kingdom and several other European countries attended, and the meeting went some way to improve awareness of hepatitis C in Europe.

Your report 'INTRON A (alpha 2b recombinant interferon) therapy for patients with chronic hepatitis C' and addendum, March 1994 and March 1995 respectively [MHRA0000311, from p. 102 – 107]

7.45. An earlier application had been submitted for Intron A (interferon alpha 2b) on 17 January 1990. An application was submitted based on four studies conducted over the period 1988-1993 to provide additional clinical data to the CPMP and the UK MCA and to apply for consideration of a labelling change to extend treatment for up to 18 months in 1994.

7.46. The summary indicates that approval for Intron A had been given for the treatment of chronic C/non-A non-B hepatitis in 42 countries. My report reviewed data from four recent large studies of longer duration of treatment beyond 48 weeks. Some of the studies suggested that the risk of relapse

would be reduced with treatment duration longer than 6 months, and that the data support the posology for treatment for longer than 6 months.

7.47. The review also provided a critique of the studies. I pointed out the relative paucity of data. I also emphasised as in my earlier report that "the studies have been too short to demonstrate prevention of cirrhosis and therefore long-term benefit cannot be assured. Studies to examine the efficacy of the drug in preventing death from cirrhosis complications of cirrhosis or HCC would have to be of much longer duration." This submission should be considered as a submission for a developing, early posology and a critique of the available data.

7.48. Subsequent, later studies indeed indicated the benefit of a sustained virologic response in improving liver mortality and all-cause mortality (see below) and distinguished the necessity for a longer duration of treatment for genotype 1. Later combination treatment with ribavirin, pegylated interferon with ribavirin, pegylated interferon and direct antiviral therapy and direct antiviral therapies in combination, framed more tailored (and improved) durations of treatment of hepatitis C. Guidelines for the use of interferon alpha gradually evolved as evidence accumulated.

Your study, "Treatment of Chronic Type B and Type C Hepatitis with Alpha Interferon: An Economic Evaluation", presented at the 29th Annual Meeting of the European Association for the Study of the Liver in Athens 7 - 10 September 1994 [NHBT0097176_023]

7.49. This abstract is addressed by two full papers published in Hepatology and the Journal of Hepatology and co-authored with Dr Jenny Roberts, health economist of the London School of Hygiene and Tropical Medicine and JL Garcia de Ancos, a PhD student at the London School of Hygiene and Tropical Medicine. (25, 29)

7.50. The aim of the studies was to estimate the cost effectiveness of treatment based on calculations of the rate of progression of the disease over a 30-year period using a transitional probability model. The costs of therapy,

monitoring and treatment of the disease were estimated. The health economic impact of therapy was expressed in terms of cost per life-year saved, cost per life saved and costs per quality adjusted year of life saved. The analysis included two rates of progression to mortality. Discounted costs per year of life saved ranged from £2142 to £17,128. The data included a sensitivity analysis of the response rates and the cost of interferon alpha which changed the pattern significantly.

7.51. The results suggested that interferon therapy had a role to play to contain the impact of hepatitis. A number of assumptions had to be made in both models, but we made the assumptions explicit. The proviso was added that these models could be adapted when better information became available but pointed out the many gaps in the available prospective information concerning the medium-term effects of therapy with interferon alpha.

7.52. An accompanying editorial in Hepatology pointed to the varying natural history and rates of progression of hepatitis C. (30) The Editorial pointed to the need for evidence of benefit and value for money spent in the management of chronic viral hepatitis. The factors that determined progression required elucidation. The editorial pointed to the limitations of therapy and the requirement for optimal doses, dosing schedules, duration of therapy, and the use of adjunctive treatment with interferon which were active areas of investigation. Whilst the authors of the editorial conceded the importance and "salute the scholarship and supported the importance of undertaking the studies" they also pointed to a number of limitations. They did not quibble with the rates used in our model of outcomes for chronic hepatitis B but highlighted our assumptions. They suggested that broad clinical experience in the United States suggest a likely response to (interferon alone) ranged from 5-to 20% for 26 weeks of interferon treatment. We had raised the idea of additional benefit of treatment of chronic hepatitis C as a result of reduction in viraemia and hence reduction in infectivity in at risk groups.

7.53. A number of cost effectiveness analyses were subsequently published, including independent analyses by NICE et al and UK investigators. (31-38) (39)

Your article 'Side effects of Alpha Interferon in Chronic Hepatitis C', Hepatology, 26, No. 3, Suppl. 1, March 1997 [WITN3754019]

7.54. This manuscript was required for the National Institutes of Health consensus conference on the management of hepatitis C and was published as a full paper in Hepatology. [WITN3754019] (40) The review is a comprehensive view of the mode of action of interferon alpha, the pharmacokinetic data, the toxicology of interferon alpha, and discusses fully the adverse effects of interferon alpha that were known at the time. In the manuscript I separated the side-effects of alpha-interferon into four categories: 1) mild to moderate adverse side effects that occur commonly and that usually do not require dose modification; 2) mild to moderate side effects that occur uncommonly (in <10% of treated patients) that may or may not require dose modification; 3) severe or life-threatening side effects and 4) irreversible side effects. I also discussed contraindications to treatment of hepatitis C with alpha interferon.

7.55. The manuscript provided a major guide to the occurrence of the side effects of interferon and their management for the practicing clinician. I included a section on risks and benefits of alpha-interferon therapy. In this section I state "chronic hepatitis C is a potentially serious disease but may also follow an indolent and slow course. Alpha-interferon remains the only licensed treatment and has been shown to be more beneficial than placebo leading to clearance of viraemia and biochemical improvement although relapses may occur." Alpha interferon represented a clinical advance for selected patients and it was suggested that interferon alpha may be useful in forestalling hepatic decompensation in patients with sustained biochemical and virological response.

7.56. To write this manuscript I collated safety data provided from several large pharmaceutical and therapeutic trial databases as well as retrospective

surveys reporting a broad spectrum of side-effects. "Adverse events requiring one or more dose reductions have been reported in 10 to 15% of treated patients. Dose reductions for adverse events were required in 5 to 8%. Serious and life-threatening side-effect occur in 1 to 2% of patients. Monitoring requires regular clinical examinations and usually monthly measurements of serum chemistry, complete blood counts and thyroid function tests. A serum pregnancy test should be performed before therapy".

7.57. There are important contraindications to therapy with alpha-interferon which I tabulated. "The decision to use alpha-interferon must be weighed carefully. Haematological toxicity can be predicted in patients with low baseline white blood cell counts or thrombocytopenia. Hypertension and diabetes, clinically significant cardiac disease, renal, neurological and psychiatric disease are factors that may seriously predispose patients to serious adverse events. The risk of serious complications from alpha-interferon is rare. However serious idiosyncratic complication such as autoimmune disorders, pneumonitis, cardiac toxicity, renal disease, visual loss, or deafness can occur, and the drug must always be prescribed with caution. I also described the importance of selecting patients for therapy and optimising response. Careful assessment was required before treatment and monitoring is required during treatment. Finally, with the development of new agents for combination therapy of hepatitis C, it is particularly important to analyse whether side-effects are more, or less frequent with these combinations. "The development of anaemia (with interferon and ribavirin) may pose a particularly difficult problem that can be dose limiting and may be severe enough to be life-threatening". (40)

Your article 'The science, economics and effectiveness of combination therapy for hepatitis C', Gut (2000); 47: 159 – 161 [NHBT0084755];

7.58. I co-authored a leading article with 3 research fellows at the Royal Free which summarised data to that point (2000). We indicate that for reasons that were not clear at the time, higher treatment response rates were

observed in patients with genotypes 2 and 3 infection. Combination therapy with ribavirin and interferon alpha has enhanced sustained response rates and improved treatment response rates in patients who had relapsed after treatment with interferon alpha alone: Many patients with a relapse after interferon alpha had been treated successfully with combination interferon and ribavirin treatment and I cited data. In patients infected with genotype 1 treatment with combination ribavirin and interferon alpha for 48 rather than 24 weeks significantly improved sustained responses. We wrote that the "side effects of combination therapy, in short, require that the treating physician is equipped to monitor and manage adverse events, and to reduce or interrupt treatment appropriately". We also wrote that although combination therapy with ribavirin and alpha-interferon "is an important new therapeutic approach, it is not the final answer. Treatment is sub optimal in patients with type 1 infection and higher viral loads; a minority of these patients have a sustained virological response after 12 months of treatment."

7.59. We pointed out that guidelines had been formulated to aid physicians including the NIH and EASL consensus statements. "Genotype should not be used as a reason to deny treatment even though patients with type 1 are less likely to respond and should be forewarned of this. The benefits of treating patients with histologically mild disease are considered to be uncertain and there is a question mark over treatment for this group." "Haemophiliacs can be treated without a biopsy, for several cogent reasons." We also summarised putative mechanisms of action of ribavirin. We stated, "there is emerging evidence that pegylated interferon may be superior to alpha-interferons". "There is a reasonable expectation that the combination of pegylated interferon and ribavirin will enhance responses, and the studies have begun." We also questioned the likelihood of funding i.e. NICE authorisation of funding and whether the NHS had identified the financial resources to meet the cost of treatment. We wrote "NICE and the Department of Health in the UK and elsewhere in the world will need to examine allocation of resources for the wider need to consider the investment in treatment of hepatitis C at this time to reduce the future

disease burden." We close with the statement "clearly current treatments meet only some of the criteria for optimal treatment of hepatitis C. There have, however, been real therapeutic and technological advances. In the absence of a vaccine, treatment forms part of the strategy for controlling the morbidity from hepatitis C."

Your article 'Side Effects of Interferon Alpha in Viral Hepatitis', (date and publication unknown) [NHBT0000109_022]

7.60. I am unsure of the derivation of the publication provided and how it was sourced by the Inquiry. It is an undated and unreferenced monograph. However please see the full publication in Hepatology which provides detailed exposition of the numerous side effects of interferon alpha. (40)

Please also consider, in addition: a newspaper report in the Weekend Guardian in which an individual was reported to have said that your clinical team 'positively' presented a trial of Interferon, which he did not go on to experience positively [DHSC0004457_055]

7.61. I note the article dated May 16, 1998, which contains heartfelt personal narratives of problems encountered by patients during interferon treatment. I was realistic, questioning and cautious in all my writing and lecturing, and advice to patients, and provided factual evidence for interferon treatment which is discernible in my manuscripts. [WITN3754019]. I witnessed considerable fortitude from numerous patients contending with the side effects on treatment, and too often, a profoundly disheartening (for the patient and the clinical team), relapse after initial response. My knowledge was transferred to patients when interferon was offered. There is no question that interferon alpha treatment was problematic and challenging and no misleading claims were made. Interferon monotherapy was beneficial in some patients, but resulted in failure to respond or relapse, in others. For all patients, the decision to accept or defer treatment meant weighing up the likelihood of response, and side effects, against the possibility of progression. With time, more information become available.

7.62. A large number of patient- reported health-related quality of life and health outcome studies of interferon treatment of hepatitis C have been published. (41-63) Quality of life indices deteriorated during treatment but could be objectively improved for patients with a sustained virological response. (41, 64) The neuropsychiatric side effects meant that the drug had to be used with great caution and judgement in patients with hepatitis C.

7.63. Some patients were damaged both by their hepatitis C disease and by interferon alpha treatment. Interferon alpha is a powerful immunomodulatory, antiviral and anti-proliferative agent. Side effects during treatment are common and, in some patients, severe; the dose related toxicity is acceptable by the majority, but interferon is dangerous in some and was absolutely contraindicated in others. Adherence to 48 weeks was difficult. Post -treatment autoimmune reactivity has been documented but the functional basis and genetic diathesis for post interferon symptoms, and a deep characterisation of the idiosyncratic effects of interferon, or any subsequent inflammatory state, has been insufficiently studied and understood.

7.64. Progressive increments in response to treatment were observed. Sustained responses were difficult to predict but some factors emerged including young age, short duration of disease, absence of cirrhosis, viral genotype, and low HCV RNA levels (66) (67).

7.65. Later, we were able dissect out the viral and crucially, genetic host factors that predicted response, but only after many patients had been treated. Extended therapy for patients with genotype 3 and advanced fibrosis was tested in the UK. (65) Some of the known baseline predictive features of long-term response became better defined; these included the absence of cirrhosis, low viraemic levels and infection with HCV of type III or IV genotype (Okamoto's classification), or Simmonds non 1 genotype. Early reports incorrectly grouped and lumped together response rates in genotype 2 and 3.

7.66. A crucial revelation followed the discovery that a favourable genetic polymorphism near the IL28B domain, encoding the interferon-lambda-4 gene, (formerly referred to as the gene region encoding interleukin IL28B) predicted an approximately twofold change in response to treatment. (68-73). Genome wide association studies showed that a favourable CC or TT allele at rs12979860 rs8099917 respectively, were strongly associated with spontaneous clearance of infection and response to treatment. We could then better predict host genetics that favoured (or conversely disadvantaged) the response to interferon alpha - providing an example of precision medicine. The advent of interferon free regimens has culminated in the 95-97% cure rates observed today - and host genetic testing in patients is no longer required.

7.67. The Guardian article also referred to an interferon ribavirin pharmacokinetic study. The latter study was designed to assess possible pharmacokinetic interactions between ribavirin and interferon alpha-2b that could affect safety and efficacy. There were numerical trends indicating that the combination of IFN and ribavirin reduced titres of HCV-RNA to a greater extent than did either treatment alone, necessitating further analysis of the combination regimen. A greater decline in HCV RNA titres was observed (74).

7.68. Interferon alpha plus ribavirin combination ultimately proved to be more effective than interferon alpha monotherapy, with an acceptable safety profile. Subsequently, interferon alpha and ribavirin proved an important treatment for those who had relapsed on interferon monotherapy. [4] (15) Other study groups reported statistically significant improved outcomes with interferon alpha -2b and ribavirin in treatment-naïve patients. [5] (75) [6] (76) Several large multicentre, randomized, controlled trials which expanded on the findings of earlier, small studies demonstrated that the combination of interferon and ribavirin was more efficacious than interferon alone; the combination of interferon and ribavirin was considered an important advance, given the projected rate of death from hepatitis C. (77).

Notwithstanding, combination therapy increased side effects, particularly haemolysis.

7.69. Preliminary results with the combination of IFN and ribavirin suggested that successful treatment improved the natural history of hepatitis C. Studies first reported from Japan (a country ahead of the epidemic curve) demonstrated that successful treatment modified the natural history of hepatitis C and reduced the risk of HCC. (78) We began to see follow-up studies of patients treated with interferon that showed histological benefit, and reduced progression to HCC in sustained virological responders who cleared HCV RNA. (79) (80) (81) Thus, the disease could be cured and arrested in a proportion of treated patients.

7.70. Meta-analyses of randomized trials have subsequently shown that IFN significantly reduces the grade of inflammatory activity and stage of fibrosis in non-cirrhotic patients, in those who respond to treatment, and suggested therefore that interferon alpha might even benefit responders with HCV cirrhosis. Histological improvement was observed in 80% of cirrhotic patients who received long-term interferon compared with only 24% in patients who were treated for only 6 months. The published papers raised the possibility that the benefit of a cure would extend logically to prevention of cirrhosis and its complications.

7.71. Moreover, higher rates of cure were observed in patients without cirrhosis: if cured, patients did not develop cirrhosis, and did not develop decompensated cirrhosis or HCC or require liver transplantation. (24) A sustained response reduced the incidence of HCC (80) (82) (81, 83-85) (87) (88). Among patients with chronic HCV infection and advanced hepatic fibrosis, a sustained virological response to interferon-based treatment was associated with lower all-cause mortality. (89) Therefore, treatment to prevent cirrhosis could be advocated. (90). At this time, reports of interferon use in children were published. (86) Reversion of a chromosomal lineage in B cells, and monoclonal B cell proliferation of B lymphocytes harbouring a bcl-2 (T14:18) chromosomal rearrangement in patients with essential

mixed cryoglobulinaemia, (presaging the development of maligant B cell lymphoma), was reported.

7.72. Our use of interferon was always tempered and not overzealous, never evangelical, and my cautious realism is writ large in my manuscripts and chapters. We neither coerced patients nor did we raise false hopes of a cure. Patients were always partners to the decision to treat. We observed gradual increments in responses as patients were treated with interferon alpha, interferon alpha plus ribavirin, pegylated interferon alpha, pegylated interferon alpha and ribavirin, pegylated interferon alpha, and protease, polymerase and NS5a inhibitors to culminate in interferon free regimens, that now cure 97%; notwithstanding, as I wrote in 2012, interferon's was a long goodbye. (91) Interferon provided a sense of the possible but the transition from interferon to oral antiviral agents was not mourned by a generation of physicians who had no other option to offer patients. [WITN3754054]

7.73. In summary, in 1998, when the Guardian article was written, a long road lay ahead. The history of interferon's discovery and decades-long application in hepatitis has been documented. (92) The first report of a beneficial effect of interferon alpha in hepatitis C was in 1986. Recombinant interferon alpha was approved in 1991. From 1986 to 2014 - 29 years - interferon and interferon alpha and ribavirin combinations were the only licenced treatment for hepatitis C. Pegylated interferon was still being recommended in combination with oral NS5A or NS5B inhibitors in treatment guidelines published in 2014-2015. (93) Without a degree of optimism there was no hope and only helplessness.

Correspondence from Professor C Lee in February 2003 in which she comments that she understands from you that Pegylated Interferon has a greater clinical effect [HCDO0000109_025, p. 3]

7.74. By 2003, there was emerging data that pegylated interferon alpha (PEG alpha2b interferon and later PEG alpha2a interferon) and ribavirin showed effects on hepatitis C which were superior to those of standard recombinant

interferon alphas. Pegylation of interferon improved pharmacokinetic and pharmacodynamic parameters of hepatitis C - but importantly, no qualitative differences in side effects (94, 95) (Pegylated interferon-α2b demonstrated delayed clearance compared with non-pegylated interferon-α2b, consistent with more convenient once-weekly administration). There was still much to learn to refine the optimal chemistry for pegylation. (Kozlowski, Charles et al. 2001)

7.75. Lindsay et al reported that peginterferon alpha-2b significantly improved sustained virologic response rates compared with interferon alpha-2b. (Lindsay, Trepo et al. 2001). Reddy et al reported that once-weekly pegylated alpha 2a interferon (40kd) was associated with a higher number of sustained virological responses compared with IFN alpha 2a three times weekly in patients with chronic hepatitis C, but had a similar adverse event profile. (96) In a clinical trials report, sustained virologic response rate increased to 61% overall for patients receiving pegylated interferon plus ribavirin, compared with 47% in patients receiving standard interferon plus ribavirin. The results were still greatly influenced by genotype. Patients with genotype 1 receiving pegylated interferon plus ribavirin achieved a 42% sustained virologic response, compared with 33% for those receiving standard interferon plus ribavirin. Patients with genotype 2 or genotype 3, achieved an 88% SVR. (97) Fried et al reported (in a randomized controlled trial conducted at 81 centres worldwide) that a higher proportion of patients treated with pegylated alpha 2a interferon plus weight- based ribavirin for 48 weeks achieved a SVR than patients treated with interferon alpha 2b and ribavirin. (56% vs 44% $p < 0.001$); for genotype 1 the difference was 46% vs 36% and for genotype 2 or 3, 76% vs 61%. (97a)

7.76. Further studies verified the benefit of pegylated interferon and the influence of genotype. Manns et al, in a trial of 1530 patients, reported a significantly higher SVR rate after pegylated alpha 2b interferon given for 48 weeks versus interferon alpha 2b plus ribavirin. The overall SVR rate in the higher dose peginterferon group in this study was (274/511 [54%]) vs 235/505 [47%] in the standard interferon group. Among patients with HCV genotype

1 infection, the corresponding SVR rates were 42% and 33%. The rate for patients with genotype 2 and 3 infections was 82% vs 79%. (97b) Body weight was an important predictor of SVR, prompting comparison of the interferon regimens after adjusting ribavirin dose for bodyweight. Side-effect profiles were similar between the treatment groups.

7.77. The NIH consensus statement on management of hepatitis concluded the superiority of PEG interferons, particularly for genotype 1 (the most common genotype in the UK) but a similar adverse event profile. (98). Treatment reduced the rate of fibrosis progression (99) with an acceptable safety profile. In the UK (Foster 2003) wrote "The new PEG-IFNs are a significant advance in the therapy of CHC infection. Their ease of administration, coupled with their improved efficacy, is likely to lead to an increase in the proportion of infected patients who wish to receive treatment." (100)

7.78. The more convenient once a week injection instead of three times a week injection meant that pegylated interferon quickly displaced standard recombinant interferon alpha (101)

The comment made in the Penrose Report that, "In retrospect, Dr Dusheiko was one of a small group of doctors claiming cure rates for Interferon which turned out later to be somewhat optimistic. However, the perception that there might be an effective cure was important in shaping opinion, and his views were relevant at the time." [PRSE0005017 p. 28 (p. 1716 of the report at 35.120)]

7.79. (1993). The comment is to some degree hearsay. Please see above. I did discuss therapeutic possibilities for hepatitis C. My review was cautiously realistic and reflected experience and the prevailing view in 1993. The "group" was not necessarily small. For several of the reports I compiled evaluating interferon for NANB hepatitis or type C hepatitis, I collated 130 publications published between 1991 and 1993 (324 if abstracts are included). Views other than my own were pertinent. By 1993 investigators worldwide had dissected out several beneficial effects of successful treatment, including normalisation of ALT, disappearance of HCV RNA, an

effect on hepatic fibrogenesis (scarring of the liver), further side effects, differences in response in many geographic regions and expanded indications for treatment, including in children. (102-115, 116 {Weiland, 1990 #793, 117, 118) (119-128) (129) (129)

7.80. There were some grounds for optimism that hepatitis C was curable in a proportion of patients by 1993.[7] [8] It took a long time to advance beyond interferon treatment as pointed out above.

This Inquiry has heard evidence from multiple witnesses that the side-effects of Interferon were frequently very severe. In answering questions (i) to (ix) below about your research on Interferon in particular, please highlight your research about of the side effects of this and other treatments for hepatitis C and whether and if so how that understanding developed over time, and whether you accept that your claims for Interferon were "optimistic".

7.81. There is no question that interferon is an unpleasant drug and poorly tolerated. Interferon administration required judgement, training, experience and caution, a careful consideration of the indications for treatment, and a team of individuals to monitor patients. Patients required motivation, needed to be appraised of the prospects and also limitations of treatments, and of the side effects of interferon; they had to be willing and able to attempt treatment with interferon, and could not have contraindications to treatment. I was asked to address the side effects of interferon alpha for the first NIH consensus conference as detailed above. [WITN3754019] However, interferon (and later, pegylated interferon) in combination with ribavirin was the only approved therapy for hepatitis C between 1991 and 2015, until the advent of interferon free regimens.

7.82. The identification of subgroups of patients more likely to respond, improved with time. Patients offered treatment could freely exercise their choice and remain untreated; I cannot think of a more relevant example in medicine where patients had to be informed, and had to be willing partners to the decision to treat, than with interferon- based regimens. We did not discourage patients with mild disease from deferring their treatment, and

closer to the advent of direct acting therapy, many patients indeed chose indeed to wait. The decision to treat or defer treatment had to be carefully weighed in conjunction with patients. The future for patients could not easily be predicted. A successful treatment response arrested progression of the disease. In a proportion of patients, the alternative, i.e. prolonged deferment (and of course, unfortunately, a lack of response) could lead to progression of the disease.

7.83. In 2012 I co-edited a review which I believe contains answers that pertain to my awareness as well as some public facing advocacy. [9] Interferon could never be utilised as a treatment as control or elimination strategy but treatment in specialist centres laid the ground work and platforms for operational delivery networks to deliver direct acting antiviral therapy and elimination programs. (91)

e. <u>Vaccination</u>

Please consider your article 'Hepatitis B vaccination: the cost effectiveness of alternative strategies in England and Wales' Journal of Epidemiology and Community Health, 1995; 49: 238-244. [DHSC0004749_113]

7.84. (The IBI cited reference was not authored by me). There is no vaccine against hepatitis C. Universal hepatitis B vaccination was delayed by 20 years in the United Kingdom and only introduced in August 2017. Years earlier, the British Liver Trust and other groups provided a consensus advocating vaccination. [WITN3754055] [WITN3754056] The delay in implementing universal HBV vaccination was shaped by evidence from Government advisors, who deemed vaccination in the UK was not cost effective. (Although the cost-effective analyses were disputed). "Imaginative" solutions had been proffered. (131) During my tenure at Public Health England in 2019 I argued for an adolescent catch up program which could be introduced with human papilloma virus (HPV) vaccination. To date this has not become government policy or deemed a priority.

7.85. The result is that in the UK, there is a whole generation not immune to hepatitis B - one of the few populations worldwide under the age of 20 years to be unvaccinated. (131-139) In England, girls and boys aged 12 to 13 years are now routinely offered the first human papilloma vaccination in school Year 8 to protect adolescent girls and boys from HPV infection before they become sexually active. The same principle would apply to hepatitis B: vaccination should similarly protect children in their teenage years and beyond. [WITN3754057]. Hepatitis B vaccination could be added to prevent an important sexually transmitted viral infection, which can lead to severe acute hepatitis, fulminant hepatitis B or chronic hepatitis B.

f. <u>Blood product safety</u>

Please consider your report to the Symposium, 'Viral hepatitis Transmission in Haemophilic patients using blood products', June 1989 [CBLA0006290, p. 3]

7.86. (6 July 1989). I am listed on the program. Hepatitis C had been newly discovered. I was fortunate to attend this meeting with Dr M Houghton, the discoverer of hepatitis C, and Dr M Colombo as well as Professor JD Cash, National Medical Director Scottish National Transfusion Service. My topic was the antiviral and immunomodulatory effects of interferon; I no longer have the presentation slides. I would have given an update of interferon treatment; discussed the physiological effects in viral infections and rationale for treatment of hepatitis B, D, NANB and hepatitis C. (130) (103, 119) (105, 118, 120, 140, 141). In 1989, the results were largely based on preliminary studies; on-treatment responses measured by normalisation of ALT were encouraging but testing for HCV viraemia was not generally possible. Relapses were frequent and disappointing. The discussion would have been cautious (105).

And your work for the Second International Symposium on HCV held on November 8-9 1990 in Los Angeles summarising studies in blood screening [NHBT0000016_036 p. 4]

7.87. I was part of a panel that reviewed a section of 44 posters.

7.88. Many studies presented at the meeting at the end of 1990 reported the utilisations of the second-generation ELISA and RIBA test. I also reviewed a poster in which investigators had used PCR to identify sera from three donors implicated in post transfusion hepatitis. Anti-HCV tests could be indeterminate in individuals who were PCR positive. Others at the meeting commented on the use of PCR. Today nucleic acid testing forms the mainstay of proving viraemia and active infection in patients with hepatitis C, and nucleic testing is used for blood screening in many countries (see below antigenic variation).

Your article 'Antigenic Variation of Core, NS3, and NS5 Proteins among Genotypes of Hepatitis C Virus' in the Journal of Clinical Microbiology Volume. 35, No. 12, December 1997 [NHBT0000109_004]

7.89. I was fortunate to work with an expert group of scientists and clinicians. In this study we measured the antibody responses from 110 patients with hepatitis C from various parts of the world, who had been infected with different hepatitis C genotypes. We found differing type- specific reactivity to antigens of hepatitis C. The rationale for the investigation was reports of falsely negative tests for antibody in immunocompetent individuals with chronic hepatitis C. (142) The findings were consistent with earlier findings of a five-fold weaker reactivity of sera from patients infected with genotype 2 and 3. The currently used (1997) third generation antibody assays were ideally to be used for screening populations; these data would have particular relevance in those parts of the world where the predominant genotype was not genotype 1.

g. <u>'Look back'</u>

Please consider your article "'Hepatitis C lookback programme: a single hospital experience' Trans Med 1999; 9: 189-1.93 [WITN3754100]

7.90. We described the experience of the Hepatitis C Look-back Programme at the Royal Free Hospital including the mechanism of the exercise, problems encountered and follow-up data. The Royal Free transfusion laboratory

received approximately 33,000 blood components per year and, between 1995 and 1997, was notified of 160 components, 131 from confirmed HCV-positive and 29 from HCV-indeterminate donors, that had issued by the North London Centre. The fate of these donations was traced, using blood bank records and patient hospital notes. We found that transfusion records were rarely complete in the patients' case notes and data were largely collected from manual and computerized blood bank records. Ninety-eight of the 123 recipients (79%) had died, usually due to progression of their underlying disease. 25 patients were alive; 19 were recipients of HCV transfusions confirmed positive, and six had received HCV- indeterminate donations. Five patients were untraceable:

7.91. Nineteen patients were tested for HCV. Nine of the 14 recipients (64%) of HCV-positive donations and 2 of 5 recipients (40%) of HCV-indeterminate donations had evidence of HCV infection. ALT levels were normal or minimally elevated in the 10/11 HCV-infected recipients. Five patients have had liver biopsies: three showed mild chronic active hepatitis and the other two, hepatic fibrosis and siderosis. Three patients had been treated with alpha interferon: patient 7 became HCV RNA negative but patients 1 and 6 failed to clear the virus; patient 1 was currently on treatment with interferon plus ribavirin.

7.92. We concluded "the national Hepatitis C Lookback Programme can successfully identify individuals with transfusion-transmitted HCV. Few of the identified recipients survive and are available for testing. Although the Programme will not detect all cases of transfusion acquired HCV, it has raised awareness of the problem of transfusion-transmitted infection. Many of the recipients traced are young so that identification of HCV infection allowing assessment by a hepatologist and optimal antiviral treatment is of the utmost importance."

7.93. The paper describes a single centre experience

And the comments reported by Professor Cash at paragraphs 35.120 – 35.124, 35.135, and 35.221 – 35.230 of the Penrose Report [PRSE0005017 pp. 28 - 29; 32 and 52 - 55 (1716 - 1717; 1720 and 1740 - 1743 of the Report)]

7.94. I no longer have my presentation slides. I recall the point of look- back being raised in the discussion and favoured the concept. The arguments for a look back were: 1) Post transfusion hepatitis C in many cases would be silent and invisible, and if the patient survived their co-morbid illness, could lead to progressive liver injury. 2) Identification of infected persons would enable the disease to be managed (for example, giving advice regarding transmission, and alcohol abuse) and possibly treated earlier than would be the case. 3) Interferon for selected patients (see above) could be envisaged thus guiding the rationale for a look back to identify HCV positive persons. 4) Early treatment before the onset of cirrhosis was associated with a more favourable therapeutic outcome.

7.95. A policy decision would be needed, and resources would have to be identified. National look back studies commenced thereafter. [WITN3754058]; [WITN3754059]. I would not overstate my influence but do not regret supporting the concept. The efficacy of interferon and ribavirin in patients without cirrhosis justified consideration of its use even in patients with genotype 1 infection. Case finding of men, women and children infected by prior transfusion and public awareness remains a challenge to this day. [10]

7.96. The Guardian newspaper highlighted the call by the Inquiry to raise awareness and increase the need for testing. [WITN3754060] https://www.theguardian.com/uk-news/2019/apr/30/infected-blood-inquiry-judge-calls-for-more-testing-for-hepatitis-c].

7.97. The Chair of the Inquiry pointed out, following the publication of the September 2019 annual Hepatitis C in England report, that the failure to identify, test and diagnose people infected through transfusions risked delayed diagnosis of silent hepatitis C infection [WITN3754061]. (My letters

written to PHE, discussed later in this report, suggesting linking testing for blood borne virus during the Covid-19 pandemic).

You may wish to consider also your letter dated 1 October 1990 to Dr M Brennan [NHBT0086194]

7.98. The letter dated 1 October 1990 was written to Dr M Brennan, locum consultant in the North London Blood Transfusion Service, no doubt in anticipation that blood donors were soon to be screened for hepatitis C. (Screening was destined to be delayed by a year). In this letter I agreed with the concept of providing clinical assistance to anti-HCV -positive blood donors as discussed with the Blood Transfusion Service. I agreed it would be prudent to assess donors in an appropriate manner and that these individuals would require appropriate workup. We would need an ascertainment of viraemia by HCV RNA testing. I suggested that general practitioners should be kept informed but patients with hepatitis C should not be lost between referral from the blood bank and the general practitioner. I also acknowledged some anxiety that would be generated for patients and offered to mitigate some of that concern. I offered to meet with the blood bank to work out details of the system.

7.99. I also shared correspondence with Dr John Gillon and Peng Lee Yap in Scotland in April 1993 regarding funding for a look back protocol. [WITN3754062]

Questions about each area of research outlined above

(i) identify and briefly explain the main studies or clinical trials which you undertook or were involved in relevant to this topic (including publication details);

(ii) describe the purpose of your research, explaining the existing state of knowledge in the field about the topic, and identifying the contribution that this piece of research was intended to make;

7.100. This question dovetails with answers given above. The purpose of my clinical trial research was to improve therapeutic outcomes from chronic viral hepatitis and to better understand the natural history and pathogenesis of the varying spectrum of disease. Most of these trials culminated in regulatory filings and NICE approval that translated into improved therapies. I was part of a large worldwide network of researchers, and a broad group of pharmaceutical industry scientists and partners who attempted to advance the field. Others would have to be the judge of my research contribution. I have detailed some of the advances and implications in the supplied publication list.

(iii) Identify the conclusions of your research, including any guidance provided or findings made;

(iv) if applicable, explain how the conclusions you drew or guidance you proposed following a particular study or trial altered practice going forward;

7.101. I believe it is fair to say that I have been a small part of a group of worldwide clinical investigators who have advanced the field of therapeutics in hepatitis B and C to a point where the prognosis has been greatly improved. There is considerable focus on the potential of new curative therapies for hepatitis B involving several classes of drugs, including RNA interference (siRNA, antisense oligonucleotides), capsid assembly modulators, entry inhibitors and immunomodulatory therapies, alone or in combination. I

continue to provide advice if asked to research groups and pharmaceutical companies.

(v) set out whether you now consider that your findings or conclusions were accurate, and if not, why not, and whether you subsequently reached any different views;

7.102. Please see above. I have added comments to my curriculum vitae and listed publications to provide a context for these findings and conclusions. I believe that the interpretation of the findings made at the time and the conclusions reached remain largely valid.

(vi) explain what your involvement in the research was and identify what other organisations or bodies were involved in the research;

(vii) explain the steps that were taken to obtain approval for the research;

7.103. I have attached the correspondence that I have in my files that dealt with the process of ethical committee and Research and Development application and approval. [WITN3754063]; [WITN3754064]. The process is complex, detailed and stringent. The correspondence pertaining to the trials below provides a fuller picture.

7.104. Typically, our unit would be invited to participate in a research study or clinical trials. These could be observational and non-interventional studies, experimental studies to examine, for example immune response to disease, new biomarkers, commercial new investigational drug trials, or expanded access programs. Once a confidentiality agreement was signed, we would be given access to detailed pre-clinical experimental data, and any early phase entry- into- man or phase 1 study data in hepatitis B, C or D infected persons. The data would include detailed pre-clinical pharmacology and toxicology. These documents required study and a judgement. Following assent, a trial protocol would be drawn up containing similar details. Examples of study protocols are provided. Investigator meetings could follow to fine tune the protocol. I might be asked to provide specific advice

via a scientific advisory board, to guide trial design, safety and further development. In parallel, the protocol would be amended. We would commence ethical committee approval and obtain a clinical trials exemption certificate.

7.105. Much attention would be focused on the design of the patient information sheet. These have changed over the past decade to become far more inclusive and comprehensive and to follow improvements suggested by EU Directives for Clinical Trials, Medicines for Human Use and Clinical Trial Registration statutory requirements, and the governance required by the NHS and NIHR and the Royal Free Hospital Research structure. Translation to different languages might be required.

7.106. The structure and function of ethical committee approvals shifted from a local Royal Free Ethics committee, to a local authority committee, to national multi-centre (MREC) approvals. Our submissions would be acknowledged, a meeting held, at which the protocol, data, rationale and patient information process would be scrutinized by experts and lay persons. Questions always followed, to which a detailed response was required before approval was granted. Approval was contingent upon the Royal Free site raising no objections and accepting the infrastructure required. A FDA financial conflict of interest form was required for certain studies. Research and Development approval was required, and contracts negotiated. Research queries, and amendments and responses were detailed and frequent. These are best examined in the correspondence submitted.

7.107. Once all these approvals were in place, we were given authority to proceed; we might advertise the study within the hospital and bring successive studies to the attention of patients. Patients would be given a patient's information sheet and given enough time to read and understand the protocol and the clinical trial. Informed consent was sought. Designated research fellows, usually a physician, assigned to a formal study site, would be required to witness consent.

7.108. Through all this process study site monitors or contract research organisations would regulate and assist. We made it clear that we wanted to be kept on our toes at all times, and that stringent oversight was in everyone's interest. Improved investigator training became the norm, at study site initiation visits. Higher levels of training and instruction, for the physicians and nurses assigned to a study (which has been an evolving process) resulted in higher quality administrative trial conduct. A Good Clinical Practice Certificate which had to be renewed every second year, was required. We would be required to notify the LREC and MREC of study progress, adverse events and extensions or amendments to these studies. Line notes were forwarded to the Ethics Committee, who were notified of the actions we intended to correct.

7.109. At this point it is important to bring to the fore the Ribavirin monotherapy trial. (Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled trial 1996) [WITN3754096] (143). I have attached relevant documents. In 1994 I voluntarily agreed to an FDA inspection after the study. I welcomed the inspection to optimize our clinical trial conduct. I subsequently received a warning letter from the FDA, (February 22 1995) [WITN3754065] despite the fact that the study was not conducted under an investigational new drug submission and they had not acknowledged (or received) my response to the inspection which I sent on December 22, 1994, [WITN3754066] before issuing the letter. Subsequently the warning letter was rescinded by Dr Francis Kelsey. [WITN3754067]

7.110. I agreed to the inspection. I recognised the importance of the audit. The inspection was rigorous and reminded me of the responsibility borne in performing clinical trials. Due to an inadvertent (but egregious) miscommunication, and an erroneous belief that the submission to the Ethical Committee for approval had been granted, [WITN3754097] we logged the first of the three required pre-treatment screening visits, when a history, and physical examination was done, and standard laboratory evaluations (clinical chemistry, haematology and virology) bloods were drawn, in seven patients in February and March 1992. All patients were

informed of the nature and purpose of the study, during the three strictly scheduled pre-treatment visits, consented to participate in the study and signed the patient information sheet. Our sequence and commencement of screening for the study did not accord with FDA regulations. We catalogued the visits for the FDA inspection and the FDA had sight of all source documents including the patient information and consent forms. The inspectors pointed out that the FDA (properly) considers that a trial begins when screening bloods are taken, not at the commencement of treatment. I indicated our misunderstanding and stated that we would need to change practice to conform to the FDA regulation. Such practice would seem glaringly obvious, and is the norm today, but variances existed at the time. I wrote to our ethics committee and sent them a copy of these regulations, pointing out the requirements for all future studies, to assist investigators at the Royal Free Hospital and to harmonize consent procedures. Our study conduct contained other deficiencies; I recognised legitimate criticism, took responsibility for the errors, and responded to these.

7.111. Leaving aside the fact that I did not conduct the study under an IND, I always recognised the importance of the 1994 FDA inspection and accepted the precepts and the schooling and the need to improve deficiencies in the administration of our clinical trials. The original protocol was ambivalent on the need for signature for routine screening blood procedures to determine eligibility for the study. All patients were fully informed of the rationale of the study, the procedures and all potential risks and discomforts, and signed the informed consent form. (None of the twenty-one patients enrolled in the Ribavirin study under my care had haemophilia or a bleeding disorder). The data provided in this study clearly provided data which did not allow the claim for six months of ribavirin as a monotherapy for hepatitis C.

7.112. I informed the Dean of the Medical School, and I kept the head of Department and the Dean informed throughout the FDA inspection and subsequently. The warning letter did not include a finding that false data was submitted to a clinical trial. Despite this, the FDA assigned code 17 to

my name. A subsequent letter from the FDA (February 21 1996) [WITN3754068] concluded that deficiency code 17 should be removed from the inspection record. Nonetheless this fact was overlooked by the FDA and code 17 and only removed seven years later, in 2001, after the error was pointed out. Dr Woollen's letter of February 26 2001 [WITN3754069] made clear that the Division of Scientific Investigation incorrectly listed code 17 after the FDA's October 1994 inspection.

7.113. Even the FDA can make administrative errors.

(viii) state how the research was funded and from whom the funds came; and

(ix) where the research was a clinical trial, state the number of patients involved and provide details of the steps taken to inform patients of their involvement and seek their informed consent.

7.114. My involvement was usually as a principal investigator and on occasion, a chief investigator. Numerous other centres in Europe and the rest of the world were involved in multicentre trials. My collaborative research was funded from University Grants, Wellcome Fellowships, other research charity grants, and University Industry partnerships.

7.115. Stating the number of patients in each clinical trials, and answering Q7 IX is a task of some magnitude.

7.116. I cannot provide the detail required. Files for clinical trials were stored for the statutory legal period, but the files are no longer accessible to me. I cannot enumerate the number of participating patients from the Royal Free in multi-centre trials. Lists of trials would be held by the Ethics committee and Royal Free University College London Medical School. I should point out that the list will not correspond to actual participation if Ethics Committee approval, Research and Development Approval or Contracts approval was not obtained, or the study withdrawn by the sponsor.

7.117. I have undertaken new drug trials in hepatitis C, in rough chronological order, of interferon alpha, interferon alpha and ribavirin, ribavirin, pegylated

interferon alpha, pegylated interferon alpha and ribavirin, viramidine, pegylated interferon maintenance therapy, hepatic fibrosis markers in hepatitis C, simeprevir, telaprevir, boceprevir, asunaprevir, sofosbuvir, ledipasvir, paritaprevir, ombitasvir, dasabuvir, asunprevir, daclatasvir and non invasive methodologies for hepatitis C, and eltrombopag;

7.118. In hepatitis B: lamivudine, adefovir, adefovir and lamivudine, adefovir versus entecavir, adefovir versus tenofovir, tenofovir plus emtricitabine versus tenofovir, telbivudine, clevudine, and biomarkers of hepatitis B.

7.119. As outlined in the chronological description of the published manuscripts, the trials were designed to answer specific questions, or were non-hypothesis driven research. For example, the trials of interferon alpha were designed to examine efficacy and safety in various subgroup while trials of the combination of interferon and ribavirin were designed to answer questions of safety, pharmacokinetics, interactive pharmacodynamics and responses in patient who had not previously responded to treatment with interferon, or maintenance therapy.

7.120. We were able to shepherd in current nucleoside analogue therapies for hepatitis B and show, together with worldwide investigators, the progressive safety, potency and lowered genetic barrier to resistance of lamivudine, adefovir, lamivudine and adefovir, tenofovir, tenofovir and emtricitabine and entecavir. These studies were designed to answer questions of safety and efficacy, resistance, use of these agents in decompensated cirrhosis and to prevent recurrent hepatitis B after orthotopic liver transplantation.

7.121. I believe is fair to say that in most cases my views were accurate and have stood the test in time. The compiled data accumulated from many centers has changed practice. Fibrosing cholestatic hepatitis B following liver transplantation has vanished. The risk of cirrhosis and HCC in nucleoside analogue treated patients had declined markedly. The number of patients requiring liver transplantation in the UK for end stage hepatitis B and hepatitis B related HCC has fallen to very low levels. The incidence of

hepatocellular carcinoma due to hepatitis C is declining markedly but has not been obviated because of the latency between disease onset and disease cure. Deaths due to hepatitis C in the United Kingdom are reducing.

7.122. The data have been documented in the PHE 2020 report: around 89,000 people in England are living with chronic hepatitis C in 2019, a fall of 30% prevalence estimates for 2015. The report sets out the necessary means to eliminate hepatitis C as a major public health threat. Testing and treatment to reduce the numbers becoming seriously ill and dying from this infection and reducing the number of people becoming newly infected or reinfected is required. There has been 20% fall in deaths between 2015 and 2018 in England. This is supported by 37% decline in crude mortality rates amongst those with an HCV diagnosis reported to PHE. [WITN3754101; WITN3754102].

7.123. Treatment with direct acting anti-viral is having an impact; there are falling numbers of liver transplant registrations (a 44% fall by 2018 when compared to pre-2015 levels) and liver transplants undertaken in those in whom hepatitis C cirrhosis and HCC is given as the indication for transplant have been observed. The proportion of all first liver transplant performed in England that were carried out in patients with HCV -related disease has halved over the last decade. Resources will still be needed and there is an ongoing demand to raise awareness and highlight requirements for testing. The principal risk groups now are recognised. Testing must be seen to rise in other groups who have been at risk of infection. The Covid-19 pandemic has posed a serious threat to the ability to continue the trend of improvement in elimination goals.

7.124. I suggested that Covid-19 antibody testing could be linked to blood-borne virus testing including for hepatitis B and C and wrote to Public Health England in 2020 but received no reply. [WITN3754070]. I and colleagues have penned a letter to the BMJ. [WITN3754071] (Published 24 June 2020)

7.125. The Covid-19 pandemic will likely have a long tail, despite the advents of vaccines. Mutational changes in the SARS-CoV-2 virus will necessitate

careful surveillance to correlate infection and vaccination induced immunity. Sentinel testing for Covid-19 serology offers an opportunity to incorporate serological testing for hepatitis B C and HIV at scale. SARS-CoV-2 Infection and mortality rates have been higher in disadvantaged communities. These are the same communities in whom there is a pressing need to identify silent hepatitis infections, which are treatable. We could add breadth and value to incomplete SARS-CoV-2 containment and research plans. I have also written to the World Hepatitis Alliance, the Hepatitis C Trust, NoHEP and NHS improvement.

8. **If you consider that you have conducted research, clinical trials, or epidemiological studies that are related to the Inquiry's Terms of Reference but which do not fall under the topics listed at 7(a) to 7(g), please detail these and, so far as is relevant, answer questions 7(i) to 7(ix) in respect of each.**

8.1. Please see above, and my citations and comments.

9. **On the whole, what do you understand to be the ethical principles that should guide research? Did you apply those principles to the research studies referred to above in your answer to question 7, and if so how? If not, why not?**

9.1. My research in viral hepatitis has been driven by curiosity, a desire to understand and to change for the better and improve the welfare of individuals afflicted with chronic viral hepatitis, not by ego and ambition. I had have witnessed considerable morbidity from chronic viral hepatitis and have sought to understand the disease and mitigate its adverse consequences. I believe that the research I have undertaken, in collaboration with others in the field, has had a clinical and social value that provided purpose. We sought answers to answerable questions and in many cases developed therapeutics that moved the field forward.

9.2. Research in human subjects requires ethical rules and principles that place the rights of individual and the protection of patients uppermost. I am cognisant of unethical research of the Second World War which have led

to the principles of the Declaration of Helsinki, binding the physician to act in the patient's best interest: This imposes an enormous responsibility on investigators who invite participation in clinical research.

9.3. Informed consent rules have been modified in the 30 years that I have been undertaking research to desirable and uniform standards necessitated today. The basic standard is that an individual must have all the information that would influence their willingness to participate and must be able to understand and comprehend what is being proposed. It is imperative that we outline the purpose of the research, the procedures involved and the disadvantages and possible dangers.

9.4. Thus, in the clinic, the rationale for collecting data, or a clinical trial was explained. We would attempt to achieve a benefit for patients but of course could not guarantee advantage and would try to explain that there were advantages as well as potential disadvantages in participating in research or a clinical trial. The probability and possibility of harms or benefits would need to be weighed by patients. I spent time explaining to patients that they would be receiving experimental drugs, of unproven benefit, and that in phase 1 and 2 trials would be receiving these treatments at a stage when relatively few individuals had been treated, so that not all potential adverse events might have been recognised.

9.5. I would go over information sheets line by line but recognised the complexity and level of comprehension that is required to fully understand a clinical trial and provide fully informed consent. Patients needed sufficient time to study the consent form and were given the requisite time and space to read these. We explained to patients and emphasized in considerable detail that their participation was entirely voluntarily, was their free choice, and their decision should be free from any coercion any undue influence; we would respect their decision. Patients had the right to decline participation and could withdraw at any time; we articulated to patients that if they did not wish to participate in any trial this would not in any way affect their treatment under our care or at the Royal Free Hospital.

9.6. We explained that the case record forms would be observed by clinical monitors, but that confidentiality would be preserved. Our research proposals would be subjected to detailed scrutiny by an independent ethics review committee and would comply with the specific guidance issued both by these committees the trial sponsor, the Department of Health, the hospital and international guidelines. My ethical principles were set at the outset of my career, but our informed consent processes became more thorough, and detailed and were guided by rules governing written informed consent that have evolved over the past 30 years. These have progressively ensured that individuals are accurately informed of the purpose, the risks and the benefits and the alternatives of the research and how a research trial might relate to their own disease management and interests so they could make an informed decision without coercion or duress. Patient information sheets frequently require modification, but would spell out risks, any discomforts that may be entailed, and post study provision. In most cases I believe the clinical trials I participated in offered a favourable risk-benefit ratio overall, and that the accumulated data have gradually inched us toward improved outcomes from chronic viral hepatitis.

10. In any of the studies that you have discussed in your answer to question 7 above, were patients involved in research studies without their express consent? If so, how and why did this occur?

10.1. Research and ethical procedures were followed. Oral consent for clinical diagnostic stored samples was requested if oral consent for residual serum taken at the time of routine diagnostic blood testing within standard care was given. The correspondence I have, including submissions, approvals, amendments granted by ethics committees is attached [WITN3754063]; [WITN3754064]. The correspondence provides some level of detail of ethical committee applications, oversight and consent procedures required. Today, permission is required to store biobanked serum samples obtained by venesection during routine care. We received line notes which are included. One line note pointed out administrative errors of consent: the physician witnessing the consent had himself dated the form rather than the

patient. Version control of numerous iterations of patient information sheets or poorly designed sheets were a trap for the unwary. We addressed these errors and notified the requisite ethics committee. Training addressed these administrative mistakes. The responsibility was mine.

11. In any of the studies that you have discussed in your answer to question 7 above, was patient data (anonymised, de-identified or otherwise) used for the purpose of research or for any other purpose without their express consent? If so, what data was used and how and why did this occur?

11.1. I cannot rule out that we may have perhaps, and only once to my knowledge, inadvertently added names against codes for HCV RNA testing when deciphering results. Soon after the discovery of hepatitis C we worked in tandem with Chiron to understand HCV RNA levels in blood. If an error occurred, it would have been corrected by me or study monitors. This, if it happened, occurred at a time when we were struggling with a newly discovered virus, to understand a "new" contagion in patients, and the clinical implications of the quantity of virus that apparently influenced the natural history, infectivity and response to antiviral treatments. The need to quantify viraemia was well intentioned and if it occurred, patients were not holistically damaged, and the work sheets corrected. We relied on the professionalism of collaborative personnel at Chiron. If it happened in the unit, I do not believe that any patients came to harm.

12. In any of the studies that you have discussed in your answer to question 7 above, was patient data (anonymised, de-identified or otherwise) shared with third parties? If so how and why did this occur and what information was provided to whom?

12.1. Please see above

Section 3: Your clinical work at the Royal Free Hospital

13. Please describe the involvement that you had:

a. directly with patients;

13.1. Please see answers above which detailed my clinical commitments and direct clinical care for in patients and outpatients.

b. with any decisions concerning the treatment of, or the provision of information to, patients with haemophilia, hepatitis and/or HIV; and

c. with the care and treatment of patients infected with hepatitis and/or HIV in consequence of infected blood or blood products.

13.2. I had direct responsibility for numerous patients with chronic hepatitis or coinfected with HIV. I would attend a haemophilia-hepatitis clinic on a regular basis. Usually, the latter clinics were attended by a haematologist, a hepatologist and a psychologist, so that patients had the benefit of a multidisciplinary consultation.

Section 4: Knowledge of, and response to, risk

General

14. At the time that you took up a clinical role at the Department, what was your knowledge and understanding of the risks of the transmission of hepatitis (in all forms) from blood and/or blood products? What were the sources of your knowledge? How did your knowledge and understanding develop over time?

14.1. I had a good understanding of the risk of transmission of hepatitis B, and NANB hepatitis. The major agent responsible for post transfusion hepatitis was discovered and identified as hepatitis C virus in 1989. NANB hepatitis remained a somewhat enigmatic entity until the discovery of hepatitis C virus. However, as summarised at other places in this witness statement our knowledge of NANB hepatitis C advanced incrementally after the publication by Kuo, Choo and Houghton in 1989. Hepatitis C virus was

soon shown to be the major agent of transfusion and community transmitted NANB. (144, 145). I was abreast of the published literature and kept up to date as data rapidly accumulated. Some of the published papers that are relevant were summarised in my detailed report to the court (A vs Transfusion Services). Although I was not involved in research on NANB hepatitis I was fortunate to have been exposed to some of privileged data presented on the campus of the NIH.

15. What if any enquiries and/or investigations did the Department and/or you carry out or cause to be carried out in respect of the risks of transmission of hepatitis? What information was obtained as a result?

15.1. I was a newly arrived senior lecturer finding my feet in a new country when Chiron scientists first announced that they had identified, cloned and expressed a protein from the long-sought NANB hepatitis virus and had developed a first generation (prototype) immunoassay for antibody to hepatitis C (10 May 1988).

15.2. I sought clarification at the Rome meeting. The chronology and lineage of available testing is set out in detail in my witness statement and by Judge Burton (A vs National Blood Authority) [NHBT0086710]; [PRSE0003333]. To summarise, in April 1989 Choo et al published the isolation of a cDNA clone derived from a blood borne non-A non-B viral hepatitis genome (145) and in the same month Kuo et al. published an assay for circulating antibody to a major etiologic virus of human non-A non-B hepatitis (144). I closely followed the evolving literature and advised the department and reported back from international meetings I had attended to update the department. I discussed results and their implications with Professor Neil McIntyre, and Professor Sheila Sherlock. We looked to the Transfusion Service to complete the evaluation and institute screening of blood donors.

15.3. Diagnostic testing was gradually instituted in the department as access to testing became available. We could test limited numbers of patients with chronic hepatitis to provide a preliminary assessment of the test, but the Liver Unit laboratory was not an accredited virology service.

16. What if any actions did the Department or you take to reduce the risk to patients of being infected with hepatitis (of any kind)?

16.1. We were well versed in the routes of person to person transmission of hepatitis and could provide advice. Patients with hepatitis B were advised on their HBeAg or anti-HBe status, and HBV DNA concentrations, and the influence of viral load on transmission and infectivity. Patients were informed that sexual transmission could occur; on the need for condom use; and the necessity for vaccination. Families were advised on the risk of household transmission and familial clustering and the need for vaccination within families. We gave specialist advice on maternal infant transmission and antiviral prophylaxis during pregnancy as data became available. (146) (147) (148, 149). Our unit liaised closely with maternal services and was called upon to provide advice on immunoglobulin prophylaxis and anti-viral therapy as well as breastfeeding. We gave advice to surgeons, obstetricians, nurses and other health care workers undertaking exposure prone procedures in line with guidelines. I was part of a Department of Health- appointed group of physicians to advise and monitor surgeons and other health care workers undertaking exposure prone procedures; treatment to lower HBV DNA concentrations could permit continued working. We were referred complex patients at risk of reactivation of hepatitis B and advise the haematology and other services on anti-viral prophylaxis to prevent reactivation. (150)

16.2. Patients with hepatitis C were advised on the known epidemiology of hepatitis C, risk behaviours and sexual transmission. The risk of sexual transmission was thought to increase with an increased number of sexual partners and condom use was advised. Injecting drug use carries a high risk of acquisition of hepatitis C via shared needles and apparatus, and patients were given appropriate advice. We gave patients advice on the possibility of transmission by intranasal cocaine. We saw increasing numbers of men who have sex with men developing acute hepatitis C, and published these findings. Individuals with hepatitis C were advised to have hepatitis B vaccination if not vaccinated and have hepatitis A vaccination,

although previous data have shown that the response to hepatitis B virus vaccination is reduced in patients with chronic hepatitis C. In view of reports of reactivation of hepatitis B in patients treated with direct acting anti-viral therapy for hepatitis C, close monitoring of such patients was required. (151). Surgeons infected with hepatitis C required a cure to continue working.

16.3. As we were a tertiary referral unit, we were also referred complex patients at risk of mother to infant transmission. Interventions and amniocentesis were problematic in some patients (152, 153). Universal or risk factor-based screening for hepatitis C in pregnancy remains debated but optimally universal screening for hepatitis C in pregnancy would be preferred. Direct acting anti-viral treatment for the treatment of hepatitis C during pregnancy and lactation is being explored.

16.4. An increased severity of hepatitis A infection has been reported in patients with chronic liver disease. (154-156). We advised patients on travel risk for hepatitis A and E and, if patients had not been tested for hepatitis A antibody, recommended vaccination.

17. What was your understanding of the nature and severity of the different forms of blood borne viral hepatitis and how did that understanding develop over time?

17.1. I would class my understanding as good and one which has continued to develop.

Response to Risk

18. Did you or the Department take any steps to ensure that patients and/or the public were informed and educated about the risks of hepatitis? If so, what steps?

18.1. Patients were advised as the data developed. Nurses and physicians in my department have been actively involved with action groups to raise awareness of hepatitis B and C. These are ongoing efforts. The lack of

awareness is iniquitous. We have struggled collectively to raise awareness of hepatitis B and C to the same level of that of HIV (or for example Covid-19), but these efforts have been hampered by the absence of an ongoing powerful media campaign focusing on positive awareness, rather than negative, somewhat judgemental advertising, such as the "Face it" campaign. Funding for a nationwide Department of Health public media campaign has not been forthcoming.

19. Do you consider that your decisions and actions and those of the Department in response to any known or suspected risks of infection were adequate and appropriate? If so, why? If not, please explain what you accept could or should have been done differently.

19.1. After the implementation of blood screening for hepatitis C in 1991, the majority of patients in the Hepatology service would not have been at risk from blood transfusion. In most instances we diagnosed our existing patients in the clinic with chronic liver disease due to hepatitis C in as timely a fashion as possible. As a specialist liver unit, most patients with raised serum aminotransferases were tested for hepatitis B and C and appropriate further testing. We dealt expeditiously with nosocomial infections and outbreaks.

20. What decisions or actions by you and/or by the Department could and/or should have avoided, or brought to an end earlier, the use of infected blood or blood products?

20.1. We ceased using blood and blood products based on the provision of non-infected blood by the regional transfusion service.

21. What actions or decisions or policies of other clinicians or other organisations, within your knowledge, played a part in, or contributed to, the scale of infection from blood or blood products? What, if anything, do you consider could or should have been done differently by these others?

21.1. I believe this has been extensively discussed by those with more knowledge. Clearly earlier inactivation strategies, avoidance of paid donors,

wet heat-treated factor concentrates, surrogate testing of blood donors and implementation of specific anti-HCV testing would have reduced the number of patients infected with hepatitis C by blood or blood products. I believe that the matter of testing for hepatitis C was extensively examined previously in court hearings, and in the Penrose report.

22. Do you consider that greater efforts should have been made to inactivate viruses in blood or blood products prior to 1980? If so, who should have made or coordinated those efforts and what steps should have been taken and when? If not, why?

22.1. I gave a brief chronology of inactivation in my deposition to the court. I am not qualified to comment on efforts made by the Blood Products Laboratory prior to 1980, or early in the 1980's: I was not resident in this country when these efforts could have begun.

Section 5: Treatment of Patients at the Royal Free Hospital

23. Explain how your approach to the clinical diagnosis of your own patients at the Department developed as a result of your research and understanding of different types of Hepatitis, referring as appropriate to the research discussed in your answer to question 7 above.

23.1. My explanations to patients utilised my evolving knowledge through different eras of discovery. Our understanding of the natural history, improvements in diagnostic tests as well as treatments for viral hepatitis has improved considerably in the past 40 years. My approach to clinical management of patients considered a broad overview of the epidemiology, virology, natural history and treatment of chronic hepatitis. This information had to be condensed to a language understandable for patients from different walks of life. The clinical information given to patients needed frequent updating. I believe that I could impart a physician's perspective to enable contemporary advances for patients under my care.

23.2. Our knowledge of NANB/hepatitis C extended back only to the mid-1970. It was important to explain to patients when the transmissible agent of non-A

non-B hepatitis was identified and characterised as the hepatitis C virus. The epidemiology of hepatitis C was initially incompletely understood. The role of sexual transmission, perinatal transmission and the natural history was also not well understood. The use of reused syringes and needles for home or hospital treatment and therapy may have played a role in nosocomial transmission of hepatitis C in some countries. In 1990, we began to understand the genetic heterogeneity of the virus. Specific means of control could be achieved to ensure the safety of the blood supply after the discovery of hepatitis C virus.

23.3. Control of community-acquired hepatitis C in the general population was a larger problem. The absence of a vaccine was challenging. Researchers were constantly examining and developing new therapeutic agents for hepatitis C and patients needed to be kept abreast of developments - as well as the constraints on NHS funding and NICE approvals. The long transition from interferon treatment to direct acting anti-viral treatment taxed patients; the advantages and disadvantages of treatment required detailed and individualised explanation. We used published guidelines and consensus statements. A deep explanation of the side-effects of treatment, and the risk versus the benefit of treatment was required. Non-invasive technologies later assisted in staging the disease without the necessity for liver biopsy. Direct acting anti-viral therapies offered an opportunity for hepatitis C elimination, but necessitated appropriate case finding, testing and linkage to treatment. New treatment advances continue to require critical appraisal including the possibility that suboptimal SVR rates occur in patients with atypical genotypes found in immigrant populations, including among the African diaspora in the UK and Europe. (157)

23.4. Hepatitis B was better understood in 1988. A sensitive serologic test for HBsAg enabled diagnos. Perinatal transmission of hepatitis B was understood, as was sexual transmission and spread by blood, blood products syringes and needles. The endemicity of the disease in different countries (and in the diverse populations referred to the Royal Free Hospital) was known. An effective hepatitis B vaccine had been developed.

Higher risk groups were recognised. The importance of sequelae of chronic hepatitis B including HCC were known. Interferon therapy conferred potential benefit to some patients, but the efficacy remained unpredictable. Nucleoside analogue treatment although not curative, advanced treatment and reduced the morbidity from the disease. Differences in outcome between genotypes of hepatitis B became better understood.

23.5. The scientific basis of the complex immunologic response to hepatitis B at different phases of the disease is still a subject of considerable research endeavour. New biomarkers of transcription of cccDNA will improve endpoints for treatment with new potentially curative therapies. Universal birth dose hepatitis B vaccination and prevention of mother to infant transmission of hepatitis B by the addition of nucleoside analogue prophylaxis to highly viraemic mothers is critical to elimination programs.

23.6. Knowledge of hepatitis D extended from 1978 when the virus was discovered in patients with chronic hepatitis B. The virus is a defective virusoid. The epidemiology and modes of transmission of hepatitis D became better known. The severity of the disease was recognised. Hepatitis B vaccination was an effective protection against hepatitis D. Treatment of those chronically infected with hepatitis D was difficult and interferon alpha, until recently (2020) remained the only applicable treatment.

23.7. Patients with acute hepatitis A and E also required an explanation of the disease, and the epidemiology, modes of transmission, endemicity, and management and control.

23.8. I have highlighted advances in research and understanding of hepatitis C in the attached curriculum vitae. [WITN3754049] Perhaps some selected references apply to this section. (1, 3, 13, 25, 26, 29, 40, 74, 91, 143, 148, 149, 157-266)

23.9. The narrative given above condenses a great body of information given to patients. Each patient was different, and the nuances of their disease would require individual interpretation and action.

Provision of information to patients

24. At paragraph 123 of your statement in the Hepatitis Litigation [NHBT0086710], you said "*General advice: Patients with hepatitis C require advice regarding the long natural history of the infection. A history of past intravenous drug use, or a blood transfusion in the past is significant. Patients require information about staging of their disease, and appropriate assessment by the range of diagnostic tests. The patient may need to be briefly informed of the chronology of the disease, including the dates of discovery of the virus (1988/1989), the development of diagnostic tests, and its elimination from the blood supply and factor concentrates. The patient should also be told that there are gaps in our understanding of the transmission of the disease. The indications for a liver biopsy, and its possible risks and discomforts must be explained. Informed patients in many centres are confused by the fact that genotyping and quantitative RNA measurement are not routinely available.*"

In respect of this, explain:

a. Why you considered that such advice was important.

24.1. Providing the patient with necessary advice was, and is, good clinical practice. It was important that we imparted what we knew in an intelligible way to patients. The advice given above forms the core elements of general advice to be given to patients. Chronic viral hepatitis is a complex, multifaceted chronic illness, and the advice must be dovetailed to individual patients. Usually, explanations had to be given on more than one occasion and oversimplified for some patients.

b. From what point in time you gave such advice and information to patients

24.2. My involvement in viral hepatitis dates to the first days of my postgraduate career. I believe it would be fair to say that I gave advice to patient in line with my own knowledge and understanding of the disease, which I constantly updated. The advice would be given at the first consultation, and follow-up consultations. Effective management advice depended upon the return and interpretation of test results, which were not available at the first consultation. I attempted to indicate to patients that I could better understand their disease once further test results were back, at follow-up consultations, and that the conversation would continue.

c. Whether you understood this to be general practice across the profession and if so the basis for that understanding.

24.3. I understand this to be general practice across the profession, but understandably levels of knowledge varied between generalists and specialists.

25. Were patients infected with hepatitis B always informed of their infection and if so how?

25.1. Yes; generally at a face to face consultation, in the vast majority of cases. It would have served no purpose to fail to disclose the fact that an individual was HBsAg -positive, and would be medico-legally indefensible.

26. What information was provided to patients infected with hepatitis B about the infection, its significance, prognosis, treatment options and management?

26.1. We would condense the core elements of hepatitis B for patients. We would have to explain the difference between acute and chronic hepatitis B. I would draw diagrams to explain the basic virology of the virus and the fact that it could integrate into the host genome; and persist even after HBsAg had cleared. (Patients receiving chemotherapy were at risk of reactivation of hepatitis B). An explanation of the epidemiology and the sources of

acquisition would be required. Patients born in endemic areas would have had little realisation that growing up in a high prevalence region had placed them at risk of hepatitis B. We explained transmission by blood and sexual transmission. We also explained needlestick exposure. We would explain to patients that varying level of hepatitis B DNA in serum and HBeAg-positive disease versus HBeAg - negative disease, conferred different levels of infectivity. An explanation was required of the use of these markers to understand and explain the natural history of the disease, and the transition and progression through characteristic stages of the disease.

26.2. The usual modes of transmission such as blood transfusion and blood products, needlestick accidents, injections with unsterilised instruments such as in tattooing, acupuncture, ear piercing or dentistry would require explanation. We saw outbreaks of nosocomial hepatitis B and also transmission from surgeons. (267) We detailed that previously, hepatitis B could be spread by blood products and plasma, such as factor VIII, factor IX concentrates, fibrinogen, cryoprecipitates, human thrombin and as a result patients with haemophilia had a higher incidence of exposure. (The introduction of HBsAg screening of plasma donors and dry and wet heating had decreased hepatitis B virus exposure from these products)

26.3. Hepatitis B was a major risk for healthcare workers who might not remember an actual percutaneous exposure. Intravenous drug use was an increasing cause of hepatitis B in many areas of the world. We explained that hepatitis B could be readily spread by sexual contact. The use of condoms and hepatitis B vaccination was recommended.

26.4. Intrafamilial spread and clustering had to be described. Cultural practices such as tribal scarification and acupuncture could transmit hepatitis B. We would elaborate the markers that distinguish past exposure and immunity, and protective antibodies, versus chronic disease, and recommend vaccination for siblings and family members not immune to hepatitis B. We explained the importance of mother - to- infant spread and the fact that newborns born to mothers with high levels of HBV DNA, or HBeAg positive,

were more likely to acquire chronic hepatitis B virus infection. We recommended routine screening of pregnant women. We liaised carefully with our maternal services to minimise risk to infants and to ensure immunoglobulin prophylaxis and birth dose vaccination. We have also pointed out the advantages of nucleoside analogue antiviral prophylaxis to highly viraemic mothers, a policy which is now advocated by the WHO. We gave advice regarding casual contact and spread of hepatitis B. We attempted to explain epidemiologic patterns to immigrants.

26.5. The highest risk groups for hepatitis B can be guessed from the description of modes of transmission disease and would include male homosexuals, people with injecting drug use, healthcare workers, prostitutes, patient who had received blood transfusions, renal dialysis patients, haemophiliacs, thalassaemics, staff and residents of institutions for the disabled, prisoners, and commonly, immigrants from area of the world where hepatitis B is common.

26.6. We attempted to explain the complex pathogenesis of the disease and mechanisms of cellular injury in hepatitis B. In simple terms we explained molecular subsets of hepatitis B virus, and variants of hepatitis B resulting in HBeAg - positive versus negative disease. We attempted to explain the typical clinical course of chronic hepatitis B, the extrahepatic manifestations, the evolution of the successive phases of the disease as well as exacerbations of the disease. We explained the risk of development of cirrhosis and HCC. The disease could be understood and staged by an appropriate panel of investigations and hepatic imaging and, if required, a liver biopsy would be performed. Fortunately, the necessity for liver biopsy could be reduced as new non-invasive techniques evolved. Finally, we explained the management of acute and chronic hepatitis B and current anti-viral therapies, including interferon alpha and later potent nucleoside analogues. We did not forget to discuss prevention of hepatitis B and the need for elimination of risk behaviours and HBV vaccination.

26.7. In patients with cirrhosis and decompensated cirrhosis we explained management and treatment including hepatocellular carcinoma surveillance and liver transplantation as well as anti-viral treatment to prevent recurrent disease.

26.8. Patients with superinfection or coinfection with hepatitis D were also managed in the Unit. The Royal Free had a good record for testing and ruling out hepatitis D by appropriate testing.

NANB Hepatitis/Hepatitis C

27. Were patients infected with NANB hepatitis always informed of their infection, and, if so, how?

27.1. In the liver clinic, after the discovery of hepatitis C we assiduously sought to test and inform patients who had evidence of liver disease (raised aminotransferases), a risk factor for hepatitis C, cryptogenic cirrhosis, or other indications for hepatitis C testing. We also sought to inform patients whether they had persistent or resolved infection by testing for HCV RNA by PCR. We tested viraemic patients for HCV genotype. The latter tests were not readily available for several years, greatly confounding the management of patients. I am aware of an exception: a patient tested in an accident and emergency (A and E) Department in 2000 was not referred on to my clinic for 14 years, and thus not treated. This has been the subject of litigation. I am also aware of a false negative PCR result which was later corrected.

28. What information was provided to patients infected with NANB hepatitis about the infection, its significance, prognosis, treatment options and management?

28.1. Soon after my appointment at the Royal Free we were able to introduce at least preliminary testing for patients considered to have non-A non-B hepatitis in whom it was obviously important to rule out hepatitis C virus. This we did to the best of our ability.

28.2. The discussion could be clarified once a positive diagnosis for hepatitis C was made and we could dispense with the outdated terminology of non-A non-B hepatitis. At an early introductory visit, we would attempt to explain to patients the history and discovery of non-A non-B hepatitis/hepatitis C. In the clinic we would attempt to understand and ascertain risk factors: this would necessitate asking non-stigmatising questions regarding occupation (for example frontline healthcare work), receipt of a blood transfusion, infusion of clotting factor concentrates before 1992, sexual preference and practice, infants born to hepatitis C positive mothers, a history of injecting drug use, individuals on haemodialysis and possible nosocomial exposure. We also needed ascertain birth in a higher prevalence country, or transfusion of un-screened blood or unsafe injections, including in healthcare settings, or other parenteral exposure to blood, use of blood contaminated instruments, traditional scarification, acupuncture, tattooing and ear piercing and also injecting drug use in other countries.

28.3. We explained the three major routes of transmission: parenteral (usually by injecting drug use or blood product transfusion) permucosal (usually sexually particularly in men who have sex with men) or vertically from mothers to children. Inhaled drug use could result in transmission. Household sharing of therapeutic injection needles was an important risk for intrafamilial transmission of hepatitis C in southern Mediterranean countries; nosocomial outbreaks have been reported.

28.4. A brief explanation of the virology of hepatitis C was required. We explained that hepatitis C comprised 6 major genotypes. We attempted to explain that in 15-40% of individuals an acute disease could resolve completely with clearance of hepatitis C RNA from serum within 4 months, but that the majority of patients infected with hepatitis C would progress to chronic infection. The onset of the disease may frequently have been silent or may have been accompanied by relatively inapparent non-specific symptoms. We informed patients that once chronicity was established, scarring of the liver (hepatic fibrosis) could occur, although the rate of progression varied greatly.

28.5. We explained diagnostic tests: anti-HCV was an indication of past or present infection and antibody to hepatitis C could even disappear after resolved infection. A positive antibody test alone did not establish that an individual had an active, chronic infection. We explained the association of serum aminotransferases to hepatic inflammation, which is different to hepatic fibrosis (scarring). We also explained how the presence of hepatitis C RNA established a definitive diagnosis of persistent hepatitis C virus – a prerequisite for treatment to be given. Tests for hepatitis C RNA were not immediately available after the discovery of hepatitis C virus. In some units, hepatitis C core antigen assays would later be used.

28.6. Patients needed to know that hepatitis C could be classified into six major genotypes with subtypes, and that definitive testing required viral sequencing in the laboratory. The different geographic localisation of different genotypes was enunciated. The common genotypes in Europe and elsewhere were elaborated. We explained that response to interferon alpha was influenced by genotype. Although all known genotypes of hepatitis C may be associated with progressive liver disease, genotype 3 conferred was associated with hepatic steatosis and more rapid fibrosis progression and possibly a disproportionate risk of HCC.

28.7. We explained the management of acute hepatitis C in patients who were referred for acute disease. Patients could be treated in the acute phase. The overwhelming majority of patients in our clinic had chronic hepatitis C. We had to clarify that the diagnosis of chronic disease was based on the detection of both anti-HCV antibodies and HCV RNA. The natural history could be insidious: the infection could go unnoticed for many years; others may have had symptoms which had not been attributed to hepatitis C.

28.8. At all times we had to explain the variability in the rates of progression of the disease, which made prediction of the ultimate outcome difficult. Increasing age at infection appear to be associated with faster disease progression. Older patients would be more likely to present with complications of cirrhosis or HCC. Several well documented extrahepatic

manifestations have been described with hepatitis C including cryoglobulinaemia, lichen planus, porphyria cutanea tarda and membranous glomerular nephritis. There is an association between non-Hodgkin's lymphoma and hepatitis C virus infection. The prevalence of type II diabetes mellitus is increased. A number of important symptoms including fatigue, anxiety and depression and cognitive impairment affecting the quality of life for chronically infected patients had been linked to hepatitis C; these and polyarthralgia were common complaints. [WITN3754072]

28.9. Patients were informed how we would evaluate their liver disease to determine hepatic function and inflammation. Would also need to test patients for hepatitis B and HIV infection and exclude autoimmune hepatitis. Although a liver biopsy could be helpful in grading the degree of inflammation and staging the degree of fibrosis, a liver biopsy was not mandatory, although was initially required to qualify for NHS treatment. Early recommendations for biopsy were superseded by non-invasive assessment of hepatic fibrosis. We would discuss the general management and clinical monitoring for patients: although all patients became candidates for treatment with newer DAA therapies, interferon treatment was generally reserved for those with at least moderate or advancing hepatic fibrosis. Those with mild histological changes might not develop cirrhosis and the disease could be monitored. We provided evidence that alcohol and hepatitis C could synergistically aggravate the liver injury, as did coinfection with hepatitis B, HIV, obesity or diabetes. Patients were advised to minimise the intake of alcohol. Those who were not immune were advised be vaccinated against hepatitis A and B. We explained that the risk of sexual transmission in monogamous partners was low, but patients were counselled to prevent transmission.

28.10. We discussed the indications for treatment. The subject of pegylated interferon has been discussed above. Previously pegylated interferon was the most widely used treatment for hepatitis C together with ribavirin. The specific posologies for treatment with hepatitis C were elaborated. Later, we instituted IL28B single nucleotide polymorphism testing after the

discovery that a single nucleotide polymorphism in the interferon lambda 4 gene was a predictor of interferon response. The side effects of ribavirin and interferon therapy would require detailed elaboration. We also utilised video tapes to inform patients. Some of the invariable influenza - like symptoms caused by interferon alpha could be ameliorated by paracetamol. Unusual or severe side effects were listed. (see above). My manuscripts and text book chapters describe optimal patient monitoring for side-effects and appropriate laboratory testing. Patients were advised of the risk of haemolysis, nausea and teratogenicity with ribavirin and the need for contraception by both sexual partners for up to 6 months after completing treatment. The different treatment regimens for genotypes 1 to 6 was elaborated in interferon treatment naive or experienced patients with or without cirrhosis.

28.11. Treatment discussions assumed increasing complexity with the introduction of interferon in combination with first generation protease inhibitors. Futility rules and stopping rules were introduced to patients. Fortunately, interferon free, direct acting anti-viral therapy eventually superseded interferon treatment. My joint publications have detailed the class of drugs and mechanism of actions of the protease, polymerase and NS5A inhibitors. (162) These were explained to patients as treatment modalities matured.

28.12. Patients with cirrhosis and decompensated cirrhosis required special management as did the treatment of hepatitis C post liver transplantation. Patients with cirrhosis required regular surveillance for HCC, even after a SVR. Liver transplantation was a consideration for patients with decompensated disease. Patients with hepatocellular carcinoma and candidates for liver transplantation were discussed at multidisciplinary meetings.

28.13. We explained to patients the impact of an SVR. Treatment rates remained low with interferon in general because of the well-known adverse events, and frequently, treatment was not possible in PWIDs. Fortunately, we have been able to scale up oral DAA treatment in people with injecting drug use:

We elaborated measures to prevent hepatitis C. We also explained the measures necessary to prevent transmission including harm reduction or household measures. Access to opiate substitution and clean needle programs were necessary harm-reduction measures for patients with injecting drug use, but their provision was inadequate. A considerable scaling up of the diagnosis of hepatitis C viraemic individuals is still required.

28.14. We also enjoyed a good relationship with other specialist services including the renal unit, for patients receiving renal dialysis and renal transplantation and haematologists for patients at risk of reactivation of hepatitis B while receiving chemotherapy for example.

28.15. It should be pointed out that this brief description of management belies some of the complexity of care of patients with chronic viral hepatitis, from diverse backgrounds and walks of life. No two patients were the same. Levels of engagement were constantly required and would necessarily vary as patients adapted to knowledge of their disease. Inevitably engagement for some patients suffered in busy overbooked NHS clinics. Initially our resources were limited. The compassion, patience, and dedicated efforts of hepatitis nurse specialists, without whom the management and treatment of patients with viral hepatitis in the United Kingdom would not have been feasible should be acknowledged: Our unit and the United Kingdom in general set international standards for nurse involvement as well as pharmacists in the care of patients with viral hepatitis. We sorely lacked psychological support for patients attending the liver clinics. More recently clinical services have benefited from peer support.

29. When did the Department begin testing patients for hepatitis C? How were patients told of their diagnosis of hepatitis C? Were they told in person, by letter or by phone?

29.1. Testing was difficult, until the service was provided and funded. Testing was provided by the virology service. Although funding was not forthcoming initially, particularly for hepatitis C RNA testing by PCR, we were later

provided with a good routine diagnostic service by the virology department at the Royal Free Hospital. Testing had to move as quickly as possible to an accredited laboratory. [WITN3754073]

29.2. Patients were generally informed at an outpatient clinic. I cannot exclude the possibility that some patients were informed that they were viraemic and should return for an outpatient visit by telephone, but I consider this mode of communication to have been unusual and exceptional and only used where there was little alternative for patients who were newly informed of their diagnosis.

30. What information was provided to patients with hepatitis C about the infection, its significance, prognosis, treatment options and management?

30.1. Please see the answer given above. Most patients with NANB hepatitis could be diagnosed with hepatitis C relatively soon after my arrival, and we were able to provide lines of management within the hepatitis clinic.

Delay/public health/other information

31. Were the results of testing for hepatitis (of all kinds) notified to patients promptly, or were there delays in informing patients of their diagnosis? If there were delays in informing patients, explain why.

31.1. By and large, undue delays were avoided as far as possible. Follow-up test results, to be given in person, were delayed until the next available clinic but we attempted, in the face of staff shortages, resource constraints and limited clinical capacity to assist patients in a timely fashion. I am aware of an unfortunate false negative HCV RNA laboratory test given to a patient, which caused a delay in diagnosis, considerable anxiety and a delay in treatment. A legal settlement was reached with the hospital. There could be delays in referral for specialist assessment. Community assessment of the virological status of patients with hepatitis B and C, including measurement of HBV DNA and HCV RNA remains incomplete.

32. To what extent, if at all, did you and/or your colleagues at the Department take into account the public health implications of HIV, AIDS, hepatitis B and NANB hepatitis/hepatitis C, when taking decisions as to what information or advice to provide to patients or what treatment to offer patients?

32.1. An immediate downward trend in the incidence of transfusion associated hepatitis C (NANB) occurred following the introduction of hepatitis C testing. Although Alter wrote in 1991 "no study has found Non-A non- B hepatitis to be associated with homosexual activity, usually a clear indicator of the potential for sexual transmission of viruses" we subsequently reported an epidemic of acute hepatitis C in HIV positive men who have sex with men linked to high risk sexual behaviours. (268).

32.2. I established a co-infection clinic at the Royal Free together with Professor Margaret Johnson and Dr Sanjay Bhagani. Numerous other publications have confirmed the risk of HCV in HIV positive and negative men who have sex with men, the incidence and transmission of hepatitis C in this population, the implications for prevention in an era of PrEP, and reinfection following successful treatment with antiviral therapy. I and my colleagues were cognisant of the epidemiology and transmission of viral hepatitis, risk behaviours and the necessary harm reduction measures, and interfaced as far as possible with alcohol, addiction services, incarceration services, Public Health England (the Health Protection Agency), civil society and the WHO to advise. The advent of safer oral and more effective therapies now means that treatment as control forms part of our endeavours. A reduction in the level of viraemia in patients with hepatitis B and cures of hepatitis C now constitute realistic targets for a reduction in the morbidity and possible elimination of these diseases in the United Kingdom and worldwide. (269-274)

33. What information was provided to patients about the risks of infecting others?

33.1. Please see above. We elaborated the implications of HBeAg positivity or high levels of hepatitis B DNA in patients with hepatitis B, and the

consequent risk and modes of transmission including sexual transmission, mother to infant transmission and prevention by vaccination. Similarly, we advised viraemic individuals with hepatitis C of risk behaviours, modes of transmission, measures to improve harm reduction and treatment as control. I was asked to act to guide and supervise treatment of hepatitis B positive surgeons on nucleoside analogue therapy to prevent physician- to - patient transmission. Unfortunately, my endeavours to ensure an adolescent catch up program for hepatitis B vaccination whilst acting as interim deputy director (BSHSH) at Public Health have not been formally accepted as part of the Public Health Infectious Disease Strategy. [WITN3754074]. As with the advocacy for increased testing to tag to Covid-19 antibody testing, one learns the limits and constraints of collective and personal responsibility and public facing advocacy.

34. A BBC press release dated 16 January 1995 [NHBT0040622, p. 4], reported that you told Panorama that 'the delay in informing patients is serious as early treatment is vital. Once the liver is damaged, nothing can be done. "I think it's important to realise that for most individuals with chronic Hepatitis C, there is a window of opportunity to treat the condition." In respect of this, explain:

34.1. By 1995 there was a growing body of evidence of the improved efficacy of interferon in patients with early ("mild") disease (minimal or moderate hepatic fibrosis) compared to patients with advanced fibrosis and cirrhosis. Early treatment would be more beneficial than treatment in patients with cirrhosis. We know now that hepatic fibrosis can, to a degree, be reversed by an SVR, but we did not know this with certainty in 1995, as no long term follow up studies had been completed. Similarly, the risk of HCC, although now known to be reduced by an SVR is not obviated if cure is achieved only after the onset of cirrhosis.

a. Why you made these statements and what were your aims and objectives in doing so:

34.2. These statements were made in light of the facts pointed out above. The implication is that individuals known to have acquired chronic hepatitis C by transfusion or blood products should be identified as early as possible. Interferon treatment was not optimal for patients with advanced fibrosis or cirrhosis: yet these were the patients who most needed to be cured to prevent decompensated cirrhosis or HCC. All my experience of interferon at that point suggested that patients without cirrhosis were more likely to respond. Patients with cirrhosis, particularly those with genotype 1, 3 and 4 were difficult to treat successfully, and remained at risk of decompensation of HCC (13, 66, 275-282)

b. Whether these comments accorded with your own practice;

34.3. Answer to 34a and 34b:

34.3.1. The statement was made to point out the necessity to limit, as far as was possible, progressive disease. And yes, to the degree that patients accepted interferon treatment, and could be treated by the conditions imposed by access and NICE approval and via relevant guidelines.

c. Whether it was your understanding that there were delays in patients being informed and if so the basis for that understanding.

34.4. As far as possible, based on access to appropriate diagnostic testing, and accurate results reporting, we informed patients of the status of their disease, and the pros and cons of treatment. Identifying progression by (repeated) liver biopsy was impracticable and unacceptable, and remained a stumbling block. Diagnosis, further testing and appropriate linkage to care to specialist centres for appropriate management remain problematic and many patients remain undiagnosed. Late presentation still occurs.

d. Whether, to your knowledge, these comments had any effect on others' practices.

34.5. It is possible that a consensus grew to suggest improved responses in patients without cirrhosis. However much later, after the advent of costly but highly effective oral DAA treatments, it was necessary to inform NICE and NHS England that the NHS ran the egregious risk of replicating the Tuskagee study if NICE and NHS England approved a pilot research proposal to follow patients for advancing fibrosis before instituting DAA therapy [WITN3754075]; [WITN3754076].

Consent

35. Were patients under the care of the Department tested for hepatitis or for any other purpose without their express and informed consent? If so, how and why did this occur? What was the approach to obtaining consent for testing?

35.1. Guidance had been provided to professionals [DHSC0004004_187]. We were aware of major routes of transmission and the risk to recipients of blood transfusions. In 2004 data indicating mother to infant transmission have been published; we were aware of the extra risk following coinfection with HIV; and of the risk of sexual transmission as well as transmission via medical and dental procedures. We were aware of the added risk to healthcare workers and workers such as police and prison staff as well as the risk to household members from for example, sharing razors. Hepatitis C testing was part of essential practice in a specialist liver clinic.

35.2. Most patients referred for liver disease would have been aware of the need for a comprehensive series of tests to ascertain the aetiology of their liver disease if not previously diagnosed. A pre-test discussion would have indicated the panel of tests required to investigate unexplained serum aminotransferases or jaundice. Generally, however the implications of a positive test were easier to discuss at a post-test discussion.

35.3. The NHS had published risk groups and reasons to be tested for hepatitis C; these guidelines indicated that testing for hepatitis C should form part of

the investigation of patients with unexplained abnormal liver function tests. Their guidance had provided current epidemiologic evidence to suggest groups who should be offered hepatitis C testing. We are also aware of stigmatisation and the implications for work and insurance. These factors had to be balanced to provide appropriate testing without introducing inappropriate barriers to diagnosis. Education and awareness are still required.

Care and treatment

36. How was the care and treatment of patients with hepatitis B managed at the Department? In particular:

a. What steps were taken to arrange for, or refer patients for, specialist care?

36.1. We were a specialist referral unit for the management of patients with chronic hepatitis B.

b. What treatment options were offered over the years?

36.2. Patients were offered antiviral treatment, if indicated, based on guidelines, NICE approval, and NHS access. Most patients would have been treated with interferon, adefovir, in a few cases the combination of lamivudine plus adefovir, and latterly with tenofovir or entecavir; the latter are potent nucleoside analogues which have a high genetic barrier to resistance. Within the unit we were aware of the efficacy and side effect of all these drugs as well as the management of resistance, based on successive published guidelines for the management of chronic hepatitis B. I assisted in drafting several of these guidelines from 2002 and was a guidelines writer for the WHO. Some examples are referenced [WITN3754077]; [WITN3754078] (283) (284). I also assisted in drafting the NICE clinical guidelines for the diagnosis and management of chronic hepatitis B (2013). These guidelines followed a careful methodological and systematic review. The NICE guidelines were heavily weighted by cost-effective analysis, but recommended that a 48-week course of pegylated interferon alpha-2 be offered as a first-line treatment in adults with HBeAg positive and HBeAg

negative chronic hepatitis B. If truth be told, patients (and indeed physicians) were voting with their feet by this time, and preferred simpler and more palatable nucleoside analogue maintenance suppressive therapy to interferon.

36.3. The NICE guidelines recommended offering tenofovir to women with a HBV DNA concentration of greater than 10^7 IU/ml in the third trimester to reduce the transmission of hepatitis B to the baby. (285) Fortunately, the WHO has finally suggested a similar recommendation in guidelines published recently (2020) to coincide with World Hepatitis Day. (286)

c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?

36.4. We provided very detailed information to patients given our knowledge of the risks and benefits of specific treatments and the side-effects of the successive treatments described above based on guidelines in existence at the time, several of which I had assisted in drafting.

d. What follow-up and/or ongoing monitoring was arranged in respect of patients who were infected with hepatitis B?

36.5. Follow-up of patients followed guidelines. Clearly management of patients receiving interferon required monthly monitoring and sooner if concerns were raised. The side-effects of these drugs were well known to the unit. Fortunately, the advent of nucleoside analogue treatments greatly simplified the management of patients and follow-up could be extended to 2-3 monthly and eventually, 6 monthly. We were also abreast of reports of resistance to nucleoside analogues and indeed published the first report of resistance to lamivudine. I had assisted in drafting guidelines for the management of hepatitis B; and the requisite treatment for resistance to nucleoside analogues.

37. How was the care and treatment of patients with NANB hepatitis managed at the Department? In particular:

a. What steps were taken to arrange for, or refer patients for, specialist care?

37.1. We were a specialist tertiary referral unit. Interferon treatment may have been offered to some patients with non-a non-B hepatitis prior to my arrival in the unit in 1988. Treatment shifted to management of patients with hepatitis C after the discovery of hepatitis C. Please see below.

b. What treatment options were offered over the years?

37.2. Please see answers to hepatitis C below

c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?

37.3. Please see answers to hepatitis C below. Every effort was made to confirm a diagnosis of hepatitis C and to confirm viraemia as well as the existing genotype in patients with hepatitis C as testing became available to reduce uncertainty and to provide a specific diagnosis.

38. How was the care and treatment of patients with hepatitis C managed at the Centre? In particular:

a. What steps were taken to arrange for, or refer patients for, specialist care?

38.1. We were a specialist tertiary referral unit.

b. What treatment options were offered over the years?

38.2. Patients were offered interferon alpha, interferon alpha plus ribavirin, pegylated interferon, pegylated interferon plus ribavirin, combinations of pegylated interferon and first generation protease inhibitors including telaprevir, pegylated interferon and sofosbuvir with or without ribavirin, and successive generations of direct acting antivirals including combinations of NS5B polymerase inhibitors (sofosbuvir) and NS5A inhibitors (ledipasvir), grazoprevir and elbasvir, and subsequently second, and third generation

combinations: sofosbuvir plus velpatasvir, glecaprevir and pibrentasvir: combinations of direct acting antiviral treatments in use today and approved by NHS England. Treatment resistance is managed by sofosbuvir, velpastasvir and voxilaprevir, or if possible by sofosbuvir plus glecaprevir and pibrentasvir. The only question now is not whether we can cure the infection in most, but how we can identify all silent carriers of hepatitis C (globally) and link them to care. Treatment would need to be affordable in low-income regions. We have come a long way since 1990.

c. What information was provided to patients about the risks and benefits of specific treatments and about side effects?

38.3. Fortunately, personnel within the unit were well versed and trained in the management of successive generations of treatment. I had also personally assisted in drafting several successive EASL clinical guidelines on the management of hepatitis C culminating in the most recent 2020 version and could train the staff to provide information to patients regarding the risks and benefits of treatments over three decades. (93, 172, 184, 189, 287, 288)

d. What follow-up and/or ongoing monitoring was arranged in respect of patients who were infected with hepatitis C?

38.4. Patients were seen according to best practice and clinical capacity. Numerous patients who were not in treatment were regularly monitored to ascertain their status. With time we were able to establish the degree of fibrosis with reasonable accuracy in patients via non-invasive tests particularly transient elastography. Patients with cirrhosis were followed with careful surveillance for evidence of complications and for HCC by regular imaging and alpha-fetoprotein monitoring. Patients were also given management advice regarding alcohol and transmission as noted above. Our patients were regularly reviewed at multidisciplinary pre-treatment and treatment meetings. These provided the advantage of collegiate input into management and were a useful training and teaching exercise. A high level of participation and engagement was enjoined at these weekly meetings.

The meeting was attended by hepatologists, infectious disease colleagues, clinical virologists, molecular virologists, nurses, pharmacists, registrars and research fellows as well as visitors to the unit. Patients with all forms of acute and chronic viral hepatitis were presented for discussion and optimisation of their management at these meetings.

38.5. Patients with advanced disease and on the cusp of decompensation were referred for consideration of liver transplantation. Patients who developed HCC were treated based on guidelines including ablative, therapy hepatic resection, chemotherapy and liver transplantation.

38.6. Patients were offered treatment based on NICE approval NHS access and their willingness to undergo treatment. Closer to the advent of direct acting anti-viral therapy patients were informed of progress in the field and, like many patients worldwide, often chose to defer treatment. Nonetheless these patients were kept under observation so that we could offer treatment in time. Patients were also offered the opportunity to participate in clinical trials which led to the development of direct acting anti-viral therapy. Without the participation of patients, progress would have been impossible, and a debt of gratitude is offered to all those who participated.

39. What arrangements were made for the care and treatment of children infected with hepatitis (of all types)? How did those arrangements differ (if at all) from the arrangements made for adults?

39.1. For the first years of my contract at the Royal Free we cared for children. However, the GMC recommendations changed so that all paediatric patients were seen by paediatricians. We liaised with the paediatricians when necessary to provide advice. Adolescents were referred for management to our clinic as they transitioned from the paediatric to adult services. Recently recommendations for the management of children with chronic hepatitis B and C have been published and I was fortunate enough to contribute to these manuscripts. (165, 166) I have been invited to serve as a member of the WHO Paediatric Working Group on Viral Hepatitis,

Counselling and support

40. What if any arrangements were made to provide patients infected with hepatitis through blood or blood products with counselling, psychological support, social work support and/or other support? You may wish to refer to:

a. Your letter to Dr M Contreras dated 19 December 1990 in which you agreed to participate in, amongst other things, counselling for patients who tested positive for HCV at the North London Blood Transfusion Centre [NHBT0000190_074];

40.1. In December 1990, the Transfusion Service sought regional Hepatology services to assist with the management of donors who had tested positive for chronic hepatitis C. I spelt out my willingness to be part of a group of consultants to whom referrals could be made, for counselling and clinical investigation and possible treatment. December 1990 was some way away from the ultimate inception of screening by the Transfusion Service, but I was not to know that at the time, and assumed that referrals were imminent. Perhaps I was ahead of my time in mentioning emerging data on ribavirin (spelt incorrectly) which ultimately proved to be a widely used treatment for hepatitis C. (289-291). (Ribavirin is still considered for use as an adjunct in patients with genotype 3 and cirrhosis with pre-existing NS5A resistance substitutions). (292) I considered it advantageous that screening of blood donors would be both a means of identifying silent hepatitis C, and of course, stopping transmission via transfusion. A treatment paradigm was emerging which would improve with time.

b. A draft press statement regarding the introduction of HCV screening in blood donations dated August 1991 which, under heading 'recommendations 42 for investigations and counselling of patients found to have positive HCV antibody test by the blood transfusion service', advised that if there are abnormal findings or a patient is anxious, they should be referred to you [NHBT0000192_126, p. 5]

40.2. This press release was released by the press office of the Transfusion Service apparently in August 1991, immediately prior to testing. It emanated from the press office of the Blood Transfusion Service. It correctly states on page 5 that I could act as a point of referral for donors (diagnosed regionally)

41. What (if any) difficulties did you/the Department encounter in obtaining sufficient funding for the treatment of people who had been infected with hepatitis C?

41.1. We encountered great difficulties in placing funding for hepatitis C on a proper footing. Hepatitis C (and B) never attracted the political support and funding that was garnered by HIV infection. The hepatitis C epidemic was recognised as an important silent epidemic, but my experience was that hepatitis C infected risk groups were subliminally stigmatised. I encountered considerable prejudice directed at individuals infected with hepatitis C, and broad risk groups. A Department of Health action plan was published in 2004. The disease was identified in the Chief Medical Officer's Infectious Disease Strategy as needing intensified action to improve its prevention, diagnosis, and treatment. Despite the introductory words of the Action Plan hepatitis C remained a "Cinderella service".

41.2. The published Action Plan is an excellent document which set out the prevalence of the disease, the risk groups, requisite laboratory testing, increasing rates of new hepatitis C virus infection amongst injecting drug users, the known risk factors, the morbidity from the disease and the fact that liver transplantation was required for serious disease. The document set out pathways of care and indicated variations in delivery of care; the

document tried to compare international outlooks and provided future predictions: that there would be no vaccine, and that illness and death due to hepatitis C were likely to increase. Surveillance actions were promulgated. There was a suggestion that there needed to be increased awareness in order to reduce undiagnosed infections, and the document set out how the Department of Health would develop awareness campaigns with stakeholders. The document indicated that specialist services should be demonstrably commissioned and that actions for prevention should be taken.

41.3. Although the Department of Health recognised the public health importance of hepatitis C and suggested best practice and comprehensive guidance, many of the suggested actions fell short of effective schemes and funding to reduce the morbidity from the disease. The written Action Plan was not accompanied by any new funding, in contrast to the Action Plan in Scotland which attracted £40 million to alter actions. Only the commissioning of delivery networks to provide direct acting viral care in 2015 provided meaningful targets and strategies to reduce the prevalence and incidence of the disease in line with the stated aims of the WHO directive on elimination of viral hepatitis.

Section 6: Safety of blood products

42. Please outline the interactions and dealings you had with the blood services, whether on a regional or national level, and/or with BPL during the time that you worked at the Royal Free. In particular, please outline the dealings that you had with the SNBT. You may wish to refer to:

a. A letter from Elspeth McIntosh, Scottish National Blood Transfusion Service (SNBTS) to Dr B T Colvin, Haemophilia Centre, Royal London Hospital, dated 19 November 1997 enclosing minutes of a meeting of the SNBTS Coagulation Factor Safety Committee on 3 November 1997 [BART0002132]

42.1. (1997) The minutes of this meeting are elaborated. My expertise lay in transfusion transmitted viruses and clinical hepatology. I was asked to be a member of the safety committee. I commented on various aspects of the study including interactive pharmacokinetics and the statistical power of the study. Hepatitis G had been reported recently in questions arose whether it should be tested; virus safety results were discussed.

b. A letter from Elspeth McIntosh to you, Dr F. G. Hill; Prof. J. C. Petrie and Dr A. Scotland, regarding SNBTS Coagulation Factor Trials and vCJD, dated 21 January 1998 [BART0002129_015]

42.2. Dr McIntosh requested an opinion on the safety of trials of the SNBTS coagulation factor products following the recent concerns about nvCJD. I note the results of studies to determine the likely effect of processing methods on the effect of agents of the transmissible spongiform encephalopathies were awaited.

c. A letter from you to Elspeth McIntosh, Clinical Research Associate at SNBTS, dated 26 January 1998 BART0002129_011]

42.3. My opinion was provided. I noted the data to date and that the SNBTS would be withdrawing stocks of factor concentrates or blood products

should they become aware of an implicated donor in line with licensing authority requirements- and the need for scientific data to guide policy

43. What if any discussions or meetings or interactions did you have with any blood service (regionally or nationally) and/or BPL in relation to:

a. the risk of infection with hepatitis from blood products;

b. the risk of infection with HIV/AIDS from blood products;

c. the steps to be taken to reduce the risk of infection?

43.1. I acted for the safety committee for a period for the SNBTS as noted above. My opinion would have been sought for the clinical safety of hepatitis viruses and for a hepatology opinion. I had no formal position with transfusion services in England and as noted above did not serve on any formally constituted advisory committees to advise on the risk of infection with either hepatitis, or HIV AIDS or CJD.

You may wish to refer to the letter to you from NBTS dated 2 August 1991, thanking you for the help and advice you had offered the service [NHBT0000075_022; NHBT0000192_132]

43.2. These letters were received from Dr Angela Gorman and Dr Jean Harrison. They thanked me for hepatology advice to be given to general practitioners dentist and donors who tested positive for hepatitis C. I had provided clinical and hepatology advice to guide the service and to indeed enable them to prepare for donor anxieties and questions; the preparations were also to provide a conduit via the NHS for untrammelled referral of positive donors. (I would have preferred direct referral to hepatology services, but within the NHS referrals are usually made via general practitioners). The second letter from the director of the North-East Thames Regional Transfusion Centre was sent out to indicate that from September 1991 Transfusion Centres would be testing all donated blood, and that anti-HCV positive donations would be tested further to confirm the result. Donors whose test was confirmed as positive would be referred to the donor's general practitioner, who would be better placed to offer advice than the transfusion centre. The advice received from myself and Dr Murray Lyon is acknowledged.

44. What if any involvement did you have with any decisions or actions taken by any blood service (regional or national) and/or BPL in response to the risks arising from blood and blood products?

44.1. As pointed out above I offered hepatology advice and a clinical service for referral. I had no formal position on either the UK Advisory Committee on Virological Safety of Blood (ACVSB) or the UK Advisory Committee on Transfusion Transmitted Diseases (ACTTD)

45. Did you personally advocate an earlier date for the introduction of testing for anti-HCV screening and if so on what basis? Please refer to the following:

a. Paragraphs 69 to 75 of your statement in the Hepatitis Litigation in which you explain the events and discussions that took place at the Rome Symposium on 14 – 15 September 1989 and conclude at paragraph 75, "I came away from the Rome Symposium satisfied that the Chiron claims were essentially sound but that as with many new screening assays so the sensitivity and the specificity would evolve and improve with time and experience." [NHBT0086710]

45.1. As noted above. I had no doubt that Chiron's scientists had discovered the hepatitis C virus. From that point in time, discourse with regional blood centres emphasized my opinion that the major viral agent responsible for post-transfusion NANB hepatitis had been discovered, that therefore, blood donor testing was inevitable and should be implemented in line with transfusion services in the USA and other countries. A first-generation test had been devised which would be used in many countries once approved.

45.2. The background was summarised. Raised serum aminotransferases, typically after open heart surgery in patients receiving blood, was taken as evidence of post transfusion hepatitis. The incidence after use of paid-donor blood was high. Volunteer donor screening and HBsAg testing had decreased the risk, but the major burden of post transfusion hepatitis was still un-characterised, because the putative viral agent(s) was undiscovered. The National Institute of Health in Bethesda had collected

blood from a prospectively followed patient with NANB hepatitis (patient H) and had proven transmissibility of the agent by inoculation into chimpanzees. The NANB agent was shown to have a lipid envelope. It was postulated that the NANB agent was most likely a flavivirus. Many candidate assays were proposed before 1989, but none proved concordant with coded positive and negative samples at the NIH, comprised of duplicate samples obtained from "pedigreed" instances of NANB, and carefully selected negative controls. During this period, although the agent had not been discovered, clinical findings progressively documented the potential sequelae of chronic NANB. The disease did not merely cause a non-icteric "transaminitis" but could lead to cirrhosis and end-stage liver disease.

45.3. From 1981 to 1987, Houghton and colleagues at Chiron had performed ingenious, painstaking and innovative cloning experiments with plasma derived from patients and infected chimpanzees. They extracted nucleic acid and reversely transcribed the RNA. The derived complimentary DNA (cDNA) was inserted into expression vectors used to infect E. coli in culture. They made the important deduction that individuals chronically infected with non-A non-B hepatitis might have circulating antibodies to the NANB agent. After many negative experiments, a single reactive clone was identified, sub-cloned and the expressed antigen used to develop an assay for detecting antibodies to what is now known as the hepatitis C virus. Chiron requested an opportunity to test the NIH coded NANB panel: After decoding, it was found that Chiron had properly identified antibody in all the chronically infected patients and implicated donors of the panel (but did not find antibody in well pedigreed negative controls), thus proving the discovery of the NANB agent.

45.4. Subsequent investigations showed seroconversion in patients with well characterised NANB hepatitis; and found a linked anti-HCV antibody positive donor in 80%, of implicated cases, using a first-generation assay (and 88% with the second-generation assay). Later, the Chiron investigators used the initial small cloned viral fragment to "walk" along the

viral genome and characterise the full-length genome to delineate structural and non-structural viral encoded proteins, and to develop additional serological and molecular assays. Critical clinical data rapidly accumulated from worldwide investigations. Importantly it was shown that hepatitis C virus (an RNA virus) existed as antigenically distinct variants known as a viral quasispecies, in part resulting from the poor proof-reading ability of the hepatitis C polymerase, allowing nonlethal variation. The existence of different genotypes became apparent within a few years. The virus is prone to mutations in several regions. The envelope region is hypervariable.

b. A newspaper article "Patients may sue over hepatitis-C in blood" in The Independent on 7 August 1991 [NHBT0000192_137] which reported, "*Dr Dusheiko said that in spite of the imprecision of the earlier test, the BTS is legally and morally bound to put it into effect straightaway, while continuing to refine it at the same time. "On strictly scientific grounds the transfusion service may have been right to wait for a better test. But I think they had little regard for the recipients of the blood and were more concerned with the effect of a wrong diagnosis on donors*", together with a letter from you to the Editor of the Independent dated 8 August 1991 [NHBT0000192_138] in which you explained that he did not intend for your remarks on the testing of donor blood to be included in the article, that your remarks had been made 'off the record' and that the article did not quote your arguments against screening using the original test. You said, "*I did not wish to criticize the Blood Transfusion Service, which in this country is an excellent organization.*"

45.5. I gave an interview to a science reporter, crystalizing the arguments, expecting a science reporter to write a balanced report. On reflection, perhaps I stumbled. I clearly indicated my side of the argument. The description of the first-generation test was lost from the interchange.

45.6. The editor acknowledged the lack of argument in the article. However, my letter to the editor should not be misinterpreted. My letter was not an approbation of the delay in testing. My letter does contain the text "as soon

as the test for hepatitis C became available, I thought that it should have been national policy to screen donor blood. But I also pointed out that they were arguments against screening using the original test."

45.7. I copied the letter to personnel at the North London Transfusion Service. At the time I thought it was the right and mature thing to do. 1) I had made clear that I believed the strategy not to test was erroneous; 2) Screening (an inescapable consequence of the long-awaited discovery of hepatitis C) was to begin and was finally a fait accomplis. 3) Clearly, I emphasized on which side of the argument I stood and distanced my thinking from the decisions taken by the Blood Transfusion Service. 4) The subtext of the letter to the North London Transfusion Service was that parameters had changed; attention was being drawn away from the failure to test toward the necessary testing and referral of donors.

45.8. The transfusion centres were days away from introducing long awaited donor screening and referral and management of hepatitis C positive donors to liver centres such as my own. The material matter then at stake was to discharge the respective duties of the Transfusion Services and NHS physicians, and to link hepatitis C positive donors to care. I saw no advantage for patients in further disjoining the transfusion service at this point. Accountability would follow. I praised the Blood Transfusion Service for the good that they do and their ethos, despite an errant decision I had disagreed with.[11]

Please comment also on the response to your letter to the Editor from Professor Cash, the National Medical & Scientific Director of the SNBTS dated 19 August 1991 [NHBT0000193_001]

45.9. I did not know my letter had been circulated. I had provided informal clinical advice to the Scottish National Blood Transfusion Service and to Dr Cash, and his letter is a polite note from a courteous cognoscenti who understood the task afoot. (see below)

c. The BBC press release dated 16 January 1995 [NHBT0040622], which reported that you said that, "*feelings within the profession ran high over the issue of screening*" and are directly quoted to have said, "*Hepatologists and liver specialists were at loggerheads with services responsible for the provision of blood and we were adamant that Hepatitis C screening should be introduced. From that time on, blood transfusion practices could never be the same again. The blood would have to be screened. And I thought that that moment had arrived once a test was authorised in several countries and that this country should do the same. [...] it was important to err on the side of censoring blood so that the individual could not be at risk of receiving blood infected by Hepatitis C.*"

45.10. Hepatologists saw the ongoing transmission of hepatitis C via transfusion through a different prism; we envisaged and foresaw the consequences for recipients of hepatitis C positive blood. Transfusion Service thinking appeared to be dominated by the perceived effect of a positive test on blood donors, the effect of potential false positives on donors and the need to provision a secure blood supply. The lack of urgency and the procrastination before screening was viewed with increasing alarm: the number of individuals being infected with hepatitis C positive blood was growing by the day.

d. A newspaper article "Blood test delay 'put lives at risk'" in the Times on 17 January 1995 [NHBT0097150_011], which reported, "*Dr Geoffrey Dusheiko [...] told Panorama: "We were adamant that hepatitis C screening should be introduced and I thought that moment had arrived once a test was authorised in several countries*", and your comments made to the Panorama programme that aired on 16 January 1995 [NHBT0000236_020].

45.11. Please see my comments above. I thought that testing of donors should have been introduced in 1990 and expected that testing would be implemented in that year, in the light of the confirmation of the discovery of hepatitis C virus

e. A transcript of the Radio 4 programme 'Munro & Forster, re: Hepatitis in Donated Blood' due to be broadcast on 16 January 1995 [HSOC0016718, p. 2], in which Dame Sheila Sherlock said, "*Dr Geoffrey Dusheiko, a world expert on the virus, was astonished when the Blood Transfusion Service decided not to screen blood when a test for the virus first became available in early 1990" , and you are reported to have said," [...] we were adamant that hepatitis C screening should be introduced.*"

45.12. Professor Sherlock exaggerates my importance as a world expert on NANB hepatitis, but I had some knowledge of the disease; Dame Sheila gives a (posthumous) statement of the unalloyed truth.

Explain the basis for your view that anti-HCV screening ought to have been introduced earlier than it was and explain your understanding of the reasons for any delay. In particular, please set out (to the extent that such matters are within your own knowledge):

45.13. I recognised from April 1989 that the NANB virus had been discovered, understood the power of the discovery, and the immediate implications and premise for diagnosis and screening of blood donors. The day was always going to come when the agent responsible for post transfusion non-A non-B hepatitis would be discovered. I thought that day had arrived with the publication of the papers by Choo et al and Kuo et al in April 1989, and development of a first-generation assay for hepatitis C infection.

45.14. From that point on, testing for hepatitis C in blood donors became "inescapable", and planning for the foreseeable inevitability of testing, became obligatory. It was imperative to get NANB type C hepatitis virus out of the blood supply as soon as testing became feasible. Justice Burton's landmark detailed judgement established liability under the Consumer Protection Act for a defective product where the defect was known, even though the current state of knowledge did not make it possible to identify which of the products was affected. I concurred then, and still do, with the primary conclusion and judgement reached by Justice Burton that

screening should have been instituted with the first commercial assay, accepting that diagnostic companies would refine the first diagnostic assay.

45.15. I did not understand the reasons for the prolonged delay in the UK; I thought test evaluations would be completed far earlier. The delay in instituting screening was seemingly an operational decision. The Transfusion Service must have understood the profound consequences of not testing. Anti-C100 antibody donor testing, although not infallible was sufficiently sensitive and specific to identify a very significant proportion of infected donors, to substantially reduce the incidence of post transfusion NANB hepatitis. Technological and test improvements in accuracy in low prevalence populations would follow, but I judged that the likely benefits outweighed the net harm and dangers of not testing.

45.16. I understood that the UK would wish to evaluate the Ortho anti-HCV assay. When I could, I discussed my viewpoint with Transfusion specialists at the North London Blood Transfusion Centre that I had access to, where and when I sensed opposition, notwithstanding the professionalism of the transfusion personnel with whom I exchanged views. I believe that all Hepatologists felt the same. I believed that the Transfusion Service needed to take prospective stock of the performance of the first-generation test but could not wait for incontrovertible certainty.

f. In your view, when screening / testing for NANB hepatitis should have been introduced across the UK

45.17. As stated above, the first generation anti-C100-3 antibody assay could be used to test for hepatitis C in blood donors. Allowing for the logistics of independently evaluating the first test(s) and implementing screening, testing could reasonably have begun in the second or third quarter of 1990. Hepatologists could only watch the wave of testing in Belgium, Switzerland, Luxembourg, Italy and Spain between July and October 1990 and the long postponement in the UK with consternation. I recognised that C100-3 antibody testing was an imperfect test – and indeed needed to. (I would be using the test as a caregiver in the clinic, where mistaken diagnoses are

costly). Although the first-generation test might not eliminate the risk of post-transfusion NANB hepatitis, a positive test was sufficiently specific and sensitive to disqualify most potentially infectious donations, and deferral of infected donors.

g. What were the competing arguments for and against the earliest possible introduction of testing?

45.18. The argument for early introduction of testing: The hepatitis C had been discovered. Data from the United States and elsewhere in Europe indicated that first-generation commercial screening test could identify hepatitis C infection. The obvious gain would be that the test would permit greatly improved donor screening procedures for the prevention of post transfusion NANB hepatitis and improved blood safety.

45.19. In my deposition to the court, I summarised the implications of the Chiron/Ortho anti-HCV assay. At the Rome meeting (Rome symposium 14 15 September 1989), Alter paraphrased early results: The NIH studies had prospectively followed open heart surgery patients, in whom NANB hepatitis had been documented by long-term serial follow-up, by liver biopsy and sometimes by secondary transmission to chimpanzees: 90% of cases had anti-HCV antibody. Each of these latter cases had chronic hepatitis.

45.20. The seroprevalence of anti-HCV was approximately 60% after testing serum collections from a diverse group of patients clinically diagnosed as having NANB hepatitis. The anti-HCV prevalence in these patients, compared with prospectively followed transfused patients suggested that antibody to hepatitis C detected by the first-generation assay was more readily detected in chronic NANB hepatitis cases than those presumed to have recovered from an acute episode of NANB hepatitis (or perhaps in patients in whom the diagnosis of hepatitis C was more accurate). Anti-HCV was also present in most cases of community acquired NANB hepatitis. (144)

45.21. Alter suggested that it was probable that the majority of individuals capable of transmitting NANB hepatitis, i.e. chronic carriers of HCV, would be detected in the existing assay.

45.22. As set out at #88 of my witness statement [NHBT0086710] I indicate that although the first enzyme immunoassay - anti-HCV test - was not optimal either in terms of sensitivity or specificity… it did provide a sufficiently reliable method of diagnosing hepatitis C in infected blood donors to prevent transmission and was generally and quickly recognised as an critical breakthrough. (As with many first-generation tests there was a need for evolution and improvement, achieved in part by RIBA (see below) 1).

45.23. As set out at #94, the primary goal of any screening test for a transmissible disease is sensitivity. A low sensitivity would miss some viraemic and infectious donors. Specificity carried a consequence for the management, treatment and counselling falsely diagnosed donors.

45.24. Arguments against: Antibody testing for antibody to the recombinantly derived C100-3 protein antigen lacked complete specificity and sensitivity. The test was not perfect and required a confirmatory assay. (see 45.29 below). HCV viraemia was not easily verifiable in donors who tested positive. Some notes of caution had been sounded. [12] I address other aspects of the C100-3 antibody test elsewhere in this statement. Please see my deposition A vs Transfusion authority: [NHBT0086710]

45.25. There was a prolonged interval (window) between HCV exposure and the first appearance of antibody (in the range of 2-4 months but could be longer). Hence antibody was generally not present during the acute phase of disease; the assay was most efficient in detecting chronic carriers.

45.26. (Alter summarised the prolonged interval between HCV exposure and the development of anti-HCV antibody and the dilemma it might impose in the prevention of transfusion transmitted NANB. For non-A non-B hepatitis there would thus be a window in which an acutely infected donor might fail

the antibody screen and nonetheless transmit infection. However, this was not deemed to be a frequent occurrence).

45.27. There was the possibility that sequence variability of hepatitis C, an RNA virus, which was reported in 1990, could have clinical and diagnostic implications for the first commercial immunoassay for anti-HCV. Seroconversion in patients with acute HCV infection was often not detected until 3 months or longer after infection.

45.28. The second-generation assay, introduced in 1991, incorporated recombinant antigens from non- structural regions (NS3 and NS4) together with an antigen from the core region of HCV, improving the sensitivity of detection of all genotypes of hepatitis C: The majority of patients with chronic hepatitis C tested positive for antibody to the conserved HCV capsid protein (c22).

45.29. Several methods were employed to confirm results obtained by enzyme immunoassay using a different assay format and utilising different antigens. The method used initially was the recombinant immunoblot assay (RIBA). RIBA 1 had some value, but was not a true confirmatory test, as confirmatory tests ideally employ a different format to the screening assay. RIBA1 was manufactured by Ortho and commercially available in United Kingdom from May 1990. The RIBA-1 assay contained immobilized bands of two recombinant HCV antigens (C100-3, produced in yeast, and 5-1-1, produced in Escherichia coli) on nitrocellulose strips. RIBA1 was not optimal due in part to the fact that it utilised the same antigen (albeit in a different format) as the first-generation screening enzyme immunoassay, potentially duplicating an error. Nonetheless RIBA-1 had some value in excluding false positive results (307-311) A second-generation RIBA HCV (RIBA-2) was developed, in which two additional recombinant antigens (c33c [derived from the NS3 region] and c22-3 [from the virus core]) were added. Both antigens were expressed in yeast. (307). Testing for antibodies to the more conserved region of the capsid later improved the sensitivity of testing for different strains (genotypes) of hepatitis C.

45.30. At # 98 of my witness statement, I noted that the full sensitivity and specificity became known retrospectively; "on these values not less than 60% of donations truly infected with hepatitis C virus would be recognised as such and not less than 99% of donations truly negative") (121, 246, 247, 295-306)

45.31. At the end of the day, the first-generation test was necessary even if not sufficient. Although antithetical arguments could be proposed by the Transfusion Service, the sensible course of action would have been to have phased in testing with the first-generation test, while evaluating first generation and later tests, and answering questions regarding the sensitivity and the specificity of evolving screening tests. The policy would have required cleverness and resourcefulness.

h. Your view of Professor Cash's comment about a need for "balancing perceptions of gains and losses" about the introduction of anti-HCV screening;

45.32. Please see above. With respect, I do not believe that this is a question that should be addressed to me or that I should put myself in Professor Cash's shoes. I have no doubt, however, that the overriding gains of the discovery of hepatitis C quickly became patently obvious to Transfusion Services.

i. What decisions and actions were taken, and by whom, in relation to the testing of blood donations. Highlight any decisions with which you disagreed;

45.33. I was not party to any of the data being evaluated by the Transfusion Service. I did not sit on any deliberations or working party and was not a member of the either the closed and confidential ACVSB and ACTTD committees, or on the Advisory Group on Hepatitis. I communicated my disquiet regarding the delay to members of the Transfusion Service but had no official authority to influence decisions. In 1988 the Transfusion Services did not put in place a body to deal with the wider and emerging clinical

knowledge of HCV to address the context of blood transfusion and NHS treatment and management.

45.34. The arguments in force by the Transfusion Service and the problems posed by the lack of a confirmatory test in low prevalence populations in 1989 and 1990 were aired by transfusion research groups and directorates. Considerable detail is given in the Penrose report which also elaborates the decision taken by other countries to take advantage of the ability to detect anti-HCV and introduce testing early in 1990. [13]

45.35. The factual material examining the deliberations that influenced the introduction of testing and evaluation of results including prevalence data, seroconversion rates, genotype specificity infectivity risk, antibody persistence costs and contracts, staffing, the economic case, policy decisions for handling of seropositive donors, counselling of donors, the necessity for the UK to move in unison, RIBA testing with products of the same NS4 region antigens, FDA approval and export permits, political announcements, ministerial sign off and logistic matters, evaluation of second generation tests, and procurement were deliberated by the ATCCD and ACVSB at numerous meetings between 1989 and the implementation of screening on 1 September 1991. These deliberations are detailed in detail in Chapter 31 of the Penrose report.

45.36. The decisions taken were those of the various Advisory Committees advising on transfusion in the UK. I was not consulted by these committees nor was I a member any of the relevant committees. These decisions were confidential and taken behind the scenes and there was no structured communication with stakeholders including clinicians and patients.

45.37. The word on the ground was that screening would be introduced in 1990. In September and October 1990 Otho published the advent of the second-generation anti- HCV ELISA test, and a second generation RIBA test.[14] The long delay in decision making, and slippage and apparent postponements from moving from National Blood Transfusion assessments to implementing testing was puzzling and frustrating; the better option would

be to introduce anti-HCV testing, with the available test, while sequentially introducing improved testing as these tests evolved.

45.38. The evaluations appeared to have been thorough and critical, but the Transfusion authorities seemed not to see the promise, the pressure or the demand imposed by the advent of the first-generation anti-HCV test, for donor screening, or to embrace a full perspective of the significance of transfusion transmitted hepatitis; the service took some time to complete and evaluate their findings, exercising an academically rigorous standpoint that did not see the wood for the trees. Perhaps the rest of the unexplained delay was due to inefficiency, bureaucracy, exceptionalism, the need for UK solidarity, political pressures and shortcomings in harmonisation? My view at the time, having recently arrived in the UK, that there appeared to be an inability to decouple the operational necessity for early implementation of testing, while continuing to evaluate sequentially-introduced newer tests. Therein lay my disagreement. I regret that I was not able to wield more influence.

45.39. Our clinical services had begun preliminary use of Ortho tests for evaluation. At 31.85 I am cited as saying "the Ortho test is not infallible." Indeed, as detailed, the first-generation ELISA was not perfect, but it was sufficiently sensitive and specific to diagnose clinically well characterised cases of chronic NANB hepatitis. The test advanced the field. The perfect could be the enemy of the good.

j. What you meant when you said (if you accept that you did) that members of the professional were 'at loggerheads' with those responsible for the provision of blood, and to whom you referred specifically (in terms of both individuals and institutions);

45.40. Hepatologists and infectious disease physicians saw the discovery of hepatitis C and the ability to test for the disease through the prism of patients, who would avoidably acquire hepatitis C via infected blood, whereas the Transfusion specialists saw the discovery through the difficulties that testing would impose on the logistics of blood screening and

the impact on donors. These counterarguments accumulated as the inexplicable delay in the introduction of donor testing played out in 1990 and 1991. I note the point raised at Penrose 31.171: "Dr Gunson explained that the transfusion services were under a great deal of pressure, not just from Ortho but from the press and increasingly, from clinicians in the field."

k. The extent to which the screening of blood donations and blood products was regulated, and, if not, whether in your view there should have been different or better regulation;

45.41. This was outside my knowledge, and the subject is extensively covered in the Penrose report and Burton judgement.

l. The difference that earlier introduction of screening would have made; and

m. Any efforts that you made to bring about the introduction of anti-HCV screening at an earlier date, whether by private correspondence, research, or publically-facing advocacy, and provide copies of any evidence to support this.

45.42. I recall meetings and discourse with the North London transfusion service, and academic or sponsored meetings and getting to my feet to ask questions. I regret now that I did not keep notes but did not envisage such a long delay until screening. I had no place at the table at which National decisions to evaluate testing or to implement screening were made. I am reasonably certain that the point of view I expressed at local centres and educational meetings would have been fed upwards.

Section 7: UKHCDO

46. Please describe your involvement with UKHCDO (including any of its working parties, committees or groups). In particular, please detail your work on / with:

a. The Chronic Hepatitis Working Party, understood to have been estimated in late 1989 (see e.g., the 'Report on the Working Party on Chronic Liver Disease in Haemophilia', 1990 [HCDO0000573])

46.1. I attended UKHCDO working party meetings on very few occasions. My advice as a hepatologist was sought. Several sequential reports were produced to guide the clinical management of chronic viral hepatitis and liver disease in patients with haemophilia. These summaries were an attempt to take advantage of the evolving knowledge of chronic hepatitis, and hepatitis C in particular, for patients and to produce guidelines. I do not recall whether all these meetings were face to face: most were not. These guidelines were framed by responses from the UK Haemophilia Centre Directors questionnaires to fathom understanding of clinical liver disease in patients. The data to fully inform aspects of practice from 1989-1993 was relatively sparse, and we lacked the resources for more complete systematic reviews, or methodologists to assist. (312-327)

46.2. Report HCD0000573 summarises findings following a meeting in July 1990. Recommendations for surveillance are outlined, including the need for regular measurement of serum aminotransferases. The report states that "since it is likely that newer tests for HCV antibody and HCV RNA will become available, aliquots of serum samples tested for HCV antibody status should be stored frozen." The statement reflects the unavailability of HCV RNA testing for most patients in 1990. The report also details the deleterious effect of the progression of chronic viral hepatitis and recommendations to restrict alcohol intake; and difficulties in identifying progression to cirrhosis in patients with haemophilia. The statement includes the advisory note that patients with cirrhosis due to hepatitis C may

progress to HCC and implied the need for surveillance. "The risk of HCC increases progressively with the duration of cirrhosis and with increasing age of patients. We suggest that serum alpha-fetoprotein be determined in all patients who have had cirrhosis for at least 10 years and those with cirrhosis irrespective of its duration in patients who are 40 years of age or older. Any suspicious increase in serum alpha fetoprotein should be checked and repeated within one month.

46.3. Other recommendations included hepatitis B vaccination and interferon treatment for hepatitis B. With hindsight these recommendations would have benefited from resources to provide a better systematic review of knowledge at the time (limited as it was).

b. The report, 'Guidelines from the Chronic Liver Disease in Haemophilia Working Group' February 1993 [HHFT0000003]

46.4. The guidelines from February 1993 were updated indicating that patients treated with blood products should be tested by second-generation HCV antibody test and also included recommendations based on what was known regarding the sexual transmission of hepatitis C virus HCV; testing in sexual partners, follow-up of HCV antibody patients by serum aminotransferases and treatment with alpha interferon (noting that interferon was not licensed in the UK at the time the guidelines were written). Treatment therefore would have to be prescribed on a named patient basis (according to the criteria that governed the use of named patient treatments).

46.5. Some evidence for the efficacy of interferon alpha was included; the aim of treatment was to reduce disease progression and the development of cirrhosis. Selection of patients most likely to benefit was difficult. The statement includes a comment on screening for HCC: "patients with cirrhosis are at increased risk of developing HCC. Patients at increased risk are those over the age of 40 years, those abusing alcohol and those who have had chronic hepatitis C for more than 10-15 years. The statement that screening for HCC "has not been shown to improve survival or to be cost-

effective" reflected the data known at the time. (328) However, the statement also indicates "if screening is embarked upon it should be systematic with 6-12 monthly estimations of alpha-fetoprotein and hepatic ultrasounds."

c. The report, 'Guidelines on the diagnosis and management of chronic liver disease in Haemophilia', December 1994 [HCDO0000576]

46.6. The 2004 report updated findings: virtually all haemophiliacs treated with clotting factor concentrates before 1985 had been exposed to hepatitis C virus and almost 100% of these are HCV antibody positive. The major problem of the propensity of the disease to cause chronic liver disease was recognised. We wrote HCC " (is) now emerging as a complication of chronic HCV infection, but this is usually a development of cirrhosis and hepatitis C". We reported that to date interferon was the only drug of proven value for the treatment of chronic liver disease (due to hepatitis C) but sustained responses are limited to no more than 25% of most treated patients. Factors associated with poor response include HCV genotype 1, high HCV viral titre, cirrhosis and increasing age." We also commented on diagnosis and treatment decisions; sexual transmission of hepatitis C; follow-up of HCV infected patients; treatment with alpha interferon; the hazard of treatment with interferon for patients with decompensated cirrhosis and the lack of response in these patients; the fact that better responses could be obtained with a combination of interferon and ribavirin; the role of liver biopsies. We reported the utility of other investigations including the need for endoscopy to rule out portal hypertension; we wrote "abdominal ultrasound is of little value in the staging of chronic HCV - related liver disease. In patients over the age of 45 years it is useful for screening for HCC. In patients known to have cirrhosis and abdominal ultrasound examination and alpha-fetoprotein determinations are recommended at approximately 4 monthly intervals." We also commented on the role of alcohol and the potential role of liver transplantation.

46.7. Concepts of screening for liver cancer in at-risk populations have improved although many aspects are still debated, and the positive predictive value of current biomarkers is still relatively poor. (329, 330). Guidelines written today would take into account recent systematically collected data. Models have shown that surveillance for HCC can be cost-effective, and that its efficacy is dictated by the incidence of HCC in patients with cirrhosis who would be effectively treated if diagnosed with HCC. Surveillance in patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis might also be recommended. In patients with cirrhosis due to hepatitis C a SVR reduces the risk of HCC but does not eliminate the risk and therefore continued surveillance is recommended. (331)

d. The report, 'Mortality from liver cancer and liver disease in UK Haemophiliac males given blood products contaminated with Hepatitis C, 23 September 1997 [HCDO0000577].

46.8. This important paper published by Darby and the UK Haemophilia Centre Directors Organisation was published as a full paper in the Lancet in 1997. (9) Sarah Darby carried out a cohort study of mortality from liver cancer and liver disease in 4860 haemophiliacs men and boys in the UK, who had been treated between 1969 and 1985 with blood products carrying a high risk of HCV infection. We showed that mortality was 16.7 times higher than in the general population for liver disease and 5.6 times higher for liver cancer. The corresponding risk of HIV infection was demonstrated. Among those not infected with HIV, the increase in all-cause mortality resulted from an attributable risk to chronic or unspecified liver disease, or liver cancer in men aged over 45. We observed that during 1969-1992 a total of 8 deaths were attributable to primary liver cancer, giving a 25-year cumulative risk of 0.57%. After 1977, the ratio of observed to expected deaths in each 4-year period increased steadily. The deaths had occurred 12, 13, 16, 16, 19, 21, 22 and 23 years after the first recorded exposure to high HCV risk blood products in men aged from 43 to 77 years. Our results therefore showed the emerging risks of mortality from HCC and liver disease in the haemophilia population in the UK.

47. If you were involved in other significant reports, studies or trials on behalf of UKHCDO, which you have not discussed in your answer to question 7 above, please set these out and answer questions 7(i) to 7(ix) to the extent that they are relevant.

47.1. I was asked to provide assistance and information. This information was transferred indirectly and sometimes informally in the clinic from hepatologist to haemophilia specialists and to patients at meetings of the various haemophilia organisations and civil society. I informed the above groups as knowledge of the natural history of hepatitis C and its progression to chronic liver disease and HCC accumulated and its treatment improved. [WITN3754079]; [HSOC0000190]

48. Explain, in so far as these are matters within your own personal knowledge:

a. the purpose, functions and responsibilities of UKHCDO, as you understood them;

48.1. The purpose of the UKHCDO was to optimise services and management of patients with haemophilia.

b. the structure, composition and role of the various committees or working groups of which you were part;

48.2. I gave advice but was not part of the formal structure of the UKHCDO. I was only formally invited to be a member of the UKHCDO in February 2001.

c. The relationships between UKHCDO and clinicians (such as yourself) who were not working at Haemophilia Centres, but were otherwise engaged with overlapping issues;

48.3. I was asked on occasion to provide advice or comment, and draft guidelines. I had no formal status within the membership.

d. the relationships between UKHCDO and pharmaceutical companies;

e. how decisions that were taken by UKHCDO were informed by the work of its committees and working groups;

f. how information or advice was disseminated by UKHCDO and to whom;

g. any policies, guidance, actions or decisions of UKHCDO in which you were involved and which relate to:

i. the importation, purchase and selection of blood products;
ii. the manufacture of blood products;
iii. alternative treatments to factor products for patients with bleeding disorders;
iv. the risks of infection associated with the use of blood products;
v. the sharing of information about such risks with patients and/or their families;
vi. obtaining consent from patients for the testing and storage of their blood, for treatment and for research;
vii. heat treatment;
viii. other measures to reduce risk;
ix. vCJD exposure; and

48.4. The answers to questions d-g are outside of my knowledge of the infrastructure of the UKHCDO.

x. Treatments for HIV and hepatitis C.

48.5. As noted above, I spoke frequently at meetings attended by haemophilia specialists, and haemophilia patient organizations and civil society in an attempt to inform patients, physicians and policy makers.

48.6. These include

48.6.1. 1994 Local symposium haemophilia

48.6.2. 1994 Association Medical Underwriters

48.6.3. 1995 Haemophilia Society

48.6.4. 1996 Word Federation Haemophilia

48.6.5. 1995 Paper Journal of Haemophilia

48.6.6. 2000 Advisory Group Haemophilia Society UK HIV HCV infection

48.6.7. 2000 Medical Advisory Board World Federation Haemophilia

48.6.8. 2001 British Society Haematology

48.6.9. 2001 International Society Haemophilia World Fed Haemophilia

48.6.10. 2002 Funding British Liver Trust

48.6.11. 2002 World Federation of Haemophilia

48.6.12. 2002 Haemophilia centre standards

48.6.13. 2002 World Federation of Haemophilia

48.6.14. 2003 Haemophilia Organisation UK

48.6.15. 2003 Legal Advice Children Haemophilia Ireland

48.6.16. 2006 Aledort Coagulation Disorders London

48.6.17. Manuscripts text book

48.6.18. 2014 Irish Haemophilia Society

48.6.19. 2014 Note Gilead and patient consortium

48.6.20. 2016 European Haemophilia Society

48.6.21. 2016 European Haemophilia Consortium World Haemophilia Day Brussels

48.7. I provided advice on hepatitis A virus

48.8. I have provided similar civil society advice to the Thalassemia Federation, and other organisations including the Thalassemia International Federation and the UK Thalassaemia Society and still provide assistance today to patients, families and physicians. [WITN3754080]

Section 8: Pharmaceutical companies and medical research / trials

49. Have you ever provided advice or consultancy services to any pharmaceutical company involved in the manufacture and/or sale of blood products? If so, please list the names of the companies and give details (including dates) of the advisory or consultancy services that you provided.

49.1. I am not a haematologist or haemophilia specialist and my advice on blood products would not be sought.

50. Have you ever received any pecuniary gain in return for performing an advisory/consultancy role for a pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details.

50.1. Please see answer above. It is likely that funding to attend international haemophilia meetings (above) would have been from educational, arm's length grants from the pharmaceutical industry.

51. Have you ever sat on any advisory panel, board, committee or similar body, of any pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details of your involvement (including dates) and of any financial or other remuneration you received.

51.1. Please see answer above

52. Have you ever received any financial incentives from pharmaceutical companies to use certain blood products? If so, please provide details.

52.1. No

53. Have you ever received any non-financial incentives from pharmaceutical companies to use certain blood products? If so, please provide details.

53.1. No

54. Have you ever received any funding to prescribe, supply, administer, recommend, buy or sell any blood product from a pharmaceutical company? If so, please provide details.

54.1. No

55. What regulations or requirements or guidelines were in place at the time concerning declaratory procedures for involvement with a pharmaceutical company? If you were so involved, did you follow these regulations, requirements and guidelines and what steps did you take to comply with them?

55.1. I have followed guidelines and my honoraria have been declared to the ABPI. My relevant conflicts of interests have been declared on my publications. I have recently advised EASL young researchers at an EASL masterclass in 2019 on conflicts of interests. [WITN3754081]

56. Have you ever undertaken medical research for, or on behalf of, or in association with, a pharmaceutical company involved in the manufacture or sale of blood products? If so, please provide details.

56.1. No

57. Have you ever provided a pharmaceutical company with results from medical research studies that you have undertaken? If so, please provide details.

57.1. Please see answers to research above.

58. If you did receive funding from pharmaceutical companies for medical research, did you declare the fact that you were receiving funding and the source of the funding to your employing organisation?

58.1. These funds were negotiated by research contracts with the Royal Free and subsequently University College London School of Medicine. My research support depended upon industry academia links; this was an inevitable necessity in the field of anti-viral research. Institutional research grant support was received from Gilead sciences, Vertex Pharmaceuticals Bristol-Myers Squibb, GlaxoSmithKline, Human Genome Sciences, Novartis, Merck, Abbott (AbbVie), Pharmasett, Presidio pharmaceuticals. All these research grant monies were deposited within University research grants. Any additional funding for consultancies were deposited within the Special Trustees grant. These funds were left with the Royal free upon my departure from the Royal Free Hospital in 2015.

Section 9: Involvement with the financial support schemes

59. In outline, what involvement did you have with the different trusts or funds (the Macfarlane Trust, the Eileen Trust, the Macfarlane and Eileen Trust, the Caxton Foundation and the Skipton Fund) which were set up to provide financial support to people who had been infected?

59.1. I served as a medical director of the Skipton Fund from March 2014-2017

Skipton Fund

60. The Inquiry understands that you were a Director of the Skipton Fund Ltd between 2015 and 2018. What did you understand the aims and objectives of the Skipton Fund to be? What principles or philosophy underpinned its establishment?

60.1. The Secretary of State for health and health ministers of the devolved administrations announced a United Kingdom wide scheme would be set up to make ex-gratia payments to individuals who had been treated in United Kingdom by the National Health Service and had received blood,

tissue or a blood product and had consequently become infected with hepatitis C. The government liaised with the McFarlane trust, a charity which had been established to assist haemophiliacs who had contracted HIV/AIDS from infected blood products in the United Kingdom and their dependents. A service level agreement was set up the Department of health England who assumed responsibility for the administration as well as the financing of the scheme. The Skipton fund was set up as a company limited by guarantee and was in operation from 5 July 2004. The stated aims of the fund was that every person in the United Kingdom who was alive by 29 August 2003 and whose hepatitis C infection was found by the Skipton fund Ltd to be attributable to NHS treatment with blood or blood products before September 1991 may be eligible for payment from the fund.

60.2. The aims and ethos of the fund was to establish a financial relief scheme for individuals infected with hepatitis C as a result of NHS treatment. The scheme excluded individuals who had cleared the virus spontaneously. The parameters for eligibility were established by the Department of Health.

60.3. The general eligibility applied to those who had received blood, blood products or tissue from the NHS before September 1991. I understood that the aims of the scheme were to provide a discretionary, ex gratia payment scheme on compassionate grounds. The Department of Health had not devised the scheme to be compensatory in nature i.e. was not designed to compensate for legal wrongs. My understanding was that the initiative was devised to go some way towards improving the lives of those infected with hepatitis C, and to alleviate the hurt of individuals. The scheme acknowledged the harm and injury suffered by individuals (chronically) infected with hepatitis C and the real or potential consequences of infection and provided a reparation for harmful treatment without acknowledging legal fault. It could be argued whether claimants should receive their payments through a charity or directly from the Department of Health, who would bear the direct responsibility.

Appointments of Directors

61. Please provide a detailed description of the appointment process for the Skipton Fund and the exact composition of the board.

61.1. These details are publicly available and can be obtained from the board of the Skipton Fund Ltd. Directors' report and financial statements are available.

62. What was the process for electing/re-electing directors at the Skipton Fund? In particular, what involvement did (a) the Department of Health (or any other Government department) and (b) any other organisation or person have in this process? Did these matters change over time?

62.1. Question 62 and b: I am unaware of the procedure for electing Directors at the Skipton Fund, or of the extent of involvement of the Department of Health, at the inception of the Fund.

63. How, if at all, were positions advertised?

63.1. I was invited to join the fund as a medical director. My invitation followed a talk I was invited to give outlining new developments in oral direct acting anti-viral treatments for hepatitis C to members of the board. I do not believe the position was advertised.

64. Were there sufficient applicants of sufficient quality or did you struggle to appoint directors?

64.1. During my tenure the clinical workload was met by the two medical directors supported by the administrative staff of the Skipton fund.

65. How many directors were appointed by the Government, how many by the Haemophilia Society and how many were 'user' trustees during your tenure at the Skipton Fund?

65.1. This question which applies to the inception of the Fund should be directed to others.

66. How long did each director serve on the board? Could a director be re-elected? If so, how many times?

66.1. I served as a medical director for approximately 3 years.

67. Were directors remunerated for their work? Please include details of any policies on this, including policies for allowances/expenses.

67.1. This question should be directed to the fund accountant. I was remunerated at the rate of £29 per hour before tax. In some years I received no renumeration. My total reimbursement for the entire body of work for the Fund for over three years was £1044. [WITN3754082] [WITN3754083]

68. Was there an overlap of directors between the Alliance House Organisations? Please explain how this worked.

68.1. This question should be directed to the Directors of the Alliance House organisations

Relationship with government

69. To what extent was the Skipton Fund independent from Government? How much oversight did the Department of Health (or any other Government department) have over the Skipton Fund?

69.1. The Department of Health was responsible for payment of funds disbursed by the Skipton fund. The Department of Health had no direct clinical input into medical decisions made by the Medical Directors.

70. Did you, or others within the Skipton Fund, raise any concerns and issues with the Department of Health about the funding, structure, organisation or running of the AHO, or about the involvement of the Department of Health, or about any other matter? If so, please explain what concerns and issues were raised. What was the response of the Department to those matters being raised?

70.1. I was able to complete my obligations to claimants within the existing structure of the Skipton Fund albeit these were constrained by the terms of reference by the Skipton Fund.

71. What if any contact did the Skipton Fund have with the Department of Work and Pensions ('DWP')/its predecessors in relation to welfare benefits?

71.1. This question should be directed to the accounts and auditing Department of the Skipton fund and to the directors of the fund

72. Please describe the working relationship between the Skipton Fund and the Department of Health. Was there a particular point of contact? If so, who was that? Were you aware of any difficulties? If so, what were they, how did they impact on the running of the Skipton Fund and how, if at all, were they resolved?

72.1. I had no direct point of contact as a medical director between the Skipton Fund and the Department of Health. I did not detect interference from the Department of Health with medical decisions other than the set parameters which had been agreed earlier by the Department of Health at the inception of the fund.

Funding

73. Please set out the process by which the Skipton Fund received funding from the Government, and whether (and if so how) this changed over time.

73.1. I would be grateful if this question could be directed to the directors and accountants of the Skipton fund.

Visibility and access

74. Explain what steps were taken by the Skipton Fund Ltd during your directorship to identify potential beneficiaries; do you consider that further steps could or ought to have been taken?

74.1. The Skipton fund was reliant on web-based statements, the press, Government announcements, word of mouth and face-to-face interactions between clinicians and patients to identify potential beneficiaries. Some of the difficulties encountered by the fund in identifying beneficiaries are outlined in the minutes of the board meetings.

75. Was sufficient practical support and assistance given to applicants to make applications? Do you consider that more support or assistance ought to have been provided?

75.1. The majority of applicants were able to complete applications. Older patients, and partners of deceased patients could encounter problems. Difficulty was encountered in tracing records and establishing proof of transfusion or receipt of blood products. These difficulties were in part surmounted by support or assistance to trace non-existent or missing records.

Eligibility and proof

76. Who set the eligibility criteria for being provided with a stage 1 and 2 payment?

76.1. The eligibility requirements were set in 2004 by consultation and determined ultimately by the Secretary of State for Health.

77. Who determined whether an applicant was eligible for a stage 1 and stage 2 payment?

77.1. The Medical Directors determined whether an applicant was eligible for a stage I or stage II payment based on the criteria specified by the Fund.

78. What supporting evidence was required for such applications?

78.1. Supporting evidence of the receipt of a blood product or blood transfusion and the receipt of evidence indicating the nature of the procedure determining blood transfusion greatly assisted decision-making. Evidence of HCV viraemia was required, except for those who had been treated or could be shown to have cleared the virus spontaneously after a defined period of chronic infection. The application forms were designed to be completed with the applicant's medical advisers so that decisions could be reached based on all reasonable evidence. Evolving guidelines specifying the utility of non-invasive assessments of hepatic fibrosis assisted.

78.2. The information required was not detailed. Claimants were asked to ask their GP to look back through GP notes and letters relating to exposure; if records were not available, patients were asked to obtain and produce a letter from the relevant hospital records department or form their GP; to provide a personal statement to the appeals panel giving details of the operation, the procedure, the accident, or illness that led to the procedure involving blood, blood products or tissue, and if the patient recollected, whether a transfusion (or other exposure) was needed or occurred. Witnesses could provide narrative statements. Applicants were asked to provide any written evidence of the treatment the claimant believed had led to the infection with hepatitis C, providing photographs or injury scars. That allowed the panel to make a judgement on the likelihood of exposure to transfusion transmitted hepatitis C.

78.3. Staging of liver disease and the degree of fibrosis by non-invasive means could be difficult and the criteria used were not entirely specific or sensitive. Evidence based on blood counts, and serum aminotransferases were required to calculate the APRI score. We attempted to use as many lines of evidence as possible to establish the diagnosis of cirrhosis and to make fair-minded decisions. The APRI score is based on a ratio of AST level to the platelet count based on the supposition that patients with advanced liver disease increase serum aspartate aminotransferase levels as platelet

counts reduce because of portal hypertension. The formula is [AST/ULN AST) x 100]/platelet count. As noted by the developer of the score it was designed to find a simple low-cost method to estimate hepatic fibrosis that could be applied anywhere in the world. The author (Dr Anna Lok) has stated "APRI provides an estimation. It is not a gospel and users need to understand the limitations. For example when the APRI result is discordant from other clinical data one should consider repeating the assessment again during follow-up and take into account all available evidence" Importantly, APRI has a better negative predictive value than positive predictive value and is more reliable in ruling out cirrhosis then ruling in cirrhosis because of its lack of sensitivity. [WITN3754084]

78.4. All other evidence including hepatic imaging, endoscopy, CT scanning or MRI imaging, histological evidence, Transient Elastography (Fibroscan) Acoustic Radiation Force Impulse Imaging (ARFI) and even clinical opinion or clinical evidence was utilised to establish the presence of cirrhosis.

79. What was the proportion of applications that were granted?

79.1. A detailed audit of the proportion of applications granted is available via the fund statements.

80. In your view, was the application and decision-making process fair and appropriate? In particular:

a. Were the eligibility requirements fair and appropriate?

80.1. The eligibility requirements were set after consultation. Occam's razor can be applied in medicine: thus two outcomes of hepatitis C infection can be delineated with reasonable certainty: 1) Recovery from infection in patients who were anti-HCV positive, but HCV RNA negative by sensitive PCR, with normal serum aminotransferases and no evidence of clinically significant liver disease. (These individuals would not be offered treatment for hepatitis C). 2) Chronic hepatitis C, defined as by the presence of a positive anti-HCV test as well as hepatitis C virus detectable by PCR. The Fund

Directors were required to adjudge payments based on these criteria. The criteria caused anxiety to some patients, but the Skipton Fund was judged in 2010 by Justice Kenneth Parker to be operating rationally and lawfully. The available evidence suggests that although a low replicative state cannot be excluded in RNA negative patients, (332-334) there is a reasonable expectation that anti-HCV positive, HCV RNA -negative individuals who recovered from hepatitis C in the acute phase will not suffer the consequences of chronic hepatitis C and are not at risk of the complications seen in chronic hepatitis C. Therefore, these individuals are not offered treatment.

80.2. The diagnostic performance of Transient Elastography for cirrhosis has been extensively evaluated. The cut-offs have varied in patients with hepatitis C from 11.9 to 14.8. (335).

80.3. There are some limitations to Transient Elastography. The technology measures liver stiffness and is not a direct measure of hepatic fibrosis. Problems arise including inter-observer variation. Obesity can affect the readings and decrease the accuracy. Factors such as oedema, inflammation, raised serum aminotransferase elevations and even food intake can affect reliability. Steatosis may influence the results. At the end of the day the Medical Directors attempted to evaluate discordant results and give claimants the benefit of the doubt wherever possible, often requesting another Fibroscan.

80.4. It should be pointed out we noted a reduction in the cut off used for Transient Elastography to define advanced fibrosis to determine DAA treatment eligibility. However, the end point and decision point determinants were different: The lower determination defined advanced fibrosis, qualifying individuals for NHS funded DAA treatment; the Skipton criteria set point was designed to determine cirrhosis.

80.5. The criteria did not allow approval for claims from individuals who had recovered from acute hepatitis C and cleared the virus, i.e. had not had detectable HCV RNA in serum for a period of six months or longer.

Compensation to anti-HCV positive, HCV RNA negative individuals who had ostensibly spontaneously recovered from acute hepatitis C within 6 months of acquisition was denied when the Scheme was established. The Scheme differentiated two health states: early recovery from hepatitis C and resolution of the infection, versus chronic and persistent infection. The fund medical directors could not ascertain, using this razor, whether some individuals who had cleared hepatitis C have foregone some health.

80.6. Unfairness could arise: Claims had to be underpinned by evidence and the strict criteria specified in the application. In difficult cases we attempted to apply fair-minded decisions to benefit claimants. The eligibility criteria could disadvantage claimants who might have acquired community transmitted infection, but who had also received NHS treatment.[15]

b. Were the requirements for proof of exposure to blood and/or blood products fair and appropriate?

80.7. The Skipton fund Ltd required the applicant to prove on the balance of probabilities proof of exposure to blood and blood products, evidence of chronic infection and evidence that allowed staging of the disease. These tenets had been earlier specified by the Department of Health as rational, and fair (in order presumably to provide compensation for individuals at risk of serious liver disease, or who had developed serious liver disease or who had suffered psychological harm from the acquisition of chronic hepatitis C).

80.8. In patients where there was a strong likelihood of a transfusion or receipt of a blood product the test of eligibility applied a low standard of evidence wherever possible. The scheme made no provision for psychologic damage or disadvantage for those who had suffered acute hepatitis C but had cleared the virus and were unable to show evidence of ongoing liver damage. For a proportion of patients who were unable to provide proof, or documented medical evidence, the criteria were detrimental. The Skipton Fund could not meet the needs of the latter claimants without contradicting

the terms of reference and infringing the criteria disbursement from the public purse.

c. Was the requirement for supporting evidence fair and appropriate?

80.9. For some patients the burden of proof was insurmountable. Poor record keeping augmented their difficulty. It may never be known to what extent missing records unfairly disadvantaged some individuals, versus those whose claims could be considered, unfortunately, truly inadmissible. In order to qualify for an ex-gratia payment individuals did need to demonstrate on the balance of probabilities that they had received blood, blood products or tissue from the NHS and had been subsequently found to be infected with hepatitis C. Although a fair-minded approach was utilised, we could only admit these applications on reasonable evidence.

d. Were decisions made fairly and in line with published guidelines?

80.10. Medical decisions were required in every case to determine whether on the balance of probabilities chronic hepatitis C virus infection had resulted from receipt of NHS blood or blood products. For stage 2 appeals, the medical directors had to determine the likelihood of cirrhosis based on the information available to us. These eligibility criteria were published.

e. Were medical judgments to inform decisions made fairly?

80.11. Please see above. I believe that the decisions were made in a fair-minded manner to benefit claimants as far as possible, although the burden of proof was placed on the claimants. The medical directors would research the likelihood of a transfusion following surgery or an accident to ascertain whether on the balance of probabilities, despite the absence of proof, the patient had received a transfusion or a blood product.

f. Were decisions made in an efficient and timely manner?

80.12. Claims were evaluated in a timely fashion. The administrators should be given credit for their effective processing of claims, medical decisions and payment. During my tenure a backlog of applications did not accumulate;

the administrators steered applications to the directors and cannot be faulted. We worked remotely whenever we were unable to attend.

g. Were applications decided in a consistent way or were there differences in the way applicants were treated?

80.13. As far as possible, objective criteria were applied to claims to take into account even tangential pieces of evidence in order to make the right decisions. I note the minutes of the board meeting [SKIP0000030_068 point B4.15] which refers to the fact that medical data published online could assist with applications where records of a medical procedure were provided …. That referenced treatment with blood or blood products. Objective evidence was utilised wherever possible.

h. Were adequate reasons given when applications were refused?

80.14. Refusals were accompanied by an explanation. Calls were also made to referring physicians and clinicians to discuss claims and difficulty.

81. Explain your views about the proportion of unsuccessful applications and appeals based on a lack of satisfactory medical evidence. You may wish to refer to the board minutes of 10 March 2014 [SKIP0000030_068], point B41.5

81.1. I believe this refers to point B 4.15 of the minutes. The medical directors would assiduously research the literature to try to reach a reason decision of the probability of a transfusion for a particular procedure. "Lack of evidence is a frequent difficulty for applicants especially those from the estates of people who died many years ago who might have progressed to stage 2 eligibility."

81.2. We researched the available literature. Although the published evidence could be abstruse, considerable effort was made to encourage patients to submit evidence favouring the likelihood of a transfusion. We considered all information for example, transmission by bone grafts or urological procedures. Difficulty could be encountered in complex medical conditions: for example, in a patient with Ehlers Danlos syndrome, (an inherited

condition that affects the connective tissues of the body affecting collagen) in whom it was impossible to determine whether an ARFI scan truly could truly reflect hepatic fibrosis given the skin fibrotic abnormality. A request to the manufacturer to explain the physical principle was made.

81.3. The most common reason for an initial refusal by the fund was the absence of documented records of eligible exposure. That situation could arise because the existing records did not mention a transfusion or other exposure, or the records were lost or destroyed.[16]

81.4. By 31 March 2014, the year I joined, the total number of applications for stage I payments that had been received since the start of the scheme was about 6100; of these 677 were rejected: Either because the applicants had cleared the hepatitis C virus during the acute stage of infection and were consequently not eligible for the scheme, or due to the fact that there were other significant risk factors, such as intravenous drug abuse, or that there was insufficient evidence that infection resulted from treatment using contaminated NHS blood or tissue.

81.5. At 31 March 2014 206 stage II applications had been deferred because they did not yet meet the scheme criteria. Since inception, by 2014, the total scheme payments made by the company totalled about £200 million. Accurate records would be required but this amount almost doubled subsequently over the next three years.

82. Explain the influence that medical directors had on the determination of appeals about eligibility.

82.1. The Skipton fund appeal panel was independent of the Skipton fund Ltd. I understand it was set up in September 2006. The members of the appeal fund were appointed by the appointments commission on behalf of the Secretary of State. Their role was to reconsider cases of all claimants who appealed against individual decisions made by the Skipton fund Ltd. The panel would consider appeals against decisions concerning both stage I and stage 2 payments. The panel would seek further evidence to confirm

or change the original Skipton fund decision. Their terms of reference were published.

82.2. The Skipton fund provided information enabling patients to appeal against a refusal decision noting that the independent appeals panel would consider each case individually. It was also pointed out that the appeals panel would be required to make its decisions on the balance of probabilities. [WITN3754085]

83. The Inquiry understands that you have provided expert advice to the Skipton Fund Ltd over several years, particularly in respect of eligibility criteria and treatment availability. You may wish to consider, for example:

a. The document entitled 'Skipton Fund Litigation: Background Note for SOL', 2001 [DHSC0011689];

83.1. DHSC0011689 enunciates that on 4th November the Department of Health issued the following guidance to the Skipton Fund. "In particular patients who had or were thought to have eliminated the virus in the acute stage when they would most likely have been asymptomatic, or where any symptoms that did occur would have been short lived because of the transient nature of the infection would not be eligible for this payment." Paragraph 15 of this document is relevant: Paragraph 19 of this document indicates that the advice emerged from an exchange with the Advisory Group on Hepatitis. At paragraph 15 it is stated that this decision was apparently agreed by the four Ministers. As a result of this guidance the Skipton Fund rejected claims from people who had cleared the infection in the acute phase of the disease.

b. The notes of a meeting discussing 'trigger points' for proposed higher payments on 14 October 1993 [DHSC0015441]

83.2. A meeting was called on 14 October 2003 to discuss the medical trigger point for the proposed higher payment. I was invited to the meeting as noted. We were asked for our thoughts on payment for a recognised stage

of disease. There was consensus that cirrhosis rather than decompensated cirrhosis would be the better trigger point, for the reason that cirrhosis would be ascertainable before decompensated cirrhosis, and thus would not be as late in the day as decompensated cirrhosis. It would be important to establish cirrhosis using non-invasive means. There was considerable debate about the test methodology that we could use as noted in the minutes of the meeting. (Technologies such as transient elastography had not been developed). We proposed a combination of non-invasive tests to form a dataset to assess the stage of liver fibrosis which was in accordance with the state of medical knowledge at the time. The test panel would need to be accessible to provide a workable paradigm. "The panel of test was not intended to be formulaic, but the result should comprise the best available data to enable an expert (hepatologist?) to reach an informed conclusion. It is expected that results will be considered on an individual basis by an expert familiar with the patient their circumstances and their medical history."

83.3. We also noted that information should be available from clinical examination, ultrasound and other imaging report and endoscopy. An experienced group of hepatologists formed the consensus. We also noted the need for policy decisions regarding the prospect of hepatocellular cancer development following successful treatment or spontaneous viral clearance. HCC would indeed form the basis for a stage 2 payment. It was also decided that patients who had cleared the virus through treatment would qualify for payment.

c. Email correspondence dated March 2014 on the subject of "Blood Safety - new HCV therapies for Skipton Fund Stage 2 people" about your suggestion of providing early access to new forms of treatment to recipients of Skipton Fund Ltd Support [DHNI0000368]

83.4. In March 2014 new direct acting anti-viral treatments which transformed the treatment of hepatitis C and greatly improved treatment response rates in patients with cirrhosis were being developed. Treatment was evolving

rapidly but the costs of treatment was high. Their prescription needed to be approved by NICE. Treatment was not yet approved. It was not yet clear how NHS England would fund treatment. The request was a logical endeavour to obtain treatment for Skipton Fund stage 2 patients, who comprised a readily identifiable and well documented at-risk group with cirrhosis. I suggested that Skipton Fund recipients be given early access in order to arrest the progression of cirrhosis.

83.5. From the correspondence, I note that there was discussion at various levels whether treatment of stage II recipients would create a problem if the route of acquisition influenced whether an individual received the perceived best possible treatment. It would appear that others did not agree to selecting out "preferential" treatment." In the end funding decisions were made by NHS England who devised a quota of patients to receive treatment.

83.6. NHS England had issued an interim commissioning statement in 2014 providing treatment only for patients with cirrhosis. In 2015 a research surveillance program was mooted to provide a "service specification" for a program to monitor all patients with hepatitis C and identify those that had progressed to METAVIR stage F3 or F4, who could then access treatment.

83.7. I was invited to a NICE and NHS England consultation in May 2015. Beforehand, I wrote and submitted a detailed submission for the meeting setting out possibilities for the group to consider that would take into account the necessity to treat to prevent cirrhosis. [WITN3754075]; [WITN3754076]. I and other attendees argued the details at the meeting. I indicated that a research study that followed patients to monitor advancing fibrosis, but which would delay treatment until severe fibrosis had developed would emulate the infamous Tuskagee study conducted by the Public Health Service in the USA: the Tuskagee study began in 1932 to record the natural history of syphilis in 600 Black men and continued for 40 years. The men never gave informed consent and were never given adequate treatment for their disease, even when penicillin became

available. New "penicillin's" were available for the treatment of hepatitis C. The NHS was fortunately dissuaded from embarking on such a study.

83.8. I also wrote to NHS England, pointing out that the newly published Urgent Urgent Clinical Commissioning Policy Statement: Retreatment of Chronic Hepatitis C Infection in Adults with Advanced or Decompensated Cirrhosis NHS England Reference: 170020/PS falls short of the values stated in the document. [WITN3754086]; [WITN3754087] "The statement suggests a policy that is inadvisably restrictive for a re- treatment policy for patients with cirrhosis due to hepatitis C. It is egregious to consider that only patients with "advanced" cirrhosis (as defined) or decompensated cirrhosis can be considered for retreatment. Take the patient I saw last week with genotype 2 and cirrhosis. She was unsuccessfully treated with sofosbuvir and ribavirin. Her platelet count is 84 and her serum albumin 37. She has never decompensated. She is apparently ineligible but would be a good candidate for either 12 weeks of sofosbuvir and velpatasvir (rather than 24 weeks) or 12 weeks of glecaprevir and pibrentasvir. The evidence base for these regimens is not large but the data from Expedition I or ASTRAL 2 in treatment experienced patients provides an adequate rationale. (1) (2, 3)

83.9. The justification given in the commissioning statement is that "two new treatments which are due to receive marketing authorisation in the summer of 2017 are being assessed by NICE through the Technology Appraisal Programme, and this is expected to include a recommendation on the use of the products for retreatment. The due date for these assessments is early 2018." I wrote that "both sofosbuvir and velpatasvir and glecaprevir and pibrentasvir have a marketing authorisation and would likely benefit numerous patients with less advanced cirrhosis. Both regimens are listed in the rate card. We know that despite relatively small numbers in clinical trials it has been possible to replicate the data in practice – largely because the DAAs in current use are highly effective drugs.

83.10. Any decompensation that occurs in patients with advanced cirrhosis would render them ineligible for pending regimens that include a protease

inhibitor, in particular glecaprevir or voxalaprevir. Thus, I would ask the commissioning group to reconsider the narrow and restrictive criteria that have been applied and to consider that any decompensation event in a patient with cirrhosis would be an ominous development.

83.11. 12 weeks treatment would suffice in the patient listed above, for example, and would pre-empt further progression (although, as you know, will not eliminate the risk of hepatocellular carcinoma). Patients with cirrhosis have in many cases been infected decades ago. The process has been driven by persistent hepatitis C infection. Re-treatment options would be best applied without further delay or progression."

Please explain:

d. Your role in working with and advising the Skipton Fund Ltd., including whether this has changed over time, and if so, how;

83.12. I provided ad hoc advice to the Skipton fund. I was appointed as a medical director and was closely involved with medical decisions during my relatively brief tenure.

e. Your advice to the Skipton Fund Ltd about eligibility for financial support, both in terms of what guidelines should be set in place and how individuals should be required to demonstrate that those guidelines are satisfied in individual cases. Provide any copies of written advice or reports that you provided to the Skipton Fund Ltd in this respect;

83.13. As stated above I along with other expert hepatologists and haematologist provided ad hoc advice on clinical aspects of the scheme prior to my appointment as medical director.

f. Your advice to the Skipton Fund Ltd about eligibility for and the availability of non-financial support or treatment, both in terms of what should be made available and how eligibility should be determined.

83.14. As stated above I along with other expert hepatologists and haematologist provided ad hoc advice on clinical aspects of the scheme prior to my

appointment as medical director. These criteria were established at the time of the establishment of the Skipton fund. I along with other hepatologists and haematologists provided advice to the fund (and the Department of Health) to encompass non-invasive testing for cirrhosis for stage 2 payments

Provide any copies of written advice or reports that you provided to the Skipton Fund Ltd in this respect;

83.15. Advice given was made at face to face meetings and the Inquiry has included the relevant documents in the J9 files sent to me: (SKIP0000030_068); (DHSC0011689); (DHSC0015441); (DHNI0000368). I have attached an email date 14 February 2014 to a member of the Policy Team following discussion at a DOH workshop. I attended a DOH meeting to review systemic effects of hepatitis C and compensation in 2016. [WITN3754088]; [WITN3754089]; [WITN3754090]; [WITN3754091]; [WITN3754092]. As stated above, I have also attached an email written to NHS England on 6 September 2017 regarding the initial re-treatment policy [WITN3754087];

g. **In particular, detail your involvement and advice to the Skipton Fund Ltd about the availability of support from for individuals who had cleared HCV spontaneously**

83.16. Please see earlier. The Fund recognised two health states but provided compensation only for those with chronic hepatitis C, and not acute resolved disease, (based on the absence of detectable HCV RNA and normal serum aminotransferases). An earlier judicial review had been conducted.

h. Explain any other aspects of advice that you provided to the Skipton Fund Ltd and provide any copies of written advice or reports that you provided.

83.17. My meetings were face to face meetings. The Inquiry is in possession of these documents.

Transition to devolved schemes and Involvement with EIBSS

84. Were you personally involved in any consultation by the DHSC or any other Government department about the establishment of the EIBSS, its functions, aims and objectives? If so, please:

a. Describe that process; and

b. Set out the contribution you made to the consultation.

84.1. I was not personally involved at Department of Health level with the decision to set up the EIBSS. My involvement may have begun with a consideration of extrahepatic conditions and quality-of-life of people living with hepatitis C. There was a need for a systematic review of the causality of these conditions and the strength of evidence.

84.2. I was invited to assist as an adviser to a group examining studies of extrahepatic conditions in hepatitis C. This was under the aegis of the Evidence for Policy and Practice Information and Coordinating Centre - part of the Social Science Research Unit, Institute of Education, University Of London. The first meeting was on 12 February 2014. [WITN3754093] A detailed analysis of studies to be scrutinised using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology was presented for comment. I cannot be certain, but the systematic review conducted by Dr Brunton and her team may have set the stage and platform to be devised by DHSC for the establishment of the EIBSS? That aim however was not explicitly clarified, although perhaps this was an unfolding if somewhat undisclosed agenda. [WITN3754094]; [WITN3754072]

85. To the extent that these issues are within your own experience, provided details of policies and practices that were retained by the EIBSS in respect of annual payments, and the increase in April 2018 when the Special Category Mechanism ("SCM") was formulated.

85.1. I was invited to a Department of Health workshop meeting to examine reform of the infected blood payment scheme. The meeting was held on 26

February 2016 and the details are enclosed. [WITN3754090] The aims and context were set out. The background was the ongoing public consultation on reforming the current payments schemes, which was to close on 15 April. Individual assessments would be pivotal to proposals for reform. The sources of criticism of the current scheme were discussed, in that people with hepatitis C stage I were treated very differently from other scheme registrants. This was recognised to be inequitable, and an equitable and affordable approach was sought. The aim for the day was to design and establish an assessment system that was fair, consistent and "light touch". The goal was to identify the spectrum of disease signs and symptoms including extrahepatic manifestations and how these could be categorised. Examples of approaches to assessment were given, including those based on the injury benefit scheme. Papers tabled by two medical practitioners were included. A more straightforward system was sought but many issues would require consideration. I was asked to give a two-part presentation on extrahepatic manifestations of hepatitis C as well as quality-of-life assessment. My presentation is attached (referred to earlier). [WITN3754091]; [WITN3754092]

86. What do you understand the aims and objectives of the EIBSS to be? What principles or philosophy underpin its establishment and operation?

86.1. The NHS business authority sought to revise payment and to assume direct responsibility for compensating patients who had acquired hepatitis C via NHS treatment. As reported, the NHS Business Services Authority replaced support for English beneficiaries provided for by the pre-existing UK wide scheme after seeking wide consultation. [WITN3953052]

86.2. As stated, the system had attracted criticism. The Department of Health responded to the need for a more accessible and equitable system of care and support and launched a consultation on its proposal for reform on 21 January 2016; widespread feedback was obtained. A full analysis of the England Infected Blood Support Scheme has been published describing the consultation exercise, the elements of the system, the transition

arrangements that were to be put in place from 2016/2017, and what the reform scheme would mean for individuals. The reforms arose out of a dialogue between key stakeholders. The aim was to inform the understanding of Government of what mattered most to stakeholders in terms of financial and non-financial support.

86.3. The respondents mentioned that fairness, equal treatment, transparency and accountability and qualified and caring staff were the most important factors. Assessment should take account of the full life impact of infection not just of the current health impact. It was also noted (2.23) that access to new hepatitis C therapies has been improving since the summer of 2015, and that the NHS would be prioritising access to treatment for all on the basis of clinical need in line with NICE guidelines.

86.4. The Department of Health therefore concluded that the fundamental principles of the consultation proposals were to be supported. The elements of the reform system were set out in detail including specific payments. A key theme to emerge was that the government was committed to creating an accessible and equitable system of care and support that was "light touch and with services sensitive to beneficiaries needs. The system would also need to take account of medical advances and make best use of available funding appropriately and equitably over the remainder of the five-year spending review period." NHS England reported that "we recognise there can be a wide spectrum of ill-health associated with chronic hepatitis C infection, some of which may be prolonged and severe and also that the older treatments for hepatitis C infection can occasionally have a long-term health impact. With this in mind a special appeals mechanism was to be introduced".

86.5. Advice was sought on the criteria and process for the mechanism which I believe might have dovetailed with the review reported above. The new system of discretionary support will be "equitable, transparent and consistent for all beneficiaries. It will have robust criteria and provide help to those who need it most, in a way that does not see them "beg cap in

hand". The consultation sought views on whether the scheme should provide enhanced access to the new hepatitis C drug treatments to be rolled out by the NHS. Over 70% of respondents felt that access to hepatitis C treatment should be part of the reform scheme. I understand that it was stated that on account of the need for fairness towards all those in need of NHS treatment, "access to hepatitis C treatment for scheme beneficiaries will be provided by the NHS on the basis of clinical need in line with NICE guidelines".

86.6. The NHS Business Services Authority would administer the England Infected Blood Support Scheme. It was explained that as part of a reform process there would be a special category mechanism to be introduced to individuals co-infected with hepatitis C stage I and who were registered; annual payments could be revised. Pivotably, the special category mechanism recognised the impact of the infection upon patients and treatment for it, or linked conditions, and aimed to be responsive to needs and health status. The form stated that individuals could get the same annual payment as stage II recipients if the infection or its treatment were believed to have a long-term negative impact on the individual's ability to carry out daily activities, had worsened, but was not stage II, had led to medical complications not associated with stage I and meant that extra treatment not associated with stage I was needed. To qualify the applicants would have had to have autoimmune disease which was due to or worsened by interferon treatment; examples were given including haemolytic anaemia, idiopathic fibrosing alveolitis of the lung and rheumatoid arthritis, sporadic porphyria cutanea tarda, immune thrombocytopenic purpura, type 2 or 3 mixed cryoglobulinaemia if accompanied by cerebral vasculitis dermal vasculitis or a peripheral neuropathy with neuropathic pain.

86.7. The special category mechanism was available if individuals were recognised and registered as a stage I beneficiary, taking into consideration whether the infection, it's treatment or associated conditions had resulted in long-term negative impacts on the ability to carry out daily activities, had

worsened, but was not stage II and would include advanced cirrhosis, primary liver cancer, receipt of a liver transplant wait-listing for transplant, development of B cell non-Hodgkin's lymphoma and type 2 or 3 cryoglobulinaemia (membrano- proliferative glomerular nephritis).

86.8. The forms explained that to make an application to the special category mechanisms, patients must already have made a successful stage I payment application to the EIBSS and have one of the specific hepatitis C associated conditions listed in section 5 or believed that the hepatitis C infection, or its treatment, and ramifications caused by the infection was affecting and individual's ability to carry out everyday activities.

87. Please describe the extent of your involvement in the transitional arrangements from the Skipton Fund Ltd (and other support schemes within the Alliance House Organisation) to the EIBSS and devolved schemes.

87.1. Perhaps my involvement began with the development of the systematic review and meta-analysis authored by Brunton el, examining depression, anxiety, pain and quality-of-life in people living with chronic hepatitis C [WITN3754072] Support for this independent report was via a commission funded by the Policy Research Programme in the Department of Health. The objective was to examine extrahepatic conditions which might have a significant impact on life expectancy and quality of life in patients with hepatitis C. The comprehensive report indicated that people with hepatitis C have statistically significantly worse quality-of-life indices than general or healthy populations. Evidence from 22 studies indicated that depression and anxiety are more severe, and depression more common among people with hepatitis C compared to those without it.

87.2. A meta-analysis identified the severity of clinical anxiety to be significantly greater among people with hepatitis C. The review also demonstrated that people with hepatitis C are more likely to suffer from arthralgia and fibromyalgia than those without hepatitis C. Thus, the conclusion of this systematic review suggested an association between hepatitis C infection and depression, anxiety and fibromyalgia, as well as arthralgia and health-

related quality of life. The studies accorded with numerous quality-of-life studies previously published. The review also examined treatment for hepatitis C and the potential influence of interferon treatment, both as a confounder and an aggravator. (41, 43, 44, 48, 50-53, 55, 58-62).

87.3. Please see above. I also recall a meeting and post meeting discussion regarding the operation of the system and initial design of the forms and accompanying literature. A group including representatives from the NHS Business Services Authority, NHSBT, a general practitioner and hepatologists met to discuss the application forms. I believe the initial meeting was held on 13 October 2017.

88. To the extent that these are issues within your own knowledge, please explain the following:

a. Why did the NHSBSA and DHSC agree on a strategy of not automatically sharing beneficiary data between the AHOs and the EIBSS? Was this decision taken pursuant to legal advice?

88.1. This is not within my knowledge.

b. To the extent that beneficiary consent was not obtained in the initial period following the establishment of the EIBSS, what consideration was given to (i) alternative methods of contact and (ii) dispensing with prior consent? If so, why and at what point? If not, why not?

88.2. The answer to this question is not within my knowledge. I and hepatology and infectious disease colleagues were asked to provide a clinical service but would not be responsible for the administration and back procedures to set up the scheme.

c. Please provide details of any other policies or procedures adopted by EIBSS in relation to data sharing and contact with potential beneficiaries.

d. Was the above strategy and/or any other relevant policies or procedures made publicly available? If so, when and in what form? If not, why not?

88.3. The answers to 88c and 88d are not within my knowledge

89. The Inquiry understands that the records the AHOs held in respect of each beneficiary were not passed over to the relevant scheme. Is this correct? If so:

a. Why was consent to share these records not part of the consent process for transferring to the EIBSS?

b. Has the absence of this information hampered the NHSBSA in the administration of the EIBSS?

c. What impact has this had, in your view, on the beneficiaries?

89.1. I am unaware of the process and consent procedures that pertained to these records

90. What steps, if any, were taken to ensure that unsuccessful applicants to each of the AHOs were contacted about potential eligibility for support from the EIBSS?

90.1. This question should be addressed to the EIBSS and AHO administrators

91. To the extent that these are matters within your own knowledge, please explain what steps EIBSS took to publicise each of the following:

a. the establishment of the EIBSS?

91.1. This is beyond my knowledge.

b. the date on which each of the AHOs would cease operations?

91.2. I was asked to assess applications from 1 November 2017

c. methods of contacting or applying to the EIBSS?

91.3. The key responsibility for the Infected Blood Scheme was assumed by the NHSBSA who had the responsibility for disseminating the information.

d. The general scope of support and other forms of assistance available from the EIBSS, including (i) types of support and (ii) eligibility criteria?

91.4. My understanding was that the EIBSS currently applies a financial award for stage I payments of a one off lump sum of £20,000, and regular payments which are currently £18,772 a year or £28,476 subject to meeting the qualifying criteria for the special category mechanism as well as an annual winter fuel payment of £540 Individuals would be eligible if they were registered as a stage 1 beneficiary, and considered their infection, it's treatment or any associated conditions had had a long-term negative impact on their ability to carry out daily activities, had worsened, but was not stage 2. A medical practitioner's input would be required. That endorsement could be based on professional judgement or balance of probabilities.

91.5. Section 5a of the form specified a number of conditions that would qualify individuals including autoimmune disease due to or worsened by interferon treatment and gave examples of these conditions. If individuals had already successfully applied to the scheme and had been diagnosed with advanced cirrhosis, primary liver cancer had been offered a liver transplant or were in receipt of a liver transplant, had B-cell non-Hodgkin's lymphoma or had type II or 3 cryoglobulinaemia they would already present be receiving hepatitis C stage 2 annual payments.

91.6. The EIBSS stage 2 payment application form allowed applicants who had made a successful hepatitis C stage I application and had received payments from the scheme and believed they met the stage 2 criteria to apply. The latter criteria included advanced cirrhosis, primary liver cancer, receipt of a liver transplant (or be on the waiting list for one) had a B-cell

non-Hodgkin's lymphoma or type II or II cryoglobulinaemia accompanied by membranoproliferative glomerulonephritis.

92. Do you consider that more could and/or should have been done (and, if so, what and by whom) to reach potential beneficiaries and offer them support and assistance through the EIBSS?

92.1. This is beyond my knowledge.

93. In relation to new beneficiaries of the EIBSS, were any of the following adjustments considered or implemented:

a. backdating payments for first time registrants to (i) the date of diagnosis, (ii) the date of first eligibility for support or (iii) the date on which the EIBSS was established? If not, why not? This question should be addressed to the NHSBSA

b. providing exemptions or waivers as to documentary record requirements for first time applicants where records (i) have been lost/destroyed by an NHS body, (ii) are otherwise unavailable through no fault of the applicant or (iii) were not adequately created or completed in the first place? If not, why not?

93.1. The details of eligibility are set out on the England Infected Blood Support Scheme

93.2. Details of who could join the scheme are listed on the NHSBSA website. https://www.nhsbsa.nhs.uk/who-can-join-scheme-and-how-apply/people-infected-hepatitis-c-stage-1-payment. (I am unable to download a PDF exihibit) The scheme set out who would be eligible for a special category mechanism payment. Individuals would be eligible if their infection, it's treatment or social conditions have had a long-term negative impact on the individuals' ability to carry out daily activities, or the condition had worsened. The website specifies who would be eligible. This would include successful stage 1 applicants.

93.3. Support was available for individuals historically infected with hepatitis C from NHS blood or blood products and families, and civil or long-term partners after the death of someone infected. People could apply to join if they were infected with hepatitis C as a result of treatment with NHS blood, blood products or tissue prior to September 1991. Individuals infected with hepatitis C by someone who was infected through treatment with NHS blood, a blood product or tissue prior to September 1991 could apply for the payment. An eligibility check would need confirmation that the individual was chronically infected with hepatitis C (individuals could qualify if successfully treated) had not already received payments for hepatitis C infection from the Skipton fund or any other UK ex-gratia payment scheme, and it was probable that the individual was chronically infected with hepatitis C through treatment in England or by a British military hospital.

93.4. Discretionary support was also available for income top-up payments to increase household income in order to help with general living costs if registered as a brief spouse civil or long-term partner who lived with an infected beneficiary. It would seem that the stringent evidence for documentation were relaxed but my involvement with the scheme ended in 2018.

94. Please describe the extent to which the EIBSS had a digital presence when it was set up and since then, including details of key information on its website.

94.1. A web site existed. Digitised forms were available. However, this question with respect, should be addressed to applicants who needed to access the scheme, rather to the clinicians. I can only state that in a very short space of time the administrations and clinicians received and attempted to complete rapidly accumulating applications.

95. Explain your experience of the relationship between EIBSS and the Department of Health and Social Care ('DHSC'), and/or its arms-length body the 'NHS Business Services Authority ('NHSBSA'), and in particular:

a. As an arms length organisation, how much direction has the NHSBSA received from the Secretary of State for Health and Social Care and the DHSC in the design and operation of the EIBSS? The Inquiry understands that NHSBSA has both designed the process the EIBSS uses, and operates the scheme itself. How much input does the DHSC have into these roles?

95.1. My understanding is that the Department of Health and Social Care would have had input as described above into the process in an attempt to meet and overcome the shortcomings of previous financial payment schemes. Widespread consultation was sought, and a large number of respondents provided information and extensive input. My involvement was to advise on clinical admissibility and design of the application template.

b. To what extent does the EIBSS operate as a scheme independent of other NHS bodies, procedures and key personnel?

95.2. This question should be addressed to the administrators of the scheme. However, NHS personnel including physicians and nurses involved in the care of applicants are asked to provide supporting information

96. In your experience, Does the DHSC seek, or does the NHSBSA offer advice to the DHSC when DHSC is setting policy? Please include:

a. Some examples of when advice has been given and accepted.

b. Some examples of when advice has been given and rejected.

c. The process by which advice passes (i.e. is it sought out or is it offered, or a combination of both?).

d. A description of whether the advice is usually taken.

e. Whether reasons are given for rejecting the advice and, if so, in what form.

97. Have you, or others within the NHSBSA, raised any concerns and issues with the DHSC about the funding, structure, organisation or running of the EIBSS, or about the involvement of the DHSC, or about any other matter? If so, please explain what concerns and issues were raised. What was the response of the DHSC to those matters being raised?

97.1. In answer to questions 96 a to e and to question 97: the DHSC no doubt provided the kernel of advice to set the policy for the scheme to be administered by the NHSBSA. I am unaware of detailed interchanges and the passing of advice between these bodies. I can state that I sought certainty from the scheme and from the DHSC to interpret the criteria to be established for applications. The impression I obtained was that indeed a "light touch" was to be followed so that symptoms such as fatigue, depression, anxiety, impaired quality of life and other extrahepatic manifestations of hepatitis C could be considered as attributable to hepatitis C, or treatment, notwithstanding any other background life events or factors, thus removing the onus from physicians to establish causation and obviating a burden of proof from patients.

98. Please describe the process by which the NHSBHS receives funding from the DHSC.

99. What do you know about how the DHSC sets the budget for the EIBSS? Please describe any particular formula or methodology for calculation.

99.1. Answers to questions 98 and 99 should be addressed to the DHSC.

100. In respect of communication between EIBSS and the beneficiary community:

a. What steps, if any, has the NHSBSA taken to ensure that staff communicate appropriately with beneficiaries, applicants for support or assistance, and their families?

b. To what extent, if at all, has the NHSBSA responded to, and acted on, any complaints in relation to its working methods or in relation to the way in which it communicates with beneficiaries, applicants and their families?

c. Please provide a detailed account of the steps taken by the NHSBSA to engage with and understand the beneficiary community?

d. What is the relationship between the senior management of the NHSBSA and the beneficiary community?

100.1. Answers to question 100 a-d are best addressed to the beneficiary community and applicants to fully understand the acceptance or otherwise of the working methodology in place and of the detailed accounts of the steps taken by the NHSBS to promulgate the scheme between beneficiary individuals and their community representatives

101. As to substantive eligibility requirements set by the DHSC:

a. To what extent are the contents of the EIBSS Specification supplemented by internal policy or guidance documents used by the EIBSS?

101.1. My initial impression was that the contents of the EIBSS specifications were supplemented by internal policy and guidance documents.

b. In what form and how are substantive eligibility requirements provided to registrants and applicants for support from the EIBSS? To the extent that this is not done, why not?

101.2. The application form provided substantive eligibility requirements that appeared to be understood by the initial tranche of applicants whom I assisted.

c. To the extent that these requirements are only available with internet access, what adjustments exist to provide them in other formats?

101.3. A recent examination of the website suggest that forms can be posted, but this advice is given on the web. However, as I have not had any recent involvement with the support scheme the question is best addressed by others

d. Does the DHSC have a view as to the publication of policies about the eligibility criteria?

101.4. I would be grateful if this question could be addressed to the DHSC; their view would have set procedures for publication of policies about the eligibility criteria.

102. To your knowledge, have there been any issues, difficulties or concerns arising out of the application of particular cut-off dates of infection as an eligibility requirement? If so, what are they and how were they (or are they being) addressed?

102.1. I am aware of individual cases with a particular cut-off dates may have disadvantaged individuals, but I have assisted.

103. How are applicants alerted to the requirements for medical evidence? To what extent are they given the opportunity to re-submit revised reports or further documents before a final determination of their application (e.g. if the Medical Assessor considers there are likely to be evidential deficiencies or gaps)?

103.1. I have not recently addressed any applications. However, I am aware that further reports would be sought on occasion in order to satisfy eligibility. Patients and applicants were given an opportunity to resubmit revised reports.

104. Please explain your experience of the practical operation of the burden of proof on the applicant, and the standard of proof applied. Do you consider that these are fair, appropriate, and functioning well?

104.1. My experience was that individuals were given an opportunity to express the impact of their disease; many eloquently and completely articulated how the disease had marred their lives. The standard of proof required was low. As described, I sought clarity from the Department of Health, which was given, and therefore it was not necessary to dissect out the contribution of possible extraneous factors that may have contributed to the physical, and psychological impairment in overall quality of life that many individuals with hepatitis C described. Ascertaining the relative contributions of other factors would have been extremely difficult and would have posed an impossible bar both for applicants and medical adjudicators. Once this bar was removed, the system could be considered fair, removing some of the impediments to successful applications and the ceiling that had been applied to the Skipton Fund.

105. To what extent is the reason for lack of medical records relevant, i.e. does it matter whether an NHS body is responsible for destruction or loss of or failure to document relevant information or the applicant personally?

105.1. In many cases it was possible to overlook the lack of medical records in a manner that was not previously possible. A small number of applications required appropriate and responsible scrutiny.

Clinical practice and financial support schemes

106. In respect of your clinical practice:

a. To what extent did the Department and its staff inform patients about these different trusts or funds?

106.1. The large number of applications that arrived in a short space of time suggest that the Department and its administrators had informed patients and patient support groups. Publicity would have been assisted by appropriate patient and civil society support groups. However, I am unable to provide accurate data and a denominator to inform the overall percentage of individuals who were insufficiently informed and thus delayed.

b. Did the Department have any policy or any guidance for staff members in relation to referring patients to the trusts and funds for support?

106.2. The Department informed staff members of the Skipton fund of the transitional arrangements and we were involved in aspects of operational guidance as noted above.

c. What kind of information did the Department (whether through you or otherwise) provide to the trusts and funds about or on behalf of patients who were seeking assistance from the trusts and funds?

106.3. We had met with the Department to smooth out and advise on the application forms and background information.

d. Did the Department or any of its staff (including you), act as a gateway for determining whether a particular patient met the eligibility criteria for the receipt of assistance from any of the trusts and funds? If so, please explain who set the criteria, what they were and how they were applied.

106.4. Please see above. Our advice was sought regarding the setting of new criteria to guide the philosophy of reform that led to the inception of the EIBSS. I provided a detailed breakdown of the existing literature pertaining to quality-of-life indices, extrahepatic manifestations of hepatitis C and the effect of both interferon treatment, ribavirin and direct acting anti-viral therapy on health-related quality of life outcomes in hepatitis C (WITN3754091]; [WITN3754092] DOH Disease impact assessment part 2)

e. Was the Department or any of its staff (including you) involved in determining applications made by patients for assistance from the trusts or funds? If so, please describe that involvement.

106.5. At the outset of the scheme three clinical directors, including myself acted to quickly clear the large number of applications. Most applications were signed in person at Skipton house. If travelling, I asked that these be sent to me securely and the forms returned remotely to avoid delay. I was unable to continue after I was asked to act as an interim director at Public Health England because of my increased workload in 2019

107. The Inquiry has had sight of many sets of application forms and appeals submitted by individuals who had difficulty satisfying the terms of eligibility for financial support from the Skipton Fund Ltd, for lack of medical evidence to support their assertions about the circumstances of their infection with HCV. You are named in many such forms. In respect of this issue please:

107.1. With respect, I would also be named in many forms where applicants were able to satisfy the terms of eligibility. Each application was discussed and examined in detail. Where there was doubt, or possible discordance we exchanged independently gauged opinions. I believe that the medical directors acted within the confines and dictates of the system to discharge

their duty of care responsibly, but also empathically, to the Fund's applicants.

a. Provide, in so far as you are able to do so, your overall impression of the issues that patients faced in establishing eligibility;

b. Explain what your role was in individual applications concerning eligibility;

107.2. My role was to adjudicate each application on an individual basis taking into account all of the parameters that could be submitted in support of applications by patients, their witnesses and the physicians and nurses who had cared for them. Many were straightforward applications. Others were far more difficult to assess and patients had unfortunately to breast a bar set by the criteria, where, as detailed above the burden of proof could rest on the applicants. We brought no preconceived notions, bias or prejudice to these rulings. Wherever possible individuals were given the benefit of doubt based on an assessment. Many hours were spent examining the forms and the supporting documentation.

c. explain whether you considered there was any conflict between your role as an expert adviser to the Skipton Fund Ltd and your role as a clinician in providing information about individual patients eligibility for financial support from the Skipton Fund Ltd (for example, in the case of *R (on the application of Moore) the Skipton Fund and Secretary of State for Health* (2010) EWHC 3070

107.3. I was in invited to assist the Skipton Fund as a Medical Director. The Board would have been aware that I was an active practicing clinician and was indeed appointed to complement the existing expertise because of my familiarity with new treatments for hepatitis C and the direction of travel. No concerns were ever expressed regarding this fact. No concerns were expressed to me regarding my previous or ongoing employment and professional affiliation within the National Health Service.

107.4. Re: R (on the application of Moore) [DHSC0011378]

107.4.1. I provided an expert report in 2008, long before accepting the post of medical director at the Skipton fund. My duty was to the courts. I included a detailed examination of the natural history of acute hepatitis C and what was known of the kinetics of clearance of hepatitis C RNA during the acute phase as well as immune responsiveness and potential psychological consequences or stigmatisation. I gave a careful and guarded opinion that in rare instances, it was possible that a prolonged acute course of viraemia could not be ruled out but was impossible to prove or disprove in this patient. The patient was receiving prednisolone (an immunosuppressive drug) at the time of her transfusion. I had earlier indicated that absent blood tests it "is not possible to either deny or prove the supposition that persistence occurred for a period". I provided objective evidence from the literature to support the statements. I also forewarned that "it may be difficult to alter the Skipton's Fund's viewpoint that, under the scheme, restricts the right of compensation of individuals who have cleared the virus as a result of treatment or who have cleared it spontaneously after a period of chronic infection." And "that the scope of the Skipton's Fund criteria may prove a high barrier." The claimant was placed in a position that she was required to prove chronic infection.

107.4.2. It was impossible to prove the period of persistent infection in the absence of confirmatory test results, and to definitively state at which point in time the infection had been cleared. The rationale and documentation are available from the Department of Health and court records. Medical evidence would be required to prove persistent infection beyond the acute phase.

107.4.3. R vs Moore came to Judicial Review in December 2010. Justice Kenneth Parker ruled the ex-gratia scheme had been operated

rationally and lawfully. The application for a judicial review was not won. Thus, the test became a legal and a societal decision rather than a clinical judgement.

107.4.4. I joined the Skipton Fund in 2014 and was thus bound by the terms and judicial rulings that preceded my employment by several years.

d. Did your experience of providing such information for individual patients affect or inform your view of the eligibility and proof requirements that patients faced in establishing eligibility for financial support from the Skipton Fund Ltd?

107.5. My views were informed by the standards required of the fund, for legitimate disbursement, and clinical information. I acted responsibly within the framework of the Skipton's funds previously determined eligibility criteria. I relied on my clinical experience and nous, knowledge of the disease and its stages and clinical judgement to adjudicate eligibility and proof. My own know and experience was provided in tandem with the larger denominator of hepatitis C disease, its manifestations, routes of acquisition, serological diagnosis, and natural history and progression that formed the bedrock of the large number of applications

108. Based on your own dealings with any of the trusts or funds and/or based on your knowledge of the experiences of the Department patients in relation to the trusts or funds, do you consider that the trusts and funds were well run? Do you consider that they achieved their purposes? Were there difficulties or shortcomings in the way in which they operated or in their dealings with beneficiaries and applicants for assistance?

108.1. During my tenure the Skipton Fund was staffed by a conscientious, able and diligent administrative staff who I hope have had an opportunity to realise their talents subsequently.

108.2. The Skipton fund fulfilled its obligation to the applicants within the stated remit of the fund. The clinical directors had a circumscribed role. They

clinical directors had to maintain objectivity without losing compassion and empathy. The governance of the fund during my tenure was exemplary. The fund was led by an experienced and cerebral board. The shortcomings and dimensional bounds of the fund have been examined after wide consultation. A proportion of applicants were unfortunately disadvantaged and potentially damaged by these bounds. Reform followed.

Section 10: Other issues

Look Back

109. The Inquiry has had sight of many sets of correspondence concerning individual patients who were identified as likely to be HCV positive following the national HCV look-back programme of the mid-1990s, much of which was copied to or authored by you. In respect of this issue:

a. explain your role in the "look-back" exercises of the mid-90s both in terms of devising such a scheme and executing it clinically;

109.1. I was involved in devising some aspects of the look-back programme and in applications for funding the programme. However this program was only placed on a proper footing once promulgated by the Department of Health and conducted under the aegis of Public Health England.

b. Provide, if you are able to do so, estimates of the number of individuals who were referred to you as HCV-positive following a 'look back' exercise;

109.2. I believe there were a total of 18 patients at the Royal Free who were identified through the look-back programme.

c. Provide your overall views of the efficacy and consequences of the 'look back' exercise

109.3. The program functioned better once under the administrative control of Dr Helen Harris at the Health Protection Agency (Public Health England). Dr Harris would have sight of recent data and has published interim findings of the results as well as answered to Parliamentary questions.

d. Explain why, as far as you are able to, why no comprehensive "look back" testing programme has been introduced whereby all people at risk (those receiving a transfusion or blood products between 1970 and 1991) are traced and advised to seek a test.

109.4. Many infections with hepatitis C and hepatitis B remain undiagnosed. They remain an important source of potential future liver disease for infected patients and a potential source for the transmission of these infections in the community. It has been said that the failure to diagnose and treat larger numbers of patients with hepatitis B is a major public health failing of the 20th century. We have failed to garner and raise awareness for the appropriate interventions in patients with silent viral hepatitis. Testing access and linkage to care has been poor. There is an ongoing need to scale up screening and to provide interventions that will reduce the risk in the infected population. Patients with hepatitis B can be given appropriate counselling and testing and if required effective anti-viral treatment. Similarly, patients with hepatitis C irrespective of the stage of fibrosis could be offered DAA's and a comprehensive package of management could be offered to all individuals irrespective of this stage of disease.

109.5. The success of a screening program will depend upon raising awareness of chronic hepatitis B and C in the community to the same level of that of HIV and to promulgate public health advertising campaigns. Case finding is important. Important strides have been made in many regions of the UK. Civil Society and peer support have provided inestimable value. Once diagnosed early treatment is possible and outcomes of infection are affected by a delayed diagnosis.

109.6. Estimates of the number of patients living with underdiagnosed hepatitis B and C in England and the United Kingdom remain unsatisfactory. Linkage to care is consequently suboptimal. Some programs have begun, to provide computer aided algorithms with general practitioners to assess risk factors for hepatitis C and improve electronic health record prompting. I am unaware of a similar program for hepatitis B.

109.7. Scaling up diagnosis in primary care would be valuable. As noted above I have suggested linking testing for Covid-19 antibody to sentinel surveillance for blood-borne viruses. I am doubtful that government will find the wherewithal to activate the program or that the political engagement and dexterity exists despite the vast resources being expended for Covid-19 surveillance. Such a screening program would have to be linked to identified surveillance and to care.

109.8. Screening pregnant woman for hepatitis C would be a start. Government has never supported a single screening for hepatitis C for individuals born for example between 1940 and 1985 but is now supporting a limited scheme in selected general practices for targeted screening for those with risk factors for hepatitis C.

110. Please provide details of any complaints made about you (in so far as relevant to the enquiry's terms of reference) to your employer, to the General Medical Council to the health service ombudsman or to any other body or organisation which has a responsibility to investigate complaints Not Relevant

Not Relevant

110.1. **Not Relevant**

110.2. **Not Relevant**

110.3. **Not Relevant**

Not Relevant

I know of no complaints pending against me.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed _____

GRO-C

Dated: 20 January 2021

G Dusheiko

2021.01.20 10:33:14

Table of exhibits:

Date	Description	Exhibit Number
13 Nov 2020	Annotated bibliography	WITN3754049
5 Feb 2004	Letters regarding HCV infections	WITN3754050
Aug 2020	PHE guidance on workers with HBV/HCV/HIV	WITN3754051
20 Nov 1994	Letter regarding Chiron v Murex/Organon	WITN3754052
16 Nov 1990	Letter regarding Hepatitis B Inquiry	WITN3754053
Dec 2012	Interferon paper, Dusheiko & Wedemeyer	WITN3754054
20 Jul 1995	Letters regarding Hepatitis B prevention	WITN3754055
28 Jul 1995	Letters regarding Hepatitis B prevention	WITN3754056
13 Nov 2020	HPV Vaccination Programme Leaflet	WITN3754057
3 Nov 1994	HCV lookback letters	WITN3754058
3 Apr 1995	HCV lookback letters	WITN3754059
30 Apr 2019	Guardian article on Hepatitis C testing	WITN3754060
18 Sep 2019	Letter by Sir Brian Langstaff	WITN3754061
1 Apr 1993	HCV lookback letter	WITN3754062

29 Mar 1994	Ethical approval documentation	WITN3754063
10 Jan 2007	Conditions of ethical approval	WITN3754064
22 Feb 1995	Letter regarding FDA inspection	WITN3754065
22 Dec 1994	Letter regarding FDA inspection	WITN3754066
27 Sep 1995	Letter regarding FDA inspection	WITN3754067
21 Feb 1996	Letter regarding FDA inspection	WITN3754068
26 Feb 2001	Letter regarding FDA inspection	WITN3754069
15 May 2020	Email regarding Covid-19 testing	WITN3754070
24 Jun 2020	BMJ article, Dusheiko Foster & Agarwal	WITN3754071
Jan 2015	EPRI report, Brunton et al	WITN3754072
20 Jul 1994	HCV testing at the Royal Free Hospital	WITN3754073
Sep 2019	PHE Infectious Diseases Strategy	WITN3754074
13 May 2015	Email regarding cirrhosis treatment	WITN3754075
Undated	HCV and cirrhosis treatment article	WITN3754076
Undated	Hepatitis B article, Dusheiko & Lemoine	WITN3754077
2009	EASL Hepatitis B article	WITN3754078

6 Sep 1995	Letter regarding HCV article	WITN3754079
25 Apr 2000	Letter from Thalassaemia Foundation	WITN3754080
2019	Conflicts of Interest presentation	WITN3754081
21 Oct 2016	Skipton Fund expenses form	WITN3754082
6 May 2015	Skipton Fund expenses form	WITN3754083
Undated	APRI score notes, Lok	WITN3754084
Undated	Skipton Fund appeals process	WITN3754085
1 Sep 2017	NHS Report on HCV Retreatment	WITN3754086
29 Nov 2017	Email regarding HCV retreatment	WITN3754087
14 Feb 2014	Email regarding DOH workshop	WITN3754088
27 Nov 2013	Email regarding DOH workshop	WITN3754089
26 Feb 2016	DOH payments workshop notes	WITN3754090
Undated	HCV presentation part 1	WITN3754091
Undated	HCV presentation part 2	WITN3754092
17 Feb 2014	EPPI meeting notes	WITN3754093
5 Dec 2017	EIBSS documentation	WITN3754094

29 Sep 2020	Emails with GMC	WITN3754095
9 Jan 1996	Ribavirin article, Dusheiko et al	WITN3754096
23 Dec 1991	Letter regarding draft protocol	WITN3754097
1986	Treatment of chronic HBV paper	WITN3754098
1985	Treatment of chronic HBV paper	WITN3754099
12 Mar 1999	Royal Free: a single hospital experience	WITN3754100
Dec 2020	PHE Report: HCV in the UK 2020	WITN3754101
May 2020	PHE Report: HCV in England 2020	WITN3754102

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Endnotes

1 Fibroscan was first introduced in Europe in 2003.

2 [PRSE0002940]

3 "Although sobering with regard to cirrhosis, …these data provide a better long term prognosis for persons with chronic HCV infection than the gloomy view on outcome that has been expressed in recent press coverage of the topic. Setting aside the tendency for the press to focus on the sensational, it is not entirely surprising that they assume this position because, even among experienced hepatologists, there are wide ranges of opinions regarding the natural history of chronic HCV infection. This derives, quite evidently, from the confounding characteristics of HCV-related liver disease itself: attributes that were, in fact, noted at the very first description of what was then called non-A, non-B hepatitis. These features include the fact that disease onset is, for the most part, silent; that persistence of infection, occurring in 80% or more of acutely infected persons, also is largely asymptomatic; and that among those in whom disease progression transpires, 20 to 30 years generally elapse before overt liver disease is recognized". 16. Seeff LB. The natural history of hepatitis C-A quandary. Hepatology. 1998;28(6):1710-2.

4 Serum HCV RNA levels remained undetectable 24 weeks after the end of treatment in 84 patients (49 percent) in the combination therapy group, but in only 8 patients (5 percent) in the interferon group (P<0.001).

5 18 (36%) of the 50 patients in the interferon alpha-2b and ribavirin group had a sustained virological response compared with nine (18%) of the 50 patients in the interferon alpha-2b and placebo group (p = 0.047). At the 1 year follow-up the proportion of patients with a virological response was greater in the interferon alpha-2b and ribavirin group than the interferon alpha-2b and placebo group (42 vs 20%, p = 0.03),

6 The rate of sustained virologic response (defined as an undetectable serum HCV RNA level 24 weeks after treatment was completed) was higher among patients who

received combination therapy for either 24 weeks (70 of 228 patients, 31 percent) or 48 weeks (87 of 228 patients, 38 percent) than among patients who received interferon alone for either 24 weeks (13 of 231 patients, 6 percent) or 48 weeks (29 of 225 patients, 13 percent) (P<0.001 for the comparison of interferon alone with both 24 weeks and 48 weeks of combination treatment). Among patients with HCV genotype 1 infection, the best response occurred in those who were treated for 48 weeks with interferon and ribavirin. Histologic improvement was more common in patients who were treated with combination therapy for either 24 weeks (57 percent) or 48 weeks (61 percent) than in those who were treated with interferon alone for either 24 weeks (44 percent) or 48 weeks (41 percent). The drug doses had to be reduced and treatment discontinued more often in patients who were treated with combination therapy.

7 “At present, a long-term beneficial response to alpha-interferon occurs in only 10-25% of patients. The modest long-term response rate and the restricted recommendations for use of interferon leave several unresolved issues regarding therapy of this disease. Do patients with atypical, severe or advanced disease warrant therapy? What is the optimal dose and duration of treatment? How can one increase the response rate to interferon? How can one predict which patients are likely to benefit from therapy? Which patients are likely to relapse if therapy is stopped? Ultimately, what is needed to answer these issues are better techniques to assess HCV infection and monitor therapy as well as more effective and better-tolerated agents that can be used alone or in combination with alpha-interferon.” 104. Hoofnagle JH, Di Bisceglie AM, Shindo M. Antiviral therapy of hepatitis C--present and future. J Hepatol. 1993;17 Suppl 3:S130-6.

8 These findings make treatment of chronic viral hepatitis with a-interferon an attractive venture. Ongoing clinical trials of a-interferon with or without other antiviral or immunomodulatory agents in chronic type B hepatitis offer promise that a practical and beneficial therapy may eventually be developed for this important and common form of liver disease. 130. Davis GL, Hoofnagle JH. Interferon in viral hepatitis: role in pathogenesis and treatment. Hepatology. 1986;6(5):1038-41.

9 The first-generation protease inhibitors of hepatitis C virus, telaprevir and the separately we wrote are the “harbingers of important advances in the treatment of chronic H CV infection.” Improved response have been observed in previously untreated and previously treated patients who have failed pegylated interferon and ribavirin treatment. Although response rates in patients with cirrhosis are improved compared with peginterferon and ribavirin treatment they remain suboptimal. Inherited IL28B haplotypes continue to influence response rates. These advances have brought higher rates of cure but more complexity to the treatment of hepatitis C -a paradox of progress. A complex process of decision-making is required to assess the indications for treatment of naive and previously treated patients and for patients with mild disease versus those with cirrhosis or advanced cirrhosis.

Shortening of treatment to 24 weeks is a major therapeutic advance. The side-effects of treatment requirement management and intensive monitoring in some. Rashes (of varying grades of severity and duration) have been reported in 55% of patients treated. Most drug-related dermatitis has been mild to moderate in intensity. Therein lies the difficulty.

The risk of severe drug-related reactions requires careful longitudinal evaluation as telaprevir induced rashes rashes may progress somewhat unpredictably to a more severe drug related rash. Drug rash with eosinophilia and systemic symptoms occurred in 0.4% and Stevens-Johnson syndrome in 0.1% in clinical trials. The management of anaemia however has proved to be most problematic. Anaemia occurs with both telaprevir and boceprevir and is a class effect of the first generation PIs. The effect on haemoglobin is unfortunate adding to the haemolytic anaemia induced by ribavirin and the bone marrow suppressive effect of pegylated interferon. Haemoglobin concentrations of less than 10 g/L have been reported in one third of patients. The fall in haemoglobin requires ribavirin dose reductions or erythropoietin use. Approximately 2% of patients received a blood transfusion in clinical trials, although the number was higher (15%) in patients with cirrhosis in the French expanded access program. The requisite backbone of pegylated interferon means that other problems associated with pegylated interferon and ribavirin use - including

depression, psychiatric symptoms, worsening of liver function and severe infections still complicate a regimen including pegylated interferon and render a large group intolerant of pegylated interferon in illegible for treatment. Treatment failure with telaprevir or perceptive it is associated with the potential development of drug resistance. Common resistant mutations to boceprevir and telaprevir have been described. Current treatments will have a limited impact on disease if the stated aim is to treat very large numbers of infected persons to reduce the morbidity from liver disease caused by HCV. For several reasons there is a concrete expectation that first-generation PIs will be displaced in the not too distant future by a next generation of PIs with fewer side effects (in particular without anaemia) and more convenient daily or twice-daily dosing. What then? Are regimens of direct acting anti-virals for example a second-generation PI or NS5B polymerase inhibitor or NS5A inhibitor with pegylated interferon and ribavirin the future of hepatitis C therapy?

Interferon free treatment would seem to hold the key to the future. Proof of concept studies have established that interferon free cures are indeed possible…. There are several realistic all oral regimens and the therapeutic landscape is undoubtedly for ever changed for the better. Who should be treated now and who might best wait for treatment? Given this broad therapeutic landscape what is the most relevant and important group to treat now?

I then go on to discuss the indications for treatment given the unfolding horizon. How can more widespread treatment be applied? If the stated aim is to treat millions of patients to reduce the burden of disease how will this be afforded? Ground-breaking anti-viral treatment will have to be priced at a cost that society will bear and will not stifle innovation. Drug pricing currently shoehorns the cost of drugs to fit cost-effective thresholds, but budget reductions to cope with declining funding may lower the currently accepted thresholds. Higher prices will reduce the effectiveness of penetration of treatment into key cohorts of infected persons and will not provide the incentive to implement wider programs of ascertainment and treatment. High costs may negate community treatment algorithms and the involvement of general practitioners in treating “easy to treat patients” thus affecting screening policies.

Finally, high prices will impair the opportunity to treat millions of patients in resource constrained regions of the world for decades.

10 Penrose 35.221. "Even if one discounts Professor Cash's more exuberant observations on the impact of Dr Dusheiko's contribution, Dr Gillon's paper did disclose that look-back had been explored in the SESBT region. However, it may be, as Dr Gillon suggested, that despite his airing of the subject only Dr Dusheiko and 'one or two others' had their interest caught by it."

11 Justice Burton although finding against the transfusion service concurred with the professionalism of the transfusion specialists in his judgement. In his assessment he also agreed that "nothing that I shall say can, or does, reflect in any way on the personal dedication, professionalism, integrity and conscientiousness of those in the NBTS the ACVCB and the ACTTD who were involved in their own waiting exercise at that time"

12 "Since no confirmatory test for repeatably reactive anti-HCV EIA results has yet been developed the true frequency of HCV infection in our population remains to be determined. The use of the same recombinant antigen material-ie, that constituting the solid phase' material in the EIA-for a confirmatory test (eg, immunoblot) would not be satisfactory scientifically." 293. Kuhnl P, Seidl S, Stangel W, Beyer J, Sibrowski W, Flik J. Antibody to hepatitis C virus in German blood donors. Lancet. 1989;2(8658):324.. Seroconversion occurred relatively late post exposure. 294. Roggendorf M, Deinhardt F, Rasshofer R, Eberle J, Hopf U, Moller B, et al. Antibodies to hepatitis C virus. Ibid.:324-5.

13 (Penrose 31.92 to 31.117).

14 31.229 Penrose The first generation ELISA detected antibodies to HCV non-structural (c100-3) antigen. The second generation ELISA detected antibodies to a combined, larger, non-structural (c200) antigen and a structural (c22-3) antigen. The second generation RIBA test was a four-antigen test, in which two additional antigens

(c33c and c22) had been added to the first generation RIBA test (containing the c100-3 and 5-1-1 antigens).

15 From the minutes: The directors have, after considerable research, implemented a model for predicting the likely rate of development of cirrhosis for those coinfected with HIV which has enabled the number of such applications rejected for lack of evidence to be greatly reduced on the basis of objective criteria derived from the greater knowledge of the disease that is now available. The company will keep under review applications that remain unsuccessful because of lack of evidence. During the year the company made another substantial drive to find those who had yet to come forward to claim their stage to top up payment and had not previously been found using the contact details on file. As a result of these efforts, 152 valid applications were received, 72 from living applicants who also received backdated regular payments and 80 from the estates of people who had died. There remain 100 cases who have yet to come forward and cannot be traced using the information available to the company. The directors believe there may still be substantial numbers of potential applications in respect of people who died before 29 August 2003, where the estates are unaware of the existence of the scheme.

16 I was appointed in March 2014.