Witness Name: Professor Christopher Ludlam
Statement No.: WITN3428001
Exhibits: WITN3428002 – WITN3428018
Dated: 25 September 2020

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PROFESSOR CHRISTOPHER LUDLAM

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 12 December 2019.

I, Professor Christopher Ludlam, will say as follows: -

Section 1: Introduction

1. Name, address, date of birth, and professional qualifications.

1) My full name is Christopher Ludlam. I live at an address known to the Inquiry team and my date of birth is GRO-C 1946. My professional qualifications are set out fully in my *curriculum vitae* at WITN3428002.

2. Employment history, including the various roles and responsibilities held throughout your career, including dates.

2) I have set out my detailed career history in my *curriculum vitae* [WITN3428002] which gives details of each post I have held since I began my training in medicine in 1971.

3. **All memberships, past and 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) All relevant memberships are set out in WITN3428002, in my detailed *curriculum vitae*.

4. **Please confirm whether you have provided evidence to the, or have been involved in any other inquiries, investigations, criminal or civil litigation in relation to HIV and/or HBV and or HCV infections and/or vCJD in blood and/or blood products. Please provide details of your involvement.**

4) In the late 1980s several of my patients entered into litigation against my employer and I was involved in discussions and the production of reports around that litigation.

In 1990 I was invited to submit a report in respect of the English class action in respect of HIV and AIDS. This was produced to the Penrose Inquiry [PRSE0000332].

5) In the late 1990s a patient raised a litigation for damages in respect of Hepatitis C. I was consulted in relation to that matter and provided comment.

6) By virtue of a complaint to the General Medical Council ("GMC") by three of my patients I was required to respond to the GMC investigations. I did so in detail through my solicitor and the Medical Defence Union ("MDU"). I am aware that the Inquiry has recovered documentation from both of those organisations and will be aware of the detail.

7) In addition to that, two of the complainants made allegations of criminal conduct. After these were referred to the police, then Lothian and Borders Police, I was visited by and interviewed by the police. Subsequently, I received a letter from the Acting District Procurator Fiscal informing me that "no criminal proceedings will be taken against you following allegations of criminal conduct made by Robert Mackie and GRO-A. [WITN3428003].

8) I next provided extensive written and then oral evidence to the Penrose Inquiry held in Edinburgh. The oral hearings began on 8 March 2011 and closed on 30 March 2012. My written statements to that Inquiry are, I believe, all available to this Inquiry and my evidence is still publicly available.

Section 2: Statements provided to the Penrose Inquiry

5. Statements and documents provided to the Penrose Inquiry

9) I confirm I provided these documents to the Penrose Inquiry, either directly or through the Central Legal Office representing NHS Lothian.

6. Oral Evidence to the Penrose Inquiry

10) I gave evidence to the Penrose Inquiry on ten occasions between 30 March 2011 and 28 October 2011.

7. Please confirm whether the contents of the statements and oral evidence referred to in questions 5 and 6 are true and accurate. If there are any matters contained in the above statements or in the oral evidence you provided to the Penrose Inquiry that you do not consider true and accurate please explain what they are.

11) At the time that I gave the evidence referred to, both written and oral, the statements were made to the best of my ability. They were based on a much more recent recollection of events than I have now and were also based on documents I had to hand at that time. I have referred to many of these statements in this response and I believe them to have been true and accurate to the best of my ability.

12) I have read some of the transcripts of my evidence to the Penrose Inquiry to assist in forming answers to some of these questions. I have not had sufficient time to read all the transcripts in full and in detail. At the time I gave evidence for the first time I affirmed that I would tell the truth. I did so to the best of my ability. Each time I gave evidence on a subsequent occasion Lord Penrose confirmed I remained under affirmation. Again, I think that the evidence I gave in 2011 and

2012 was likely to be better evidence than I can give now, simply by virtue of its closer proximity in time to the events I am being asked about.

13) One error I am aware of in my evidence was that I initially referred to the meeting of patients which took place on 19 December 1984 as having occurred on 16 December. That error was corrected during my evidence.

Section 3: Decisions and Actions of the Haemophilia and Thrombosis Centre at the Royal Infirmary of Edinburgh regarding the use of blood products.

8. Please describe the roles, functions and responsibilities of the Haemophilia and Thrombosis Centre at the Royal Infirmary of Edinburgh ("the Centre") during your period as director.

Background

14) The Edinburgh Haemophilia and Thrombosis Centre has provided, within nationally prescribed arrangements, care for patients and families with haemostatic and thrombotic conditions. The Health Service in Scotland has for a long time been a devolved responsibility and was overseen directly by the Scottish Office's Scottish Home and Health Department (SHHD). Prior to 1980 Haemophilia Centres were established in Aberdeen, Dundee, Edinburgh, Glasgow and Inverness. In general, all these Centres participated in UK arrangements for service provision under the guidance of Health Circulars and other UK national guidance, e.g. HC (76) 4, SGX 92, Haemophilia Alliance National Service Specification, as well as UK Haemophilia Centre Directors Organisation (UKHCDO) activities and guidelines.

15) The arrangements in Scotland, however, have been different from the rest of the UK, in several aspects. All Haemophilia Centres in Scotland were given equal standing by SHHD but the directors of the two largest Centres in Edinburgh and Glasgow were enabled to attend the UKHCDO Reference Centre Directors meetings. The Reference Centres comprised a small number of Centres in England and Wales designated by the Department of Health as providing a very specialist service for haemophilia. The directors of the Reference Centres were responsible for leading the UKHCDO guidance for the provision of haemophilia services. It was welcome that representatives from Scotland could attend the

Reference Centre Directors meetings as this provided a conduit for coordination of services.

16) A further distinct feature of arrangements in Scotland has been close liaison between haemophilia centres, Scottish National Blood Transfusion Service (SNBTS) and SHHD. This took the form of regular meetings between these three organisations to coordinate developments. These arrangements included also representatives from Northern Ireland Department of Health, the haemophilia director for Belfast and the Blood Transfusion Service. This close relationship with Northern Ireland was because plasma collected in Northern Ireland was processed at the Protein Fractionation Centre in Edinburgh.

17) Another unique feature of the arrangements in Scotland and Northern Ireland was the setting up of regular meetings for all haemophilia directors to consider the development of the service. To this collaborative arrangement were added various national initiatives to develop particular aspects of the service, e.g. the establishment of the Factor VIII Working Party with SNBTS and SHHD to plan the development and manufacture of new treatments, and the setting up subsequently of the Recombinant Factor Consortium.

Edinburgh Centre

18) The Edinburgh Centre was thus developed within the SHHD overseen arrangements, but in conjunction with the activities and guidance of UKHCDO, and has provided a service under guidance provided by the Department of Health (DOH) (supported by SHHD) as itemised above. The Edinburgh Centre was and remains situated within the Royal Infirmary which is a university teaching hospital, and as such, the expectation of the provision of service to patients would be at the forefront of medical science. The principal responsibilities for adults and children were as follows:

a) Provide a clinical service for patients with heritable haemostatic disorders, including platelet disorders, and rare, usually single coagulation factor acquired disorders, e.g. acquired haemophilia

b) Provide a 24-hour treatment service for acute bleeds

c) Provide for review and clinical monitoring of patients as appropriate

d) Provide prophylaxis for appropriate patients

e) Ensure good co-ordination with other specialties, e.g. virology and infectious disease, hepatology, orthopaedics and physiotherapy, dental, obstetric and gynaecological services, usually by holding regular combined clinics with these specialists at the Haemophilia Centre

f) Ensure appropriate therapy was available

g) Maintain treatment records

h) Register patients on National Haemophilia Database and send in annual treatment details and other appropriate details, e.g. causes of death

i) Issue Haemophilia Cards

j) Maintain and hold available medical records

k) Provide advice and counselling for patients and their families in relation to bleeding disorders and their complications, genetics, social and psychological support, school and employment advice and as necessary visits

l) Provide laboratory services able to perform appropriate assays for coagulation factors and other assessments of the coagulation system, quantitate acquired coagulation inhibitors, undertake assessment of platelet function, assay coagulation inhibitors. The Laboratory also provided the haemophilia specialist genetic service for Scotland which was responsible for characterising each patient's genetic variant, and for identifying carriers. The laboratory participated in the National External Quality Assessment Scheme (NEQAS) for blood coagulation.

m) Provide teaching for medical, dental, nursing, physiotherapy staff and students and laboratory staff

n) Undertake research and participate in clinical trials

19) The Centre also had specialist expertise in the field of thrombosis, its prevention and treatment, particularly venous thromboembolism. This field covers much medical practise, as many patients in hospital are predisposed to venous thrombosis and pulmonary embolism. The Centre's expertise was in advising on the writing of national guidelines, e.g. in Scotland the SIGN guidelines prepared by the Royal College of Physicians, as well as preparing and implementing local guidelines. Patients with difficult acute and chronic thrombotic problems were referred to the Centre for advice.

9. Please describe your role and responsibilities as director of the Centre

Introduction

20) I was appointed to the post of consultant haematologist to South Lothian in 1980. My remit was, along with one other consultant colleague, to provide a clinical and laboratory haematology service directly for 'south Edinburgh'. At that time, as a consultant, my responsibility was to help lead the service, whereas today the emphasis is much more on consultants providing the service. The clinical work-load comprised patients with haematological conditions living within the broad geographical area of south-east Scotland.

21) My role as director of the Centre was to enhance the provision of services for patients with heritable bleeding disorders and this role continued for the following 30 years. Acquisition of appropriate resources, whether staff, physical facilities, or clotting factor concentrates, required considerable investment of time in order to participate in very full and at times protracted discussions and negotiations. In 1980, I was assisted by a registrar who also helped with all the other clinical and laboratory activities I was responsible for. In 1982, a Haemophilia Sister was appointed. In 1986, two Clinical Assistants were recruited, two further staff nurse and a secretarial post were created. Later an Associate Specialist and a further consultant were appointed. With these increasing numbers of staff being recruited it became important that I ensured they were appropriately knowledgeable and supported, especially during some of the more challenging aspects of service provision. I produced a staff list at the time of the Penrose Inquiry which I append [WITN3428004].

Background to haematology service at the Royal Infirmary of Edinburgh

Clinical Service

22) The clinical service was dominated by the large number of patients with malignant disorders, e.g. acute and chronic leukaemias and lymphomas. There were also patients with a wide range of non-malignant conditions, e.g. anaemias. The clinical service also provided advice, and, when appropriate, direct, management for patients within the hospitals in south Edinburgh, particularly the Royal Infirmary, who presented with problematic or acute haematological features, e.g. acute haemorrhage. The patients with hereditary bleeding disorders were a relatively small but important component of the clinical case load.

23) When I was first appointed, patients with leukaemias, lymphoma and bleeding conditions were seen at my out-patient clinics in the Medical Out Patient Department in the hospital. Patients requiring admission were accommodated under my care in the general medical ward, wards 23 (males) and 24 (female). We offered 24-hour open access for patients with hereditary bleeding disorders to Ward 23 to attend for treatment of acute bleeds.

Laboratory Service

24) The haematology laboratory at the Royal Infirmary was reputed to have one of the largest work-loads of any hospital laboratory in the UK. It provided a service for all the hospitals and GPs in south Edinburgh and included performance of large numbers of routine blood counts and blood coagulation tests for control of oral anticoagulants. The laboratory provided specialist investigations for diagnosis and management of leukaemias and bone marrow transplantation. The coagulation laboratory undertook a range of routine investigations for patients with, or at risk of, acute haemorrhage, as well as specialist tests for patients with hereditary bleeding and thrombotic conditions. One of the medical responsibilities was to alert clinicians to serious abnormalities that were detected during the processing of the blood samples for both hospital and GP patients.

I was responsible for ensuring that the performance of the laboratory was acceptable and therefore arranged participation in the UK National External Quality Assurance Scheme for Blood Coagulation. Later with the establishment

of Clinical Pathology Accreditation we were one of the first UK laboratories to be accredited. We were also invited by National Institute for Biological Standards and Control to participate in the arrangements for the calibration of World Health Organisation international standards of clotting factor concentrates.

Teaching and Research

25) As the Royal Infirmary was a teaching hospital, and especially as I was appointed as a part-time senior lecturer at the University of Edinburgh when I took up my appointment, teaching, particularly for medical, nursing and dental students, about bleeding disorders was an important activity. This was carried out by formal lectures, clinical demonstrations, teaching ward rounds and tutorials. Authoring publications was also an important route through which experience could be shared. An essential responsibility of a Comprehensive Care Centre is to undertake research to enhance the care of people with haemophilia and their families.

Service for patients with hereditary bleeding disorders in the early 1980s

26) When I took up my appointment I was keen initially to develop the record keeping arrangements and improve the facilities in ward 23 for treating patients with acute bleeds. A relatively small room at the entrance to the main ward was designated as the 'Haemophilia Centre'. Patients were seen there at presentation with acute bleeds or other presenting medical conditions. As only a very few patients were on home therapy, each morning there was a group of patients in the room with acute bleeds requiring assessment and treatment. It was my responsibility, along with my registrar, to see these individuals and arrange treatment. By this means I quickly got to know the majority of individuals with severe haemophilia. It was readily clear that the physical arrangements in the ward were suboptimal particularly in relation to patient privacy, arrangements for managing the patients, and the availability of medical records.

Initial improvements to service

27) I addressed these shortcomings by seeking and acquiring funds to arrange for the 'Haemophilia Centre' room to be divided to accommodate a compact consultation

room with examination couch, a sink and work surface and space for two filing cabinets for the most recent volume of each patients' medical records, and a small 'waiting and treatment' area. The waiting area had a notice board for Haemophilia Society and the local haemophilia group notices. The Haemophilia Society routinely sent multiple copies of its bulletin and other publications and these were placed in the waiting area for patients to read and take away.

28) There was a requirement for a 'Haemophilia Sister' and for greater input from the ward 23 nurses into the out-patient and in-patient management of patients. At this time, it was common for there to be 4-5 individuals with haemophilia as in-patients. After negotiations with the nursing service and the Health Board, I eventually secured funding for the post of 'Haemophilia Sister', and Iona Philp, with an 'extended' nursing role, was appointed in 1982 These innovations markedly enhanced the arrangements for the reception of patients during the working day in ward 23.

Out of Hours Service

29) It was important for there to be a responsive out-of-hours arrangement for patients attending ward 23. This was provided by the House Officer on call for ward 23, the on-call haematology registrar and the consultant. The consultant was required to be available one night in two and on alternate weekends, and continuously when my consultant colleague was on leave. It was uncommon for known local patients to attend the hospital's Accident and Emergency department, but if an individual with haemophilia, or someone suspected of having haemophilia attended there, the duty haematology registrar was contacted for advice.

Routine Review of Patients

30) Routine review of patients was undertaken at my haematology clinics in the Medical Out-patient Department. In an attempt to be of greater assistance to patients I set up, with my secretary, an evening clinic in ward 23, because I was keen that as much as possible patients should not miss time from work or school. This arrangement appeared initially successful, but after some time attendance declined. On inquiry of the patients I was told that they would rather attend during

the day, and this proved a learning experience for me about the importance of seeking users' views.

31) At this time we held combined clinics with an orthopaedic consultant in the Medical Out-Patient Clinic. At the routine haemophilia review appointments all patients were seen by a physiotherapist and records kept of their joint goniometry measurements. Social work input was provided by an identified social worker who was based within the hospital. There was good liaison with the hospital oral surgery department.

Arrangements for Cryoprecipitate or Concentrate Therapy

32) Treatment with cryoprecipitate or concentrate was held by and issued from the SNBTS blood bank in the Royal Infirmary. Initially, most treatment of out-patients was with cryoprecipitate because of a paucity of concentrate. As cryoprecipitate was stored deep frozen, prior to use it had to be thawed at 37 degrees centigrade and about 20 donations pooled to make up one dose of treatment. This all took considerable time, together with the portering delay in getting the made-up cryoprecipitate conveyed from the blood bank to ward 23. To address this, we asked patients to phone in to let us know of their intending arrival, so that hopefully the cryoprecipitate would be available on their arrival at the ward. Many patients were brought to the hospital with acute bleeds by ambulance and after infusion with cryoprecipitate had to wait an appreciable time for an ambulance home. Some individuals might attend several times in a week either with persistent or recurrent bleeds.

33) The few patients who were on home therapy with concentrate used to telephone the haematology registrar when they were running short and arrange to collect a new supply from the hospital blood bank. Following the appointment of the Haemophilia Sister this became one of her responsibilities; the home treatment was collected from her in ward 23. This had the great advantage that there was an enhanced way of monitoring patients treating themselves at home, particularly to ensure that bleeds had settled and were not persisting.

34) A small number of patients, e.g. those with inhibitors, required to be treated with commercially produced concentrates. I negotiated their purchase at discussions with the Lothian Health Board.

Safety of therapy for patients with heritable bleeding disorders

35) One of my responsibilities was to provide a treatment which was as safe as possible with the resources potentially available. My aim was to give priority to use of blood products produced in Scotland, for reasons set out elsewhere, although this was to the detriment of being able to give home treatment to all the patients requesting it. To optimise supply of therapy for treating haemophilia A, I had strategic discussions with SNBTS both locally, within the Royal Infirmary, and at a national level. I continued and further developed arrangements established by my predecessor for the monitoring of patients for the side effects of treatment, including retrospective assessment of the safety of clotting factor concentrates.

Wider responsibilities for haemophilia in the early 1980s

SHHD, SNBTS and Haemophilia Director Meetings

36) The SHHD provided the framework for collaboration, between its activities and responsibilities along with SNBTS and Haemophilia Directors for Scotland and Northern Ireland, by convening regular meetings to consider arrangements for the provision of the service for patients.

Haemophilia Directors for Scotland and Northern Ireland

37) In 1983, because of the need for more frequent meetings to consider issues related to provision of the service to patients, Dr George MacDonald (Co-director Glasgow Haemophilia Centre) was invited to convene these meetings. In 1985, I was invited by SHHD to lead meetings of Haemophilia Directors for Scotland and Northern Ireland. These meetings took place every few months and developed co-ordinated arrangements for haemophilia care. This was a unique arrangement within the UK for collaboration between local providers of haemophilia services. Subsequently, Professor Lowe joined me as the co-chairman and for over 20

years these regular meetings successfully provided the development of co-ordinated arrangements for patients.

UKHCDO

38) After taking up my appointment in 1980, I was invited to join the UK National Haemophilia Reference Centre Directors Committee. My predecessor was a member of the Hepatitis Working Party, under the chairmanship of Dr John Craske (virologist), and I was invited to join the Working Party when I took up my appointment.

Developments in the mid-1980s

39) With SHHD and SNBTS collaboration I was able to obtain an increased supply of locally produced factor VIII concentrate which allowed me to fulfil the patient desire for greater availability of home treatment. My active programme for monitoring the safety of blood products allowed early recognition of the exposure of patients to HTLVIII towards the end of 1984 and the almost immediate introduction of heat treatment in Scotland, followed by and the decision nationally to recommend the use of such concentrates throughout the UK. As a result there were no further infections by clotting factor concentrates with HTLVIII in Scotland.

Move of Haemophilia Centre from Ward 23 to Ward 45

40) As a result of the identification of HTLVIII exposure, there was an immediate need to provide greater monitoring of patients, and to offer information and counselling. This applied to both those exposed to HTLVIII and those in whom there was no evidence of exposure. The minimal 'Haemophilia Centre' room in ward 23 was quite inadequate to fulfil these requirements and there were insufficient medical, nursing and other staff available to review the patients. This necessitated a major enhancement to the service, the process of achieving this is detailed below. Eventually, in 1986, this led to the move of the Centre from a single room in ward 23 to a suite of rooms at the entrance to Ward 45, consisting of a patient waiting area, treatment room, Sister's office, two consulting rooms, doctors' office,

reception/office and seminar/meeting room. Two further doctors were appointed along with additional nursing staff.

41) The new Centre was geographically situated a long way on the Royal Infirmary campus from ward 23, the Department of Haematology and the blood bank, which led to challenges in keeping the service together. To assist in this, I promoted the development of, what at that time was, a unique computer arrangement that enabled the results of investigations and treatment to be available at the different hospital locations. (This innovation resulted in an invitation to form and chair a hospital computer committee to promote their use.)

42) During the early days of HTLVIII, much counselling was provided by the medical and nursing staff, the social worker, and later by the Clinical Psychologist, whose post I had helped establish and appoint. This was a very difficult and stressful time for patients and all staff. Further details of the difficulties and arrangements are described in the response to Question 86.

Monitoring of Patients

43) The routine monitoring arrangements of patients at the Haemophilia Centre was enhanced following the first reports of AIDS and immune abnormalities in patients with haemophilia. In addition to the previous routine investigations, there was a need to increase the surveillance of the immune and virological status of all patients. As the necessary laboratory investigations were not available routinely in the NHS, additional resources were sought and acquired to do this from providers of research funds. With the arrival in Edinburgh of HTLVIII, a completely new, severe, disease, there was an urgent need for all the potential providers of resources, e.g. Lothian Health Board, University of Edinburgh, and SHHD, to collaborate, and I took part in many meetings and activities to promote the necessary infrastructure developments.

Arrangements for patients to be managed safely

44) Due to press publicity, it quickly became known that some individuals with haemophilia attending the Royal Infirmary had been exposed to HTLVIII. These were the first group of individuals known in Edinburgh to have been so exposed.

There was immediately much anxiety amongst some clinical and laboratory staff about their own vulnerability to infection. As the difficulty involved the patients in my care I gathered together a group of colleagues who could advise staff about appropriate safety procedures. In early 1985 this became the Lothian AIDS Advisory Committee which I was invited to chair. Following discussion and consultation we developed arrangements for managing patients who presented a 'risk of infection'. One of our principal tasks was to respond to concerns and inquiries from a wide variety of clinical and laboratory facilities, including surgery and dentistry. Guidelines were developed and disseminated. The activities of this committee were important to ensure that staff were safe and patients were able to access all necessary investigations and procedures.

Medical management of people with Haemophilia infected with HIV

45) In 1985, there was no specific therapy for those infected with HIV, and the patients were keen to continue to be evaluated at the Haemophilia Centre rather than being referred to the Infectious Diseases Unit. For much of each patient's life the Centre had often provided a GP-type service for ailments, as well as treatment for bleeds. This arose because it was not always immediately clear when a patient's symptoms might be due to a bleed, and many GPs were ill-equipped to offer advice. As a haematologist looking after patients with leukaemia, I was very conversant with preventing and treating 'opportunistic infections', e.g. candida and pneumocystis carinii infections. These were the commonest serious infections arising in individuals with HIV infection. Initially therefore, because the patients were keen to remain under the care of the Haemophilia Centre and because we were experienced in managing immunosuppressed patients, we provided the out- and in-patient care at the Centre and in ward 23. Other clinicians developed expertise in the management of HIV infected patients. I was keen not only to learn from their experience, but it was also important that such expertise was made available to those with haemophilia. Dr Ray Brettle, Infectious Diseases consultant, who had experience of treating patients in New York, developed a service at the City Hospital in Edinburgh. He generously came to the Haemophilia Centre where we discussed each patient's situation in detail and he offered management advice.

46) When treatment with prophylactic pentamidine inhalations became recommended we had an adjacent room at the Centre converted with suitable pumps and air

extraction facilities to enable appropriate patients to receive this therapy. After some time, it was superseded by regular oral cotrimoxazole a much more acceptable and equally effective therapy. To be able to offer as many therapeutic options to patients as possible, I made application to the MRC to involve our patients in the clinical trial of AZT.

47) Subsequently further medicines were developed to treat HIV and at this point I considered that this aspect of their therapy should be under the direct guidance of a physician with extensive experience of treating HIV. Dr Brettle therefore agreed to take over the management of this aspect of the patients. Although this was, from my perspective, optimal and medically preferable for the patients, I did appreciate some of the patients' reluctance to attend another clinic in a different hospital with a varied clientele.

Genetic Services

48) One of the important responsibilities of a Haemophilia Centre is to advise individuals about the risk of being a carrier of a heritable bleeding disorder. In Edinburgh this clinical and laboratory service was provided in collaboration with the Department of Clinical Genetics at the Western General Hospital. Following the identification and characterisation of the factor VIII and IX genes, genetic techniques were developed to identify carriers more accurately by DNA technology. I promoted assessment and use of this technology, including later, the identification of individual patient genetic variants. The Royal Infirmary Haematology Laboratory became the designated laboratory to provide this service for Scotland. Patients and families were offered the clinical service both at the Haemophilia Centre and at the Department of Clinical Genetics for those who wished to be seen in a non-haemophilia environment.

49) In 1993 I was invited by UKHCDO to chair its Genetics Working Party. It developed and published national guidelines on arrangements for service provision which were subsequently updated to take into account the rapid developments in gene technology [1].

Development of new blood products

50) Following the introduction of SNBTS factor VIII concentrate heated at 80 degrees for 72 hours, there was a need to develop new concentrates within Scotland. To consider how this should be undertaken I was invited by SHHD in 1988 to convene a Coagulation Factor VIII Working Party which consisted of senior representatives of SNBTS, Haemophilia Directors, and SHHD. This Working Party developed arrangements for the manufacture and assessment of an ion exchange, purified, solvent detergent, treated factor VIII concentrate [2]. Subsequently an additional heat-treatment step (80-degree, 72 hour) was added to the manufacture to enhance safety.

51) Subsequently, the working party's remit was broadened to include factor IX concentrate development and it was renamed Coagulation Factor Working Party for Scotland and Northern Ireland (CFWP). This became the principal arrangement for reviewing concentrate development and use within Scotland and Northern Ireland.

Developments from the mid-1990s

52) I became involved with some important developments nationally in relation to blood safety in the mid-1990s which impacted on the provision of haemophilia care in Edinburgh.

Introduction of recombinant concentrates

53) I was invited in 1996 by UKHCDO to chair a Working Party to update the UKHCDO Therapeutic Guidelines [3]. The principal recommendation, which was controversial, was to recommend the preferred use of recombinant concentrates. In 1996, Scotland became the first country in the UK to introduce recombinant concentrates partly due to the generosity of SNBTS, which offered to donate £1 million and SHHD committed to provide further funding. A national committee, the Recombinant Coagulation Factor Consortium, was established to oversee their introduction to be led by a Health Board General Manager. Clinical guidelines for the introduction of recombinant concentrates were devised by Haemophilia Directors for Scotland and Northern Ireland. Recombinant and other concentrate

contracting and purchase was subsequently overseen by National Services Scotland.

54) Subsequently, in 2003 [4], I was invited to lead the update of the published UKHCDO therapeutic guidelines.

Blood safety in relation to variant CJD

55) As chairman of UKHCDO, in 1996 I became concerned about the possibility that variant CJD (vCJD) might be transmissible by blood products. I convened a major meeting of experts and stake holders, and as a result of discussions the UKHCDO Executive Committee proposed that it might be safer for plasma-derived concentrates to be manufactured from plasma collected in countries without vCJD [5]. This was at a time when there was no public consideration of the safety of blood in relation to vCJD. Initially, this was a very controversial proposal but subsequently it was accepted and supported by the Department of Health, Committee on Safety of Medicines and the blood transfusion services. As a result, the use of UK-sourced blood products was suspended and they were replaced by imported ones. UK plasma fractionation facilities substituted plasma from non-UK countries for the manufacture of clotting factor concentrates.

56) Thereafter discussion took place with 'Public Health England', the national CJD Surveillance Unit, and UKHCDO to agree on appropriate surveillance arrangements. Patient information was developed by Public Health England which Haemophilia Centres were requested to send to patients.

57) In Edinburgh we responded to patients who indicated they wished further information or counselling after receiving the information packs sent to patients.

Move of Haemophilia and Thrombosis Centre to New Royal Infirmary in 2003

58) During the planning of the new Royal Infirmary I was much involved in discussions about whether the Haemophilia Centre should move to the new hospital in the south of Edinburgh, or instead to the Western General Hospital in the north of the city. It was decided to accommodate it at the new Royal Infirmary where reasonable accommodation was offered. From a patient perspective there was

easy access from especially reserved 'haemophilia' parking spaces close to the ground floor entrance and a light and spacious waiting area, with a play area for children. The treatment, consultation, and office accommodation was good. One disadvantage was that it was situated a long way from the haematology laboratory.

References in respect of Question 9

1. Ludlam, C.A., et al., *A framework for genetic service provision for haemophilia and other inherited bleeding disorders.* Haemophilia, 2005. 11(2): p. 145-63.
2. Ludlam, C.A., G.D. Lowe, and E.E. Mayne, *A pharmacokinetic study of an ion-exchange solvent-detergent-treated high-purity factor VIII concentrate. Haemophilia Directors for Scotland and Northern Ireland.* Transfus Med, 1995. 5(4): p. 289-92.
3. UKHCDO, *Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders.* Haemophilia, 1997. 3: p. 63-77.
4. UKHCDO, *Guidelines on the selection and use of therapeutic products to treat haemophilia and other hereditary bleeding disorders.* Haemophilia, 2003. 9: p. 1-23.
5. Ludlam, C.A., *New-variant Creutzfeldt-Jakob disease and treatment of haemophilia. Executive Committee of the UKHCDO. United Kingdom Haemophilia Centre Directors' Organisation.* Lancet, 1997. 350(9092): p. 1704.

10. Approximately how many patients with bleeding disorders were under the care of the Centre when you became director? (If you are able to give exact rather than approximate figures, please do so).

59) My recollection is that there were about 40-50 patients with severe bleeding disorders under the care of the Centre. I cannot provide an exact number, but there were approximately 150-200 patients with non-severe bleeding disorders.

11. What decisions and actions were taken, and what policies were formulated, by you and by the Centre, regarding the manufacture, importation and use of blood products (in particular factor concentrates) during the time that you were director?

Introduction

60) During the 30 years I was director of the Centre many decisions were made about the use of blood products. The Centre was responsible for patients with a wide variety of heritable bleeding disorders mainly due to coagulation disorders, but there were also some patients with congenital platelet conditions. Although many

of the patients had haemophilia A and B, there were individuals with other coagulation disorders, e.g. hypodysfibrinogenaemia, factor XI, and factor XIII deficiency. There were also patients with von Willebrand Disease. The Centre was also responsible for providing care for patients with some rare acquired conditions, e.g. acquired haemophilia, which were often challenging to manage. All these patients required different treatments with platelets or clotting factor containing products.

61) Therefore, over this 30-year period, there were many changes in the treatments available to this broad group of different patients and I tried to be vigilant to the changing landscapes of benefit and risks. I shall describe some of the factors that I took into consideration when monitoring treatment arrangements which I hope will address the very broad question set out above.

62) The legal basis for the issue and prescription of blood products and medicines has changed since 1980. Apart from the ability to prescribe licensed medicines, there was the option to use medicines outwith a licenced use, either on the basis of a CTX, DDX or on a 'named patient basis'. Additionally, some therapeutic products were produced and issued under the system of Crown Immunity. These matters had to be considered when making clinical decisions.

63) Treatment decisions: in many instances the choice of treatment depended greatly on the precise date that it was made. For example, there was a general assumption in the early 1980s that NHS clotting factor concentrates were probably safer than those derived from commercial sources, yet in 1997, following the recognition of vCJD, there was a view that non-UK concentrates might be safer [1]. Furthermore, many decisions had to be made with incomplete information. Today's world, with the facilities offered by the internet, is a very different environment from that of the 1980s. Some decisions had to be made by trying to balance different risks, e.g. the decision to heat-treat concentrates.

64) The use of blood products was influenced by guidelines, particularly those developed by UKHCDO, which were periodically updated. Within Scotland, the use and availability of potential treatments was under regular review by the Haemophilia Directors for Scotland and Northern Ireland, the Coagulation Factor Working Party, the Recombinant Clotting Factor Consortium for Scotland, and in regular meetings with SNBTS and SHHD.

65) For plasma-derived concentrates decisions about use of a particular one depended on a wide variety of factors including:

a) **Source of clotting factor.** Until the advent of recombinant concentrates, most clotting factor concentrates were manufactured from human plasma.

Since 1980, the only non-human other source of factor VIII was porcine – this had a particular place in the treatment of patients with anti-factor VIII antibodies.

b) **Blood donor selection criteria.** This is an important topic for which the criteria have changed markedly over the past 40 years. Although in the early 1980s volunteer UK blood donors were viewed as being a relatively safe source of plasma, compared with US paid donors, the situation changed radically in 1997 with the appearance of vCJD.

c) **Screening processes used to monitor the donations for the presence of infective agents.** This is a complex and technical field; the techniques have developed and changed over time. Edinburgh studies demonstrated that despite screening donations for hepatitis B, this virus could still be transmitted by blood products [2-5]. Issues relate to the susceptibility to infection; for example, it appears that only a small dose of hepatitis B virus will result in infection in a susceptible individual, whereas a larger dose may be necessary in the case of another virus. The sensitivity of the tests to detect contaminating viruses may therefore need to be different for different viruses. Techniques have evolved over time to increase their sensitivity. For example, the initial screening for HIV was by anti-HTLVIII testing, but this failed to detect the early months of infection prior to antibody response, and it was only with the subsequent introduction of nucleic acid testing (NAT) techniques that this was addressed.

Although it was important to note the presence of viruses it was also sometimes critical to consider the significance of the presence of virus neutralising antibody in some donations. When pooled with donations that were contaminated by the relevant virus, it might have neutralised, so preventing infection in recipients, or exclusion of the virus-antibody complex by the manufacturing process.

As well as bearing in mind the techniques being used to screen donors, it was necessary to be alert to potential known viruses which might be undetected or resistant to some viral inactivation techniques. Parvovirus is an important example of this and because, if it mutated to be more pathogenic agent (as happened with canine parvovirus), it could pose a very serious threat to patients. Additionally, there was a requirement to be vigilant to new infectious agents that might be transmissible by blood; West Nile virus was a pertinent example. It was readily transmissible by blood, but fortunately susceptible to all the existing viral inactivation processes which meant that it was not transmitted to the recipients of clotting factor concentrates.

d) **Manufacturing Process.** Leaving aside the manufacture of cryoprecipitate and fresh frozen plasma (considered elsewhere), over the past 40 years, clotting factor concentrates have changed very radically from relatively low purity plasma-derived products, through to much higher purity concentrates. Although recombinant concentrates appear to be 'plasma free', the initial ones used plasma constituents in the manufacturing process as 'nutrients' or as an excipient in the final treatment vial, e.g. human albumin.

Briefly stated, the techniques used to purify clotting factors during the manufacturing may tend either to enrich or to exclude contaminating viruses; this will vary between viruses.

Some of the factors that need to be considered in reviewing manufacturing processes include evidence that the clotting factor being purified retains its 'native' structure, can prevent and treat bleeding in patients, and does not develop neoantigens which stimulate the production of inhibitory antibodies in the recipients, as has been reported arising from minor modifications to the manufacturing process [6, 7].

Clotting factor purity has been an important topic in the assessment of clotting factor concentrate manufacture over this period, particularly during the 1980s. In the early part of that decade concentrates were of relatively low purity, with the bulk of the material in the therapeutic vial being non-clotting factor proteins, e.g. fibrinogen and immunoglobulins. The significance of the purity to recipients was the subject of intense concern, described in detail in response to Question 21. The advantage of a higher purity concentrate was

that it was usually easier to dissolve when diluent was added to the vial. It was usually possible to increase the concentration of therapy and thus reduce the volume of infusion. These were important considerations when arranging treatment for patients at home and for treating small children, in whom a small infusion volume is easier to administer. One of the drawbacks of increasing purity is that often in the manufacturing process there were greater losses of the clotting factor, i.e. the yield of clotting factor available for treatment was reduced. As a consequence, in an NHS facility there might be less clotting factor manufactured which would have an impact on the 'self-sufficiency' target.

In the late 1980s, there was a view that prognosis of HIV infected patients might be adversely affected by the non-clotting factor plasma proteins in the therapeutic concentrates [8]. This was very difficult to investigate in the context of many HIV infected patients starting to develop symptoms. Our clinical monitoring studies to try to assess the influence of purity within the UK context did not demonstrate an effect [9, 10].

e) **Viral Inactivation Techniques**

Although there had been research prior to December 1984, both in Scotland and elsewhere, it was not until this date that a specific viral inactivation step was introduced into the manufacture of clotting factor concentrates. As is well described elsewhere, the viricidal processes of both heat and solvent-detergent treatment were introduced. There was much greater and earlier recognition that the solvent-detergent was effective against HIV and subsequently non-A non-B hepatitis. The efficacy of heat treatment at 80 degrees for 72 hours took considerably longer to be internationally accepted as being 'equivalent' to the solvent-detergent, and even in 1988 doubts were expressed about its viricidal efficacy [11]. Consideration of efficacy of the viricidal processes vs the potential viral load in the source plasma had to be carefully weighed especially in the mid-1980s.

f) **Nature of the clotting factor in the final vial**

The importance of the clotting factor retaining its native configuration has been briefly alluded to above.

In the case of recombinant clotting factors there were concerns as to whether the recombinant protein was equivalent to the native protein in non-haemophilic individuals. The clearest example of this is whether the clotting factor has the same complete sequence as the native protein or has it been altered to aid manufacture. An example was the production of recombinant B-deleted factor VIII concentrates (in which the B part of the molecule is not present in the factor VIII molecule manufactured). The reason for manufacturing B-deleted factor VIII was because the process was simpler and the yield of factor VIII was higher compared with the 'full-length molecule'. When initially introduced there was concern as to whether this modified molecule was equivalent to the complete molecule when used to treat patients. The issue was further complicated by questions as to whether it was 'equivalent' to the complete molecule when measured in factor VIII assays.

The other aspect in which recombinant proteins may not be equivalent to the native protein is in the way the protein is processed by the cell in which it is synthesised. This has been studied in relation to sugar residues which are added to the primary amino acid structure. This has been one of the arguments for the use of human, rather than animal, cell lines for the manufacture of concentrates.

The question of the structure of the clotting factor molecule was further considered in relation to modifying it to increase its life span in the circulation (usually expressed as a 'half-life'). This led either to the production of clotting factors (linked to whole plasma proteins, e.g. albumin, or to parts, e.g. the light chain of immunoglobulin), or to the addition of polyethylene glycol, of differing molecular weights, whether to a specific site on the protein or by being randomly attached. These offered potential therapeutic benefits but there were reservations including concern about possible polyethylene toxicity.

g) **Measurement of clotting factor content in the final vial**

This is a very important topic because there must be confidence that the amount of clotting factor on the label of the final vial relates to the amount that will be 'recoverable' in the circulation of the patient. The significance of this for patients should not be underestimated, affecting concerns that the patient was receiving the correct dose for treatment, as well as having financial implications because the concentrates are usually sold on a cost per unit basis [12].

The situation is made more complex because biological assays are used to assess the amount of concentrate in a vial. The assay results are highly dependent on the reagents and techniques used. Further complications arose because historically speaking, the FDA has licensed concentrates using one-stage clotting techniques, whereas the EMA has preferred chromogenic assays. Moreover, the B-deleted molecule and some of the modified recombinant molecules behaved differently in the various assays.

All of this had further implications from a financial perspective, because the cost was either per unit (as stated on the vial) or for a nominal unitage per vial, e.g. 1000 units. These were measured by the manufacturer and also assessed by the National Institute for Biological Standards and Control (NIB&C), and then passed for issue if the unitage was within an acceptable tolerance. There was evidence that in some instances, manufacturers over-estimated the vial content of clotting factor, thereby apparently increasing the cost [12].

For some clotting factor concentrates, the situation was very different because they were not assessed by conventional assay measurements. This applied particularly to activated clotting factor concentrates used to treat patients with anti-factor VIII antibodies, e.g. Factor VIII Inhibitor Bypassing Activity (FEIBA). This was administered as a standard weight-based dose and assessment of response was clinical, i.e. there were no appropriate laboratory assessments available to monitor therapy.

A similar situation arises in the use of recombinant VIIa for the treatment of Glanzmann's disease. Beyond clinical assessment, there is no laboratory method with which its efficacy can be measured.

h) **Clinical assessments of concentrates**

With the introduction of a new potential therapeutic concentrate, there are a series of clinical evaluation processes usually undertaken prior to a licence being issued, Phase 1 to 3 studies. I do not need to set out the standard arrangements for licensing concentrates, except to note that the FDA and EMA regulations differ and have changed over time. One of the responsibilities of a Comprehensive Care Haemophilia Centre is take part in appropriate clinical trials to assess new treatments. Much of what is set out above is pertinent when considering whether to assess or use a new concentrate.

As haemophilia is a rare condition it is difficult to undertake large scale pre-licensing studies and therefore, increasingly, a condition of gaining a licence is that an active Phase 4 assessment post-licensing process is established.

Part of the on-going routine clinical assessment of a concentrate is to have arrangements to record adverse effects and for these to be monitored. Some adverse events are extremely rare or absent, e.g. HIV or HCV transmission, and require a very large population of patients to be surveyed, e.g. as in the EUHASS arrangement. Other adverse events are relatively common, e.g. development of anti-factor VIII antibodies, but it is important to monitor these as their frequency may vary between different treatments.

i) **Platelet transfusions**

Some patients with congenital platelet disorders require treatment with platelets to prevent or treat bleeding. The infective risks of therapy are very different from those due to use of virally inactivated concentrates and are similar to those of red cell transfusions. There are other quite distinct risks in the form of alloimmunisation against platelet membrane proteins. Although platelets should be included in addressing the above question they will not be considered further.

j) **Availability**

For a blood product to be of use it had to be available. In the early 1980s, there was not a ready supply of commercial factor VIII concentrate and manufacturers tended preferentially to provide a more secure supply to large users. This did not cause major difficulty in Edinburgh because the use of commercial factor VIII concentrate was very limited but it did limit choice of supplier.

In developing policy, it was necessary to take into consideration whether the product was available and whether the supply chain could be relied upon. One way to reduce risk was to have a supply of equivalent products from several sources; this was a policy that was adopted after the introduction of recombinant concentrates.

k) **Appropriate product for an individual patient.**

Policy decisions on the use of different therapies depend upon many of the questions discussed above. However, decisions about use may also depend upon the situation of an individual patient, e.g. some patients have reactions to particular concentrates. Only certain concentrates are suitable to be given as continuous infusions, for example, to cover surgery. If large doses need to be administered for a patient, its purity is an important consideration. For patients to be able to use the concentrate at home it has to be easy to reconstitute and infuse.

Summary

66) Over the 30 years of my term as director of the Centre, many decisions were made about which blood products should be stocked and to whom they should be given. Decisions often had to be made with inadequate knowledge and occasionally at short notice, e.g. heat-treatment in December 1984, and the use of non-UK plasma-derived concentrates in 1997. It was important, however, to have good arrangements for the monitoring of the efficacy and side effects of treatment and for this information to be accumulated in respect of a large patient population.

References in respect of Question 11

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3. Stirling, M.L., et al., *Incidence of infection with hepatitis B virus in 56 patients with haemophilia A 1971-1979.* J Clin Pathol, 1983. 36(5): p. 577-80.

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9. de Biasi, R., et al., *The impact of a very high-purity factor VIII concentrate on the immune system of HIV-infected haemophiliacs: a randomized, two-year comparison with a high-purity concentrate.* Haemophilia, 1996. 2(2): p. 82-7.

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12. Austen, D.E., I.R. Rhymes, and C.R. Rizza, *Factor VIII concentrates: What the label says.* Lancet, 1981. 2(8256): p. 1167.

12. What responsibility did the Centre, and you as its director, have for the selection and purchase of blood products? How, and on what basis, were decisions made about the selection and purchase of blood products? What were the reasons that led to the choice of one product over another? What role did commercial and/or financial considerations play?

67) My responsibility, as director, was to ensure that there were appropriate blood products available for treatment of patients registered at the Centre. Selection of treatments was influenced by a broad range of factors particularly national guidelines and recommendations especially those compiled by UKHCDO, Haemophilia Directors for Scotland and Northern Ireland, and Recombinant

Clotting Factor Consortium for Scotland. For commercial concentrates, contracting for purchase was undertaken by National Services Division of National Services for Scotland. There was consultation with SNBTS and the Lothian Health Board when appropriate.

68) In my response to Question 11, I have set out some of the issues which were important. It was necessary to ensure so far as possible that treatment for each patient was:

1. Available
2. As effective as possible
3. As safe as possible
4. Possible to monitor response
5. There was a legal basis for the prescription

69) As well as treatment being available for acute bleeds, there were also other considerations which were sometimes important to consider. Examples of these include: is the treatment suitable to cover surgery? Can it be given by continuous infusion? Is the product suitable for immune tolerance? How readily can it be used by patients at home? Is the product stable at room temperature? Consideration of security of supply was important both for NHS and commercially sourced products. Where equivalent products were available from different commercial sources, there was a preference to have a supply from several sources as an insurance against one supplier being unable to deliver.

70) There had to be available products for the treatment of each disorder, e.g. haemophilia A and B, von Willebrand disease, and other deficiency disorders. Treatment was also required for those with inhibitors, both with auto or alloantibodies.

71) The majority of decisions were made in collaboration with haemophilia director colleagues, particularly in Scotland and the organisations referred to above.

72) Commercial considerations were managed by National Services Scotland which latterly collaborated with the purchasing authority for England and Wales. There was a system of competitive tendering for equivalent products.

13. What was the relationship between the Centre/you and the pharmaceutical companies manufacturing/supplying blood products? What influence did that relationship have on the Centre's and your decisions and actions?

73) As director of the Centre it was important for me to know what commercial coagulation factor concentrates were available and their specifications. It was also important to know what developments were taking place to produce new products.

74) From time to time I would receive mailings from companies about their products and occasionally representatives would come to see me. In the 1980s Edinburgh was a very small user of commercial concentrates and therefore I received very little information from commercial suppliers.

75) When I required commercial factor VIII concentrate in the early 1980s it was not easy to obtain these because there was a shortage because commercial companies were not able to supply the total demand. Manufacturers gave preference to large users of commercial concentrates.

76) I collaborated with commercial manufacturers when appropriate for the assessment of products. For example, recombinant VIIa was available for treating patients with anti-factor VIII antibodies. I helped in 2000 with the assessment of its efficacy in managing orthopaedic surgery in patients with these antibodies.

77) What I learned from pharmaceutic companies contributed to my overall knowledge about therapeutic options, but I am not aware that the nature of my relationship influenced my decisions about the purchase of products. I was always keen to promote Edinburgh as primarily a user of NHS products and therefore we were not viewed as a good commercial opportunity for the manufacturers.

78) When significant amounts of commercial products were being purchased, e.g. recombinant concentrates, the contracting arrangements were handled by the National Services Division of National Services Scotland.

14. To what extent, and why, were people with mild or moderate bleeding disorders treated with factor concentrates?

Introduction

79) Use of concentrate in mild and moderate bleeding disorders depends upon the diagnosis, clinical indication, and characteristics of the available concentrates. This means that this question cannot be answered in simple terms. The use of factor concentrates has changed markedly since their development because of changes in perceived indications, in benefits and risks at different times, as well as in developments in the manufacturing processes. Concentrate use has increased over the past 50 years and to describe to 'what extent' this has occurred will depend upon the diagnosis of the patient in question, the severity of their disorder, and the characteristics of the concentrates available at any particular time.

80) The UK guidelines on treatment since 1983 have addressed the issue of concentrate use in haemophilia compared with cryoprecipitate and fresh frozen plasma [1-8]. In the early 1980s, cryoprecipitate and NHS concentrates were perceived as safer from the risk of transmission of viral infections and were preferred, when available, to commercial concentrates. In the early 1980s, the risk of a single donation of cryoprecipitate transmitting non-A non-B hepatitis was in the order of about 1%. A typical dose of treatment for a patient might be 20 individual donations of cryoprecipitate; thus after about 5 infusions there was a high likelihood the recipient would be infected. With the introduction of viral inactivation measures in the concentrate manufacturing processes, the use of cryoprecipitate and fresh frozen plasma were seen to be less safe than virally inactivated concentrates.

81) In the UK, the situation was further complicated by the view that developed in 1997, that, because of the potential risk of vCJD, concentrates derived from plasma collected outwith the UK might be safer than concentrates manufactured from UK plasma. Thus, from the early 1980s there has been a clear movement away from cryoprecipitate and fresh frozen plasma towards virally inactivated concentrates for patients of all severity of bleeding disorders. It is now agreed policy, both in the UK and internationally, that virally inactivated concentrates are safer, with respect to risk of virus transmission, than fresh plasma products (WFH

Guideline 2012). The point at which a concentrate was perceived as becoming less likely to transmit a viral infection to patients only requiring occasional treatment varied for the different bleeding disorders as outlined below.

Haemophilia A

82) Many patients with moderate haemophilia A experience bleeding episodes both with and without a history of trauma. The frequency of these varies both within a patient and between patients. Some bleed as frequently as many patients with severe haemophilia, whereas others bleed much less often. It is clear that many patients with moderate haemophilia develop a similar degree of arthropathy to those with severe disease (UKHCDO Annual Report 2019). This emphasises the importance of prompt treatment of all haemarthroses and in many patients the need for effective prophylactic therapy for moderate haemophilia. This approach to treatment is only possible with the use of clotting factor concentrates.

83) Patients with mild haemophilia A bleed less frequently than those with moderate disease and this occurs usually in response to trauma or following surgery. Recommended treatments have changed over time. When DDAVP is not appropriate (see its use in (v) below) treatment has been with cryoprecipitate or a factor concentrate. Over the past 50 years, cryoprecipitate use has been greatly reduced and virally-inactivated or recombinant factor concentrates have become the treatment of choice.

84) To cover surgery, or bleeding due to minor trauma, in mild haemophilia A, it may be possible to raise the factor VIII level for a short period of time with DDAVP sufficiently to allow surgery to be safely undertaken. The rise in factor VIII by DDAVP depends upon the basal factor VIII level, but the response is very variable between patients. Furthermore, repeat injections result in a diminished response (tachyphylaxis). As DDAVP results in an increase in tissue plasminogen activator (which promotes the dissolution of clots) it is also necessary to give a fibrinolytic inhibitor concurrently, e.g., tranexamic acid. DDAVP and tranexamic acid are not without potentially serious side effects and contraindications for use. If DDAVP is not suitable then use of a factor concentrate needs to be considered. The indications for factor concentrates have increased over the past 50 years to a

situation where current concentrates are considered the treatment of choice when DDAVP is not appropriate.

Haemophilia B

85) For haemophilia B those with moderate and mild severity depend upon factor concentrates primarily for a number of reasons. Following infusion of factor IX its recovery in the circulation is only approximately 50% of that expected for a variety of reasons, including it's binding to endothelial cell and other receptors, and its diffusion into the extravascular space. Unlike treatment for haemophilia A, there is no equivalent to cryoprecipitate, nor does factor IX increase following DDAVP infusion, and therefore the only alternative to a factor IX concentrate is fresh frozen plasma. As only a limited volume can be infused, to avoid circulatory overload, it is not possible to obtain large rises in factor IX level with its use. As with factor VIII, the indications and contraindications of factor IX concentrates varied with the type of concentrate and its mode of production since the 1970s. Currently available licenced concentrates are considered treatment of choice for haemophilia B for all degrees of severity of haemophilia B.

Other Coagulation Disorders

86) There are mild bleeding disorders due to other coagulation deficiencies, e.g. factor XI, factor XIII or fibrinogen deficiency, which might be treated with a concentrate (when available) or with cryoprecipitate or fresh frozen plasma. As with haemophilia A and B, the indications for using cryoprecipitate, fresh frozen plasma or concentrate will vary between disorders, both in the level of rise required to achieve or maintain haemostasis and how long this has to be maintained. The availability of concentrates, and again their viral safety characteristics have changed radically over the decades. As for haemophilia, in general a recombinant or virally-inactivated concentrate is considered safer from potential viral transmission, than a fresh plasma product for all patients.

Von Willebrand Disease

87) Von Willebrand disease in most patients is a mild bleeding disorder. Its treatment is potentially more challenging because of the broad spectrum of its molecular pathology. As for haemophilia the response to DDAVP varies markedly between patients and depends on their particular molecular subtype. Furthermore in many instances it is contraindicated for certain subtypes, e.g. 2B. It should be remembered that patients with pseudo or platelet von Willebrand disease may require platelet transfusion, as well as a therapy containing von Willebrand factor.

88) Historically, cryoprecipitate has for many patients been effective treatment because it is enriched in 'native' von Willebrand factor. Over the years a variety of 'concentrates' have been used particularly following the introduction of viral inactivation steps in their manufacture and these have replaced cryoprecipitate. The concentrates have mostly been primarily factor VIII concentrates that possess a significant amount of 'native von Willebrand factor protein' and these are currently widely used for patients in whom DDAVP is not appropriate. A plasma-derived von Willebrand Factor concentrate has been manufactured and licenced which has only a low content of factor VIII. This is usually not adequate alone to treat an acute bleed because of the associated low plasma factor VIII level in von Willebrand disease. It has a potential place in the preparation of patients for elective surgery or in prophylactic therapy of severe von Willebrand disease. As for the other mild bleeding disorders, the characteristics of different concentrates over the years has changed markedly. A recombinant von Willebrand concentrate has recently been developed.

Platelet Disorders

89) Many mild congenital bleeding disorders are due to platelet abnormalities with either a reduction in number or function or both. In some instances platelet transfusions may be appropriate. Glanzmann's thrombasthaenia can present as a mild bleeding disorder, and if the patient is 'resistant' to platelet transfusion, use of recombinant factor VIIa may be considered.

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7. UKHCDO, *AIDS Advisory Document*. 1984.

8. UKHCDO, Acquired Immune Deficiency Syndrome. 24 June 1983.

15. What alternative treatments to factor concentrates were available for people with bleeding disorders?

90) Alternative treatments to factor concentrates for people with 'congenital' bleeding disorders have been:

- Fresh frozen plasma
- Cryoprecipitate
- DDAVP
- Tranexamic acid
- Platelet transfusions

16. What was your/the Centre's policy as regards the use of cryoprecipitate for the treatment of patients with bleeding disorders?

91) In 1980 in Edinburgh, cryoprecipitate was the principal blood-derived treatment for haemophilia A, von Willebrand Disease and factor XIII deficiency. For haemophilia A this was because of the very limited availability of NHS factor VIII concentrate and my desire to avoid the use of commercial concentrates. It was not made available for home treatment principally because of the risk of allergic reactions. Thus, as a result of this policy many patients with acute bleeds had to attend hospital for treatment. At this time there were only six patients on home

treatment with NHS concentrate and very many more, especially those bleeding frequently, who were keen to have this available. In general, the patients who bled most frequently had priority for home therapy, although the distance they had to travel from home with an acute bleed was also a factor taken into consideration.

92) Cryoprecipitate, however, was still used for the majority of in-hospital treatments, to conserve the concentrate for home therapy. It was also used for patients who might only require treatment occasionally, if DDAVP was not appropriate.

93) During the early 1980s strenuous efforts were made by SNBTS to increase factor VIII concentrate production and the resulting increase allowed more patients to benefit from home therapy. Donor blood plasma was redirected from cryoprecipitate production to concentrate manufacture.

94) The above policy was in accord with the UKHCDO guidance issued in June 1983 which emphasised that cryoprecipitate and NHS concentrate were preferable when available to commercial concentrates for haemophilia A [1].

95) With the introduction of heat treatment in December 1984 it was considered likely that NHS factor VIII concentrate might be safer than cryoprecipitate in relation to the risk of HTLVIII [2]. Despite it starting to become appreciated that non-A non-B hepatitis could have long term adverse effects on the liver, it was the risk of AIDS that was of very great concern to all at this time.

96) After 1985 there continued to be a small use of cryoprecipitate to treat bleeding patients with von Willebrand disease and factor XIII deficiency. When virally inactivated concentrates became available to treat these conditions they became the treatment of choice because they were virally attenuated.

References in respect of Question 16

1. UKHCDO, *Acquired Immune Deficiency Syndrome*. 24 June 1983.
2. UKHCDO, *AIDS Advisory Document*. 1984.

17. What were, in your view, advantages and disadvantages of those alternative treatments? Do you accept that they should have been used in preference to factor concentrates? If not, why?

Introduction

97) I propose to answer these questions separately in relation to each product listed above in the response to Question 15.

Fresh Frozen Plasma (FFP)

98) This contains all the plasma coagulation factors and von Willebrand factor. Its use will increase the level of any deficient factor in a patient, although this will be modest because only a limited volume can be infused due to the risk of circulatory overload. It has had a place in the treatment of haemophilia B (rarely), the rare factor V deficiency (for which there was not until recently a concentrate available) and for factor XI deficiency (because of the risk of thromboembolism with factor XI concentrates).

99) The drawback of using FFP is that recipients are prone to allergic reactions [1, 2] including TRALI (transfusion related allergic lung injury), and viral or other infectious agents. Solvent-detergent FFP was later developed, to reduce the risk of lipid-coated virus transmission, but this reduces the level of some of the coagulation factors and usefully the incidence of TRALI.

Cryoprecipitate

100) Production was developed by Pool in 1965 [3] and came into clinical use rapidly because it was simple to produce by blood transfusion services and it was the first potentially readily available factor VIII enriched plasma product. Cryoprecipitate transformed the treatment of patients with haemophilia A and allowed most bleeds (in non-inhibitor patients) to be treated effectively. As well as factor VIII, cryoprecipitate contain therapeutically useful concentrations of von Willebrand factor, factor XIII and fibrinogen and has been used to treat deficiencies of these disorders.

101) The advantage of cryoprecipitate over plasma-derived concentrates is that the yield of factor VIII is higher from the starting plasma than for concentrates. During the manufacture of the latter there are significant losses of factor VIII. One of the trade-offs of moving a plasma supply from cryoprecipitate manufacture to concentrate is a loss of factor VIII unitage. Furthermore the introduction of viral inactivation steps led to a further reduction in factor VIII yield. The other advantage is that its use is likely to expose the recipient to fewer donors compared to exposure with concentrate. The importance of this depends upon the prevalence of 'infectious donors' – this being very different for different viruses and potentially the prevalence of neutralising antibodies in donors, the number of infusions a patient receives, the number of donors contributing to the plasma pool, and the concentrate manufacturing process.

102) The principal disadvantage of cryoprecipitate is that it is not a virally inactivated product.

103) There are many other disadvantages of cryoprecipitate. It has to be stored in a deep freeze. It is labour-intensive to produce at a blood transfusion centre and it is time-consuming and messy to make up in the hospital laboratory. It requires thawing of perhaps 20 polythene bags in a 37 degree water bath and pooling each into one bag as a patient dose. It is not a good product for home therapy for these reasons, but more importantly it can give rise to unpredictable reactions in patients (similar to those described for FFP above) which can be life-threatening. Its use is therefore confined to treating patients in hospital.

104) The amount of factor VIII in a single unit of cryoprecipitate is very variable, depending upon the level in the donor plasma (there being a very large normal range in the general population) and the way individual bags are prepared at the blood transfusion centre. The average unit of cryoprecipitate would contain about 70 units factor VIII, but when pooled with other donations there was no way of being assured as to the dose of factor VIII the patient is receiving, unlike concentrate, where the factor VIII content in the vial has been carefully measured for the batch.

DDAVP (Desmopressin)

105) This is a vasopressin (hormone produced by the posterior pituitary gland) analogue which raises factor VIII and von Willebrand levels approximately 2-4 fold in recipients. The response is vary variable between patients, but predictable within patients. It is usually only of value in patients with mild haemophilia, because a basal level of factor VIII over 10% is necessary, and it is not useful in all subtypes of von Willebrand disease, e.g. Type 2. It may be useful for raising factor VIII or von Willebrand levels over a short period, repeat injections result in a diminished response (tachyphylaxis). Reactions include flushing, tachycardia, fits due to water retention (especially in babies under 2 years) and in those with atherosclerosis of precipitation of cardiovascular events. As DDAVP also increases the plasma level of plasminogen activator, dissolution of clots is increased, and therefore this activity is inhibited by concomitant administration tranexamic acid (see in ix below).

Fibrinolytic Inhibitors

106) Tranexamic acid is a synthetic drug which inhibits lysis (dissolving) of fibrin clots. Its use therefore stabilises a fibrin clot and, in a patient with a mild bleeding disorder, it may be sufficient to prevent bleeding after a surgical procedure. It is usually used in conjunction with treatment with a factor containing therapy as a way of improving haemostasis. In general, it is a very well tolerated drug with few side effects. It is contraindicated in renal bleeding and in patients with large haematomas.

Platelet Transfusions

107) Platelet Transfusions may be useful for those with congenital platelet disorders.

Do you accept that they should have been used in preference to factor concentrates? If not, why?

108) **Fibrinolytic inhibitors** have widespread application as a method for reducing surgical bleeding and have a particular use for oral and gut bleeding in an

environment where there is heightened fibrinolytic activity. Their use is usually as an adjunct to other therapy to raise the level of the deficient clotting factor. Generally, they are safe and well tolerated.

109) **Desmopressin** may be very appropriate for some patients with mild haemophilia and some with von Willebrand disease. When it is not appropriate therapy the alternatives are FFP, Cryoprecipitate, or factor concentrate.

110) For treatment of haemophilia A and von Willebrand Disease, FFP is not effective (for reasons stated above). It had a minor place in the treatment of haemophilia B, but suffered from similar drawbacks to its use in haemophilia A. Furthermore, FFP was not virally inactivated and therefore has the risk of transmitting infections.

111) Advantages and disadvantages of cryoprecipitate for haemophilia A and von Willebrand Disease are set out above.

To what extent should they have been used in preference to concentrates?

112) The answer to this question is not straightforward and changed during the 1980s with increasing knowledge becoming available about the risks associated with different concentrates. Practice within the UK was influenced by recommendations made by UKHCDO in 1983, 1984, 1988, 1989, 1997, 2002 and 2008. The following is a review of the use of cryoprecipitate and factor VIII concentrates (both NHS and commercial) with respect to their relative safety with respect to HIV and non-A non-B hepatitis.

113) The principal drawback of FFP and cryoprecipitate was that they were not virally inactivated and could transmit viruses. In the early 1980s, it was considered that NHS concentrate had a lower risk of transmitting non-A non-B hepatitis than commercial concentrates, but the studies of Rizza and, separately, Kernoff demonstrated that NHS concentrates were as infectious as commercial ones [4, 5]. What emerged later was that commercial concentrates, however, had a higher hepatitis C content than NHS ones. The other factor to be taken into account in the early 1980s was the view that the risk of transmitting non-A non-B hepatitis was about 1% for each donation received. A usual dose of cryoprecipitate for an adult was approximately 20 donations and this gave the recipient therefore a 20%

chance of infection. Thus, if a patient was likely to receive a total foreseeable requirement of less than 100 donor units, cryoprecipitate might be considered safer than concentrate.

114) With the appearance in people with haemophilia of 3 cases (out of approximately 20,000 individuals) of AIDS in the US in 1982, and 2 cases (of approximately 5,000 persons) in 1983 in the UK, would a switch from concentrate to cryoprecipitate have been appropriate? The extent of infection with HIV in people with haemophilia in UK at this time was unknown, although it is now known that many were already infected with HIV around 1981 [6]. Furthermore, initially it was not clear that HTLVIII infection would lead to a clinical syndrome with an almost 100% fatality if left untreated.

115) It was completely unknown in the early 1980s to what extent factor concentrates might be infectious. Even if a viral aetiology was assumed it could not be concluded that many concentrates would be infectious because the putative virus might be preferentially fractionated to a non-factor VIII containing product, e.g. albumin. It might be diluted by the majority of uninfected plasmas; it might be neutralised by specific antibodies in donations; or the virus might be damaged and degraded during the manufacturing process.

116) In England, if patients had stopped using all concentrates there would not have been an equivalent amount of cryoprecipitate available, both because of a shortage of donor plasma and the blood transfusion's capacity to manufacture large amounts of cryoprecipitate, and because a significant amount of factor VIII was derived from commercial concentrates. Thus, a switch to cryoprecipitate would have reduced substantially the amount of factor VIII available, and additionally patients would have had to revert to hospital-based therapy.

117) In Scotland, SNBTS had strenuously increased blood donor recruitment in the early 1980s and redirected its effort from cryoprecipitate to factor VIII concentrate manufacture in response to the demand for home treatment from patients and their families. Scotland continued with NHS concentrate production, because of the perceived low risk of the putative AIDS virus in Scottish blood donors in 1983 and 1984, rather than reverting to cryoprecipitate. To have done so might have reduced HTLVIII exposure in 1983 and 1984 in people with haemophilia, but it would not have been possible to introduce heat treatment in December 1984. This

was because all the plasma would have been processed as cryoprecipitate which cannot be heat-treated and none would have been available for concentrate manufacture.

118) It is clear from the Penrose Report that a minimum of 18 people in Scotland became infected with HIV by fresh blood components, probably from red cells and platelets. Therefore, as virtually all plasma was directed to people with haemophilia, at least this number might have become infected by cryoprecipitate over the mid-1980s, and it might be argued that it is possible that there could have been considerably more infections.

119) In Scotland, following the introduction of heat-treatment for factor VIII concentrate in December 1984, there were no further HTLVIII infections despite it being found retrospectively that batches of concentrate contained plasma donation that were likely infected with HITLVIII [7].

120) In England, NHS factor VIII concentrate was not all heat-treated until October 1985 and thus patients could have received cryoprecipitate or unheated concentrate or commercial heat-treated concentrate. Not all heat treated, or otherwise virally attenuated concentrates, were equivalent from the perspective of HTLVIII safety and some as late as 1986 were reported as transmitting HTLVIII, summarised by Pierce et al [8]. It was only with diligent long-term surveillance that the safety of different concentrates could be assessed. By 1988 viral inactivation processes used for licenced concentrates prevented the transmission of HIV and non-A non-B hepatitis and these were clearly safer than cryoprecipitate.

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4. Fletcher, M.L., et al., *Non-A non-B hepatitis after transfusion of factor VIII in infrequently treated patients.* Br Med J (Clin Res Ed), 1983. 287(6407): p. 1754-7.

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18. What was your/the Centre's policy and approach in relation to home treatment and prophylactic treatment?

121) My policy was to enable as many appropriate individuals as possible to benefit from home treatment and later long-term prophylaxis.

122) The Centre was keen to offer prophylaxis to appropriate patients when supplies of concentrate allowed. The use of prophylaxis developed over time, from short-term intermittent use to prevent bleeding in an attempt to encourage a 'target site' to settle, to long-term prophylaxis for individuals with severe and moderate haemophilia.

19. What was your/the Centre's policy in relation to the use of factor concentrates in children?

123) The policy has evolved over the past 40 years. It took into account the child's age, severity of haemophilia, parents' views, and the characteristics of the concentrates at any particular time.

124) In the early 1980s, for haemophilia A, when there was a limited supply of NHS concentrate, treatment would be hospital based with cryoprecipitate for bleeding episodes. As NHS supplies of concentrate improved, and after heat treatment was introduced, NHS concentrate became the treatment of choice when a factor VIII infusion was needed as per UKHCDO guidance 1983 and 1984 [1, 2]. Subsequently, further viricidal processes were introduced into the manufacture of both NHS and commercial concentrates, resulting in concentrates safe with respect to HIV and hepatitis C. The relative safety of NHS concentrates, derived from UK plasma was reviewed in 1997, in response to vCJD, and for a period commercial concentrates manufactured from non-UK plasma were preferred [3]. At this time in 1996, recombinant concentrates were recommended by UKHCDO as treatment of choice [4] and they became available in Scotland under the auspices of the Scottish Recombinant Consortium. Their use was prioritised in

agreed national guidance in Scotland which gave priority to children. I have attached as WITN3428005 the guidelines issued in 1996 and 1997.

125) For haemophilia B, in the early 1980s, there was a supply of factor IX NHS concentrate which was offered to children with severe and moderate haemophilia to treat bleeding episodes. As with factor VIII concentrates, subsequently heat-treated and other virally inactivated products became available and the preferred treatment. In relation to recombinant factor IX this became treatment of choice for patients, although a few continued on plasma derived concentrates because of reactions to the recombinant concentrate.

References in respect of Question 19

1. UKHCDO, *Acquired Immune Deficiency Syndrome*. 24 June 1983.
2. UKHCDO, *Recommendations on choice of therapeutic products for the treatment of non-inhibitor patients with haemophilia a, haemophilia B and von Willebrand's disease*. 1988.
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20. What viruses or infections, other than HIV, HCV and HBV, were transmitted to patients at the Centre in consequence of the use of blood products?

126) Following reports in 1992 that hepatitis A had probably been transmitted by clotting factor concentrates, patients in Edinburgh were assessed for evidence of prior infection. Those without detectable antibody were offered hepatitis A vaccine.

127) Although patients were screened for evidence of parvovirus infection, many were found to be anti-parvovirus positive, but it was not clear on an individual patient basis if infection had been acquired from blood product administration. This was an important topic and was addressed by the Coagulation Factor Working Party for Scotland and Northern Ireland in hosting a conference on the topic in 1995 [1].

128) I do not recall whether there were any patients with HDV.

129) Following the identification of hepatitis G virus and TTV, the importance of these was assessed. Both were transmitted by non-virally inactivated concentrates [2-5].

130) Bacterial infections will have occasionally have occurred as a consequence of the use of blood products; these usually affected the skin around long line catheters or implantable devices, although there was also the potential for infection of the catheter itself.

References in respect of Question 20

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Section 4: Knowledge of and response to risk

General

21. When you became director of the Centre in 1980, what did you know and understand about the risks of infection associated with blood and/or blood products. How did that knowledge and understanding develop over time?

131) Knowledge about infections transmitted by blood and blood products between 1980 and 2011 is a huge topic and there were very many crucial discoveries during this 30-year period. The question appears to seek a full response and to provide this would require more time than I judge able to provide. I did my utmost to keep up to date with relevant observations and reports, but it should be remembered that in the early part of this period there was no internet or simple way to be automatically informed of developments. I have highlighted below some of the issues and how I responded to these. Please let me know if there are

specific topics on which you require more detail. I provided to the Penrose Inquiry a document entitled 'Statement AIDS/HIV and Self Sufficiency' which attempted to provide a chronology in relation to the development of my knowledge about HIV/AIDS and the treatment of individuals with haemophilia with clotting factor concentrates' [PRSE0000669].

Non-viral infections

132) There are many infective risks of blood other than viruses and these are relevant to the treatment of patients with congenital bleeding disorders, e.g. individuals with platelet disorders, or patients with a coagulation disorder who bleed and require a transfusion of red cells. For example, it has been known for a long time that syphilis can be transmitted by blood and for this reason all donors are routinely screened for this infection and this makes its transmission now very unlikely. There are a range of bacteria that can be transmitted as a result of transfusion of cellular components and concentrates. The product may become contaminated when it is collected from the donor, either because the blood of the donor contains an infectious agent, or because the process of donation becomes infected from a donor skin contaminant. The recipient may become infected from the blood component, or in association with administration of the blood or product by bacteria in association with the recipient, either from their skin or in their circulation. In the case of haemophilia, this applies particularly to the use of methods used to ease venous access, e.g. prolonged use of indwelling intravenous catheters (e.g. Hickman lines and indwelling implantable subcutaneous devices) can lead to local infection in the skin or systemic infection and the potential for thrombosis in association with catheters. Thus risk of bacterial infection over this 30 year period was a continual concern and the risks varied with clinical practice, being lowest with single infusion of clotting factor concentrate, but being greater in those with use of semi-permanent long intravenous lines.

133) It is necessary to remember that there are a whole range of other types of infections which can be transmitted by blood, some of which are rare but potentially very serious, e.g. yersinia enterocolitica, and others which are uncommon in the UK, e.g. protozoan infections, such as malaria.

Viral Infections

134) To focus on viral infections and their relationship with congenital bleeding disorders, the situation has transformed over the period from 1980 onwards [1]. Some of the factors that needed to be considered have been set out in my response to Question 11 (above) and these were very much under active review especially during the 1980s. Further details are given in my document 'Long term safety monitoring for transfusion transmitted infections' [PRSE0002404] which records actions to monitor viral infections at the Edinburgh Haemophilia Centre.

135) At this time in the early 1980s it was clear from our own studies and those of others that hepatitis B could still be transmitted by cryoprecipitate and concentrates [2, 3]. It was also considered that hepatitis A was not transmissible by blood. The cause(s) of non-A non-B hepatitis (NANBH) and its consequences were uncertain. In summary, there was evidence that there might be at least two different potential viruses (with different incubation periods), or even that the intermittent liver function abnormalities were an allergic reaction of transfused products. There was a view that the risk of hepatitis was probably greater from commercial rather than NHS derived concentrates, but a study at Oxford demonstrated that both were equally infectious [4]. There were studies to ascertain whether heat treating concentrates would prevent transmission of hepatitis, but it was difficult to discover what conditions prevented transmission while preserving the utility of the concentrates. Heating freeze dried concentrates can significantly reduce their solubility during reconstitution and heat can damage the clotting factor molecule, e.g. factor VIII. The situation was further complicated when it was discovered that humans were apparently more susceptible to NANBH than primates. The consequence of this observation was that the safety of concentrates could only by reliably assessed in humans. Despite this, there was much essential in vitro experimental work during the 1980s to assess viral inactivation, both of known human pathogens, e.g. HTLVIII, and of model non-human viruses which were analogous to know human ones.

136) In relation to the potential transmission of viral infections there appeared to be clinical differences in the clinical manifestations of AIDS and susceptibility to various viral infections. For example, homosexual men were developing Kaposi's sarcoma (which was not a feature of AIDS in haemophilia) and were at risk of CMV infection. What became clear was that Kaposi's sarcoma was due to Human

Herpes Virus 8 (HHV8) and that it and CMV could only be transmitted by live cells from the source of the infection. In the preparation of both cryoprecipitate and clotting factor concentrates any cells remaining from the original donor blood are destroyed in the manufacturing process – hence these viruses are not transmitted by concentrates. This is the reason people with haemophilia do not develop Kaposi's sarcoma.

Initial cases of AIDS

137) Like many others I was very interested in the first reports of AIDS amongst homosexual men in the US in 1981 and three people with haemophilia in the US in 1982. Clearly there was a possibility that AIDS was due to a virus, but there were many other possible aetiologies were being considered. My two documents 'Expert Report on Human Immunodeficiency Virus Infection in Haemophiliacs' [PRSE0000332] and 'Historical Summary of AIDS in Haemophilia 1981-1985 [PRSE0000960], prepared in the late 1980s, summarised my understanding of some of the issues in relation to AIDS in people with haemophilia.

138) To summarise, in the first half of the 1980s there was no laboratory test for AIDS and diagnosis was based purely on clinical criteria and even these changed over time. Furthermore, there were other clinical criteria, possibly associated with AIDS, e.g. lymphadenopathy, and it was unclear whether individuals with these features would develop AIDS. These clinical features were not unique to AIDS and could occur in other settings. The situation was further complicated because AIDS in homosexual men appeared to be different from AIDS in people with haemophilia, and different from AIDS as seen in Africa.

139) Along with the clinical picture of AIDS, a series of publications reported on immune disturbances in those with the clinical condition and those in potentially 'at risk' groups were published. This was a topic I was particularly interested in because of the contemporary Edinburgh studies on hepatitis B and NANBH [1, 2]. The background to this topic is presented elsewhere [PRSE0000332 and PRSE0000960], as is my early acknowledgement of the situation and my response as part of my responsibility to monitor patients for potentially infectious agents [PRSE0002404].

140) I was aware of many of the early publications which related to the potential aetiology of the AIDS syndrome and the complexities of considering causes. The situation was also under active review by various specialist groups of which I was a member, e.g. SHHD/SNBTS/Haemophilia Director for Scotland and Northern Ireland (HDSNI) and UKHCDO. I was also aware of and helped to develop guidelines issued by UKHCDO.

Initial test for anti-HTLVIII

141) As soon as I learned, as a result of the publication in the BMJ in September 1984, that an antibody test had been set up by Dr Richard Tedder in London, I contacted him to ascertain if he would test serum samples from Edinburgh people with haemophilia [6]. Because the test had been set up on a research basis, he was not able to agree to test more than a small number of samples and he had some reservations about the accuracy of the results. The results of the initial samples sent to him revealed that several individuals who had been treated exclusively with NHS products were anti-HTLVIII positive. These individuals did not have any clinical features associated with AIDS or AIDS-related complex. This was one of the first pieces of evidence that the aetiological agent for AIDS had contaminated the UK blood supply. I immediately reported this to SNBTS and the UKHCDO Chairman.

142) This observation was one of the important developments that led to the meeting of 10th December 1984 between UKHCDO Reference Centre Directors and UK Blood Transfusion Services [HCDO0000394_117]. At this meeting much discussion was around whether to recommend use of heat-treated concentrates and in particular the relative safety of heat-treated commercial versus non-heat-treated NHS. Subsequently, UKHCDO issued guidelines, they also summarised some of the difficulties in making treatment decisions [7].

143) In 1983 and 1984, in conjunction with SNBTS, I arranged for the assessment of samples of heat-treated factor VIII concentrates in a very small number of patients. At least one of these had been associated with adverse reactions. My recollection is that, in November 1984, I assessed SNBTS factor VIII concentrate dry heated at 68 degrees for 2 hours in a very small number of patients without adverse effect.

144) Although, when viewed from the perspective of 2020, heat treatment was the correct decision, in the mid-1980s there was considerable unease about its introduction, as exemplified by Bird and colleagues in immunology and blood transfusion in Newcastle [8], which was rebutted by Bloom in a subsequent letter to the Lancet [9]. At this time, there was very little information available about the development and use of heat-treated concentrates by commercial plasma fractionators, because such information appeared to be considered commercially sensitive.

145) As a result of the 10th December 1984 meeting, dry heat-treated factor VIII (68 degrees for 2 hours) was issued to all patients registered at the Edinburgh Haemophilia Centre [HCDO0000394_117]. Those on home treatment were instructed to bring in existing unused factor VIII and exchange it for the heated product.

146) Subsequent follow-up of anti-HTLVIII negative patients in Edinburgh revealed that no further patients developed anti-HTLVIII, despite at least two of the batches of 68 degree/2 hours treated concentrate containing presumed HTLVIII positive plasma donations [10]. Thus the heat-treatment appeared effective in preventing HTLVIII infection.

147) Having identified a group of people with haemophilia who had been exposed to HTLVIII as a result of their treatment, I considered that it would be essential to monitor clinically both the viral and immune status in detail, not only for these individuals, but also for those who were anti-HTLVIII negative. This would be of benefit to all the patients who had immune abnormalities and assist understanding of the implication of HTLVIII exposure and how and when treatment might be appropriate.

148) I was particularly fortunate to have advice and guidance of two Edinburgh based international experts on viral infections transmitted by blood (Dr John Peutherer and Dr Peter Simmonds) along with a medical cell biologist and immunologist (Dr Michael Steel). Dr Ray Brettle (Infectious Diseases and HIV expert) and Dr Peter Hayes (Hepatologist) helped with the management of patients.

149) Guided by these, and other, experts, the individuals with haemophilia and other congenital bleeding disorder patients in Edinburgh were monitored in greater detail after 1984 as a result of their exposure to HTLVIII. Time does not allow me to reiterate much that was learned about the safety of blood and blood products during the latter half of the 1980s, except to emphasise that there were neither simple nor readily implemented procedures that could be applied to treatment modalities that would guarantee their non-infectious state. Scotland was the first country in the world to make available in 1984 to all patients with haemophilia A, factor VIII concentrate that did not transmit HTLVIII, and by 1987, we were able to offer treatment, again to all patients, that did not transmit NANBH.

Development of clotting factor concentrates with enhanced safety in Scotland

150) It became clear in the 1980s that there were many factors involved in attempting to manufacture concentrates which ensured increased safety. One factor was the need to produce concentrates of higher purity to withstand viral inactivation procedures. Another was how to assess safety from NANBH when the aetiological agent was unknown. The generally accepted international standard for assessment required frequent blood sampling.

151) In response to the evolving situation during the 1980s, it became clear to SHHD and others that new safe clotting factor concentrates were needed for treating haemophilia. To address this, I was invited to establish and chair the Factor VIII Working Party for Scotland and Northern Ireland, a tri-partite group with representation from SHHD, senior SNBTS staff and Health Directors Scotland and Northern Ireland (HDSNI). Subsequently, this evolved into the Coagulation Factor Working Party for Scotland and Northern Ireland when the development of a new factor IX concentrate was added to its remit. The minutes and annual reports of this committee are available and they reflect the wide range of issues considered in the development, assessment and licensing of these new concentrates. To address the issues, international collaboration was sought and specialist meetings and conferences were arranged. Two new high purity factor VIII and IX concentrates were developed and manufactured by SNBTS. This major development was very generously assisted by patients very willingly giving of themselves in the assessment processes to demonstrate the safety and efficacy

1) of products. The success of the process was the awarding of licence for the Factor VIII concentrate.

Identification of Hepatitis C

2) With the identification of the likely aetiological agent for NANBH in 1989, I was keen that Edinburgh patients benefited from this development. With Dr Peter Simmonds and Dr Peter Hayes, first generation HCV antibody testing was established, but our studies revealed its shortcomings and our evaluation resulted in greater confidence in the second generation test. With establishment of the HCV PCR test it was possible to identify more accurately those patients who would benefit from the then current anti-HCV treatment.

Other viruses transmissible by blood and blood products

3) Although much of the emphasis (and anxiety) during the 1980s and early 1990s was related to HIV, during this time it became clear that a number of other viruses (non-HBV and non-HCV) might be transmitted by blood products. These included:

a) **Hepatitis A.** Traditional teaching was that hepatitis A was not transmissible by blood or blood products. In 1992, Mannucci reported evidence that hepatitis A infection appeared to have been transmitted by clotting factor concentrates and this was supported by reports from other centres [11]. This was of importance for a number of reasons. Firstly, that this virus appeared to be resistant to some viral inactivation techniques, and secondly because a vaccine was available to protect susceptible individuals.

b) **Parvo B19.** Although the initial report suggesting that a parvo-like virus was transmitted by a clotting factor concentrate in 1983 [12], it was not until the early 1990s that this topic was further examined. The importance of parvovirus is that it can cause severe disease in some individuals (e.g. hydrops fetalis and severe arthropathy). It is also important because it is a non-lipid coated DNA virus that is resistant to some heat treatments and solvent-detergent action. The infection is difficult to study in adults with haemophilia because many children get infected in their normal environment

with outbreaks typically occurring in spring and autumn (when it is known as 'fifth disease' or 'slapped face condition'). The importance of studying it is twofold. Firstly, if it is not fully inactivated during the viricidal manufacturing process of concentrates, there is not only the potential for it to infect recipients, but it suggests that should other viruses with a similar structure potentially infect donors, and possibly the blood supply, they may not be inactivated by the manufacturer's viricidal processes. Secondly, there might be the potential for B19 to mutate into a more pathogenic virus which could produce new pathology in recipients. This has been observed to occur with canine parvovirus with the result that there was a global epidemic with much loss of canine life.

Because of the importance of parvo-like viruses the Coagulation Factor Working Party for Scotland and Northern Ireland organised an international symposium (with speakers from UK, mainland Europe, and North America) on the topic in Edinburgh in 1995 [13].

c) **Hepatitis G.** Original studies initiated by Dr Peter Simmonds in Edinburgh revealed that the then termed Hepatitis G virus was very similar in structure to HCV, particularly being surrounded by a lipid coat. Our studies demonstrated that it was quite a common virus in blood donors, that it could be transmitted by non-virally inactivated concentrates, but not by virally inactivated ones. Assessment suggested that the virus was probably not pathogenic and there was no evidence that it caused liver disease [14-16].

d) **TTV (torque teno virus)** This was initially described in a Japanese patient in 1997 with post-transfusion non-A, B and C hepatitis. Because of its possible importance, investigations were instigated in Edinburgh by Dr Peter Simmonds at this time. Our studies demonstrated TTV was common in blood donors and that it could be transmitted by non-virally treated blood products. Although it was possible to detect the viral genome in virally inactivated products, however, these were probably not infectious [17, 18]. As for hepatitis G, further investigation revealed that the virus was probably not pathogenic.

e) **Parv4.** This parvo virus was reported to be parenterally transmitted by blood products by studies in Edinburgh by Dr Simmonds, although there is much uncertainty as to whether this virus is pathogenic in man [17, 18].

f) Other viruses have arisen which are transmissible by blood transfusion and potentially by blood products, e.g. west Nile virus, Zita etc. Fortunately for recipients of virally inactivated products these viruses are susceptible to the current licensed viral inactivation procedures and therefore do not present a risk to those with haemophilia. They may pose a risk, however, to recipients of non-virally inactivated products if the donation is collected in a region in which the virus is prevalent.

Potential enhanced safety of recombinant factor VIII and IX concentrates and their introduction.

154) With the availability and licensing of recombinant concentrates in the mid-1990s, UKHCDO recommended these in preference to those derived from donor plasma in 1996 [19]. Because of their cost and availability, their introduction had to be phased. In Scotland in 1996, there was a national arrangement established under the aegis of the Recombinant Coagulation Factor Consortium for Scotland which received initial funding from SNBTS and subsequently from SHHD. A roll out programme was agreed with guidelines for their issue. At this time in England there was no national arrangement despite attempts to engage the DOH [20].

155) It should be remembered that although in the initial recombinant concentrates the coagulation factors were synthesised in the manufacturing facility, the incubation vats contained some human proteins, some of the purification procedures used mouse monoclonal proteins, and the final vial contained human virally-inactivated albumin. Subsequently, modification to the manufacturing conditions allowed production without any exposure to human proteins.

156) There was a concern that viral contamination might occur during the manufacture of recombinant products and a viral inactivation step was therefore subsequently introduced into the manufacturing process.

The situation posed by vCJD

157) vCJD was described in 1996 and was clinically distinct from other forms of Creutzfeldt-Jakob disease. The aberrant prion protein in vCJD was demonstrable in lymphoid tissue and suggested that it was likely that it had gained access to this tissue through haematogenous spread. With the developing number of cases being reported in the UK, there was concern that the abnormal prion might be transmitted by blood or blood products. In the absence of explicit concern in the UK about the safety of coagulation factor concentrates, UKHCDO highlighted the potential threat [21] and suggested that the risk might be lower if plasma-derived concentrates were sourced from countries with a lower incidence of vCJD. Eventually, this view prevailed and regulators and blood transfusion services banned the use of UK plasma for fractionation into coagulation factor concentrates. This resulted in the use of commercial, licensed plasma-derived clotting factors sourced and manufactured outwith the UK. NHS plasma fractionators imported plasma derived from donors in countries with a low prevalence of vCJD in the population for the manufacture of plasma-derived clotting factor concentrates. That the risk of contamination from blood transfusion was real, was supported by the reporting of vCJD arising in three recipients of blood transfusion who received blood from asymptomatic donors who had subsequently developed vCJD [22-24].

158) More recently, two cases of sporadic CJD have been reported in two patients with bleeding disorders who have been treated with coagulation factor concentrates in the UK, but it appeared unlikely they acquired the CJD from the blood products [25].

References in respect of Question 21

1. Watson, H.G.W. and C.A. Ludlam, *Replacement therapy and Other Therapeutic Products*, in *Haemophilia and other inherited bleeding disorders*, C.R. Rizza and G.D. Lowe, Editors. 1997, Saunders: London. p.151-199.

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24. Turner, M.L. and C.A. Ludlam, *Variant Creutzfeldt-Jakob disease.* Transfus Med Rev, 2000. **14**(3): p. 216-22.

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22. What advisory and decision-making bodies were in place, or put in place, (i) at the Centre and (ii) in Scotland to consider and assess the risks of infection associated with the use of blood and/or blood products?

159) The following were some of the local and national arrangements in Scotland for considering risk of infection associated with the use of blood and/or blood products;

a) Local liaison between Haemophilia Centre and local SNBTS staff. The Haematology Department and Blood Transfusion Department were adjacent. There was frequent opportunity for informal and formal discussions about infective risks of blood and blood products.

b) Reporting arrangements for infections to organisations which included SNBTS, Scottish Centre for Infection and Environmental Health, UKHCDO, Committee of Safety of Medicines, Coagulation factor Working Part for Scotland and Northern Ireland, European Haemophilia Safety Scheme.

c) There were discussions with senior Lothian Health Board staff, e.g. Chief Administrative Medical Officer in relation to safety.

d) Scottish Home and Health Department, SNBTS and Haemophilia Directors for Scotland and Northern Ireland meetings.

e) Coagulation Factor Working Party for Scotland and Northern Ireland.

f) Hospital Transfusion Committee.

g) Advice was considered from a wide variety of sources, including UK Departments of Health, UKHCDO, World Federation for Haemophilia, International Society for Thrombosis and Haemostasis, Serious Hazards of Transfusion Committee.

23. What was your understanding of the relative risks of infection from (i) the use of commercially supplied blood products, and (ii) the use of NHS blood products?

160) The above questions raise a large range of issues occurring over a 30-year period. Many of these issues have been addressed in the response to Question 21 and include;

a) During this period, there were major changes in the way blood products were procured and manufactured, and these in turn changed markedly the relative risks of infections, both for commercially sourced, and NHS derived, products.

b) The risks during this period not only related to the manufacturer, i.e. NHS or commercial, but also to the source of the plasma.

c) The perceived infective agents changed during this period.

d) The relative risks for different infections changed during this period.

e) The risks were different for plasma-derived compared with recombinant concentrates.

f) The risk from recombinant products was perceived to be related to the way in which they were manufactured which also evolved during the period.

g) The risks were different for human-sourced plasma compared with that derived from animals.

161) To respond directly to the question's two parts:

Infective risks of commercial human plasma-derived concentrates included consideration of:

a) Hepatitis B virus: Important even after the introduction of viral inactivation

b) Hepatitis D virus: Known to have been transmitted since 1970

c) Non-A non-B hepatitis: Important but risk reduced after 1988

d) HIV: Risk reduced in 1985 and abolished by 1987 in the UK

e) Hepatitis C virus: Important but risk reduction demonstrated after 1991

f) Hepatitis A virus: Reported in 1992 and preventable by vaccination

g) Parvovirus B19: First recorded 1983 and importance reviewed 1990s

h) Hepatitis G virus: Discovered in 1992 but sensitive to viral inactivation

i) TTV: Discovered in 1992 and probably inactivated

j) vCJD: Commercial concentrates derived from populations with lower risk of vCJD than UK.

k) West Nile virus, Zita etc.: Sensitive to viral inactivation processes.

Infective risks of NHS human plasma derived concentrates included consideration of:

NHS concentrates were infectious for the same range of viruses above except for

a) Non-A non-B hepatitis: Important but risk reduced after 1987

b) HIV: Risk abolished Dec 1984 in Scotland. Different arrangements in England.

c) vCJD: Risk considered greater from NHS concentrates from UK derived plasma.

Infective risks of animal-derived concentrates after 1980

Porcine viruses, e.g. porcine parvovirus

162) In some instances of viral infection, both NHS and commercial concentrates, transmitted the infections, but the risk was considered lower for NHS products, e.g. transmission of non-A non-B hepatitis in the early 1980s. What emerged is that NHS and commercial concentrates were equally infectious but the commercial ones were reported to contain more virus [1, 2].

References in respect of Question 23

1. Fletcher, M.L., et al., *Non-A non-B hepatitis after transfusion of factor VIII in infrequently treated patients.* Br Med J (Clin Res Ed), 1983. 287(6407): p. 1754-7.

2. Simmonds, P., et al., *Hepatitis C quantification and sequencing in blood products, haemophiliacs, and drug users.* Lancet, 1990. 336(8729): p. 1469-72.

24. You told the Penrose Inquiry that "it was generally known that I wished to avoid using commercial concentrates" [PRSE0000669]. Please explain why you wished to avoid using commercial concentrates and what steps you took in light of that wish.

163) The quotation "it was generally known that I wished to avoid using commercial concentrates" relates to my view in the early 1980s.

a) Prior to 1980, there had been a policy in Edinburgh to prefer the use of NHS produced products. This was primarily related to the perceived potential infective risks chiefly related to source plasma. SNBTS products were sourced from donors within Scotland. In the early 1980s the nature of the virus (es) or agent causing NANB hepatitis was unclear. It was possible that there might be local causative virus (es) to which some of the recipients might be immune and therefore protected.

b) To use concentrates prepared from oversees donors might risk exposing recipients to completely new and different viruses.

c) Commercial plasma-derived clotting factors were predominantly prepared from remunerated donors who were known to be at greater risk of viral infections [1].

164) My view was that NHS concentrates were probably therefore safer than those derived from remunerated donors. Patients were informed of my policy and each was given a small printed insert to keep with their Haemophilia Card which stated that if the individual presented to another Haemophilia Centre with a bleed, they should, if possible, receive an NHS derived product rather than a commercial one.

165) One of the disadvantages of this policy, as there was only a very limited supply of SNBTS manufactured factor VIII concentrate, was that patients were denied home treatment in the early 1980s. In 1980, only a very small minority of patients were on home treatment and there was very considerable pressure from many patients to be able to have home therapy.

166) I addressed the issue of the availability of factor VIII concentrate directly with SNBTS. This was the subject of much local and national discussion to develop arrangements to increase supply. The difficulties were not inconsiderable and required SNBTS to increase blood donor numbers. In the early 1980s it was the need for factor VIII concentrate manufacture that was the driver to increase donor numbers. The further difficulty was that there were greater losses in factor VIII during manufacture of concentrate compared with cryoprecipitate, and this lower yield had to be taken into account. By 1984, factor VIII production had been markedly increased as a result of a major logistic effort by SNBTS and home therapy was therefore available for many more patients.

167) This policy in the early 1980s related to factor VIII and IX concentrates for treating acute bleeds. There were a few occasions when concentrates not manufactured by SNBTS were required; these included the occasional use of a relatively high purity concentrate (SNBTS concentrate at this time was of a relatively low purity), and clotting factor concentrates for treating patients with anti-factor VIII antibodies.

168) My view at the end of 1984 was that heat-treated SNBTS concentrates accorded with the UKHCDO guidance, and that as it was probably safer from HTLVIII than heat- treated commercial concentrate, I was therefore prepared to continue with its use. In retrospect, that this was the correct decision was confirmed by demonstrating that there were no further infections after December 1984, despite the probable infection of the starting donor plasma [1].

169) When recombinant concentrates became available in the mid-1990s, I led the case for recombinant clotting factors being considered preferable to plasma-derived ones. All the recombinant concentrates at this time were prepared by commercial companies. This view was endorsed by UKHCDO and set out in its guidance [2].

References in respect of Question 24

1. Cuthbert, R.J., et al., *Efficacy of heat treatment of factor VIII concentrate.* Vox Sang, 1988. **54**(4): p. 199-200.

2. UKHCDO, *Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders.* Haemophilia, 1997. **3**: p.63-77.

25. What decisions and actions were taken by the Centre and by you to minimise or reduce exposure to infection?

170) This is a very broad question. The Centre and I addressed the need to minimise and reduce exposure to infection with a wide range of activities which included:

a) Keeping up to date with knowledge and developments of infective risks;

b) Discuss with colleagues risks and emerging risks and responses. Promote knowledge and discussion amongst staff;

c) Explain to patients and discuss how the risks were being managed as appropriate. Respond to inquiries. Collaborate with patient groups and societies and respond to requests for information and presentations;

d) Promote education including publications and research into risks and consequences, and disseminate emerging knowledge;

e) Promote treatment that minimises risk, e.g. can a blood product's use be avoided e.g. with use of fibrinolytic inhibitor or desmopressin? If a blood product is necessary which ones are available and most appropriate to the patient's circumstances?

f) Ensure there is a stock of the safest products that are available to treat acute bleeds, provide prophylaxis, and to cover surgery;

g) Promote development of guidelines;

h) Work with manufacturers of concentrates to develop and assess concentrates;

i) Promote the development of national and international arrangements to assess risk, e.g. post-marketing surveillance;

j) Collaborate with regulators to establish mechanisms to assess risks of infection;

k) Inform managers and funders of services of the risks of therapies;

l) Work with colleagues to ensure that resources are available to acquire the safest products.

Hepatitis

26. When you became director of the Centre in 1980, what was your knowledge and understanding of the risks of the transmission of hepatitis (including hepatitis B and NANB hepatitis/hepatitis C) from blood and blood products develop over time?

171) My understanding of the risks of virus transmission, including viruses that cause hepatitis, along with the development of knowledge and actions taken, has been set out in my response to previous questions, e.g. Questions 11 and 21.

172) The issue of hepatitis in haemophilia is a complex one and depends on how it is defined. In strict terms, hepatitis is a histological diagnosis and requires a tissue sample to make a diagnosis. What is usually referred to as 'hepatitis' is the finding of an elevated level of an enzyme in the blood, e.g. alanine amino transferase (ALT), which may reflect inflammation in the liver. There is a wide range of different causes and types of hepatitis which may be characterised by different clinical and laboratory features. This broad spectrum must be borne in mind when considering abnormal liver function test results in a person with haemophilia.

173) I was fortunate to be able to collaborate with and be guided by a senior and experienced academic virologist, Dr John Peutherer. In 1980, it was clearly established that hepatitis B was transmissible by blood products. Studies investigated this in Edinburgh in the 1970s and 1980s and demonstrated that despite the development and use of increasingly sensitive tests for hepatitis B infection to exclude infectious blood donations, clotting factor concentrates continued to transmit the virus [1-4].

174) It was known that a small number of individuals became chronic carriers of the virus. It was known that hepatitis D was a potential risk. Hepatitis A was not considered to be transmissible by blood products.

175) NANBH was well known as an entity in the early 1980s, but its nature was uncertain, again reflected by studies in Edinburgh. It was unclear how many viruses might be causative of the condition. Although it is now believed that much was due to hepatitis C virus, other blood transmissible viruses can cause NANBH, e.g. parvovirus. At this time, there was much uncertainty as to the severity and long- term consequences of NANBH with publications reflecting a spectrum of findings [5-8].

176) An important study in 1983 demonstrated that virtually all batches of clotting factor concentrates could cause NANBH and that the risk with NHS sourced material was similar to that from commercial concentrates [9]. Attempts to inactivate the presumed aetiological virus by heat treatment were underway, but it became apparent that the responsible agent(s) were not only resistant to the then available heat treatments, but that primates were not a suitable model for assessing viricidal efficacy [10]. The only way to assess efficacy of viricidal procedures was by testing in humans and to assess with fortnightly serial non-specific serial ALT measurements for many months using internationally agreed criteria [11].

177) During the second-half of the 1980s there was intense debate and studies to assess the efficacy of various viral inactivation strategies. These were initially primarily aimed at ensuring safety of concentrates from HIV but also to inactivate the cause(s) of NANBH. It was not until 1988 that there was a developing consensus that the then current viricidal processes were probably effective against the transmission of NANBH, although even at this time there was some uncertainty about the efficacy of dry heat treatment at 80 degrees for 72 hours

[12]. It was only with further studies that it was possible to demonstrate the safety of concentrates from NANBH, e.g. studies of newly developed SNBTS factor VIII and IX concentrates overseen by the Coagulation Factor Working Party for Scotland and Northern Ireland.

178) In addition to that of Dr Peutherer, I was fortunate to have the benefit of the expertise and guidance of further virologist who had taken a major lead in the assessment of the HTLVIII virus, and whose main area of study was viruses potentially transmissible by blood and blood products. Following the identification of HCV in 1989, Dr Simmonds set up and refined the diagnostic tests for the assessment of the virus. Additionally, he assessed the potential transmission of other viruses including ones that might cause hepatitis, e.g. hepatitis G virus.

179) A report in 1992 indicated that hepatitis A could be transmitted by concentrates manufactured with viral inactivation procedures. In response in Edinburgh, we reviewed the immune status of patients to this virus and offered hepatitis A vaccine to those without demonstrable immunity. Following development of new SNBTS manufactured clotting factor concentrates in the early 1990s, under the auspices of the Coagulation Factor Working Party for Scotland and Northern Ireland, studies revealed that their use did not result in hepatitis A transmission [13].

180) Reports have indicated that parvovirus can be transmitted by concentrates[14] manufactured with viral inactivation steps [15]. This virus has been reported to cause hepatitis.

181) There is no evidence that currently available licensed plasma-derived clotting factor concentrates transmit hepatitis C virus.

References in respect of Question 26

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5. Mannucci, P.M., et al., *Asymptomatic liver disease in haemophiliacs.* J Clin Pathol, 1975. **28**(8): p. 620-4.

6. Preston, F.E., et al., *Percutaneous liver biopsy and chronic liver disease in haemophiliacs.* Lancet, 1978. **2**(8090): p. 592-4.

7. Stevens, R.F., et al., *Liver disease in haemophiliacs: an overstated problem?* Br J Haematol, 1983. **55**(4): p. 649-55.

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9. Fletcher, M.L., et al., *Non-A non-B hepatitis after transfusion of factor VIII in infrequently treated patients.* Br Med J (Clin Res Ed), 1983. **287**(6407): p. 1754-7.

10. Colombo, M., et al., *Transmission of non-A, non-B hepatitis by heat-treated factor VIII concentrate.* Lancet, 1985. **2**(8445): p. 1-4.

11. Mannucci, P.M. and M. Colombo, *Revision of the protocol recommended for studies of safety from hepatitis of clotting factor concentrates. International Society for Thrombosis and Hemostasis.* Thromb Haemost, 1989. **61**(3): p. 532-4.

12. Mannucci, P.M. and M. Colombo, *Virucidal treatment of clotting factor concentrates.* Lancet, 1988. **2**(8614): p. 782-5.

13. Watson, H.G., et al., *Absence of hepatitis A virus transmission by high-purity solvent detergent treated coagulation factor concentrates in Scottish haemophiliacs.* Br J Haematol, 1995. **89**(1): p. 214-6.

14. Mortimer, P.P., et al., *Transmission of serum parvovirus-like virus by clotting-factor concentrates.* Lancet, 1983. **2**(8348): p. 482-4.

15. Lyon, D.J., et al., *Symptomatic parvovirus B19 infection and heat-treated factor IX concentrate.* Lancet, 1989. **1**(8646): p. 1085.

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

182) An integral part of my work was to keep abreast of developments in the field of viral hepatitis and ensure that patients would receive the best current advice. There were a broad range of activities from the regular clinical monitoring of patients to being alert to developments.

183) I was fortunate to have guidance of the local virologists, Dr John Peutherer and Professor Peter Simmonds, who had a special interest and expertise in viral infections which might result in hepatitis.

184) My range of activities included reporting on the outcome of investigations on all forms of hepatitis as exemplified in the publications listed below.

185) As evidence of my interest in the topic, I was invited to join the UKHCDO Hepatitis Working Party and participate in its activities. This included national activities to

oversee hepatitis in the UK by way of questionnaire and the development of national guidelines.

186) As chairman of the Coagulation Factor Working Party for Scotland and Northern Ireland, I oversaw the development of investigations to assess the safety of newly developed clotting factor concentrates.

187) As co-chairman of the Interdisciplinary Working Group, I oversaw with colleagues the establishment of the European Haemophilia Surveillance Scheme (EUHASS) which monitors infections arising in over 40,000 patients across Europe. I also served on its Steering Group when initially established.

188) Publications related to hepatitis include the following:

1. Ludlam, C.A. and J.F. Peutherer, *Hepatitis B infection in hemophilia.* Lancet, 1982. **2**(8301): p. 776-7.

2. Stirling, M.L., et al., *Incidence of infection with hepatitis B virus in 56 patients with haemophilia A 1971-1979.* J Clin Pathol, 1983. **36**(5): p. 577-80.

3. Ludlam, C.A., *Treatment of the haemophilias*, in *Supportive therapy in Haematology*, P.C. Das, C.T. Smit Sibinga, and M.R. Halie, Editors. 1985, Martinus Nijhoff: Boston. p. 167-174.

4. Simmonds, P., et al., *Hepatitis C quantification and sequencing in blood products, haemophiliacs, and drug users.* Lancet, 1990. **336**(8729): p. 1469-72.

5. Watson, H.G., et al., *Use of several second generation serological assays to determine the true prevalence of hepatitis C virus infection in haemophiliacs treated with non-virus inactivated factor VIII and IX concentrates.* Br J Haematol, 1992. **80**(4): p. 514-8.

6. Jarvis, L.M., et al., *Frequent reinfection and reactivation of hepatitis C virus genotypes in multitransfused hemophiliacs.* J Infect Dis, 1994. **170**(4): p. 1018-22.

7. Hanley, J.P., et al., *Treatment of hepatitis C infection in haemophiliacs: the Edinburgh experience.* Haemophilia, 1995. **1** Suppl 4: p. 36-8.

8. Jarvis, L.M., C.A. Ludlam, and P. Simmonds, *Hepatitis C virus genotypes in multi-transfused individuals.* Haemophilia, 1995. **1** Suppl 4: p. 3-7.

9. Ludlam, C.A., *Liver Biopsies.* The Haemophilia Society Bulletin, 1995.

10. Ludlam, C.A., *Therapeutic use of Factor IX concentrates.* Transzfuzio, 1995. **28**: p. 21-27.

11. Preston, F.E., et al., *Guidelines on the diagnosis and management of chronic liver disease in haemophilia.* Haemophilia, 1995. **1** Suppl 4: p. 42-4.
12. Preston, F.E., et al., *Heterogeneity of hepatitis C virus genotypes in hemophilia: relationship with chronic liver disease*. Blood, 1995. **85**(5): p. 1259-62.

13. Watson, H.G., et al., *Absence of hepatitis A virus transmission by high-purity solvent detergent treated coagulation factor concentrates in Scottish haemophiliacs.* Br J Haematol, 1995. **89**(1): p. 214-6.

14. Hanley, J., et al., *HCV and non-Hodgkin lymphoma*. Lancet, 1996. **347**(9011): p. 1339.

15. Hanley, J.P., et al., *Interferon treatment for chronic hepatitis C infection in hemophiliacs--influence of virus load, genotype, and liver pathology on response.* Blood, 1996. **87**(5): p. 1704-9.

16. Hanley, J.P., et al., *Investigation of chronic hepatitis C infection in individuals with haemophilia: assessment of invasive and non-invasive methods*. Br J Haematol, 1996. **94**(1): p. 159-65.

17. Hanley, J.P., et al., *Development of anti-interferon antibodies and breakthrough hepatitis during treatment for HCV infection in haemophiliacs.* Br J Haematol, 1996. **94**(3): p. 551-6.

18. Jarvis, L.M., et al., *Investigation of the relative infectivity and pathogenicity of different hepatitis C virus genotypes in hemophiliacs*. Blood, 1996. **87**(7): p. 3007-11

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19. Ludlam, C.A., *Clinical Relevance of Clotting Factor Characteristics*, in *Trigger Factors in Transfusion Medicine*, C.T. Smit Sibinga, P.C. Das, and E.L. Snyder, Editors. 1996, Kluwer Academic Publishers: Dordrecht. p. 91-102.

20. Watson, H.G., et al., *Hepatitis B serology and DNA detection in multitransfused haemophiliacs and factor VIII and IX concentrates.* Haemophilia, 1996. **2**(4): p. 229-34

21. Darby, S.C., et al., *Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation.* Lancet, 1997. **350**(9089): p. 1425-31.

22. Ludlam, C.A., *Viral safety of plasma-derived factor VIII and IX concentrates.* Blood Coagul Fibrinolysis, 1997. 8 Suppl **1**: p. S19-23.

23. Ludlam, C.A., *Treatment of haemophilia*, in *Recent Advances in Blood Coagulation 7*, L. Poller and C.A. Ludlam, Editors. 1997, Chruchill Livingstone: New York. p. 235-260.

24. Ludlam, C.A., J.P. Hanley, and P.C. Hayes, *Liver biopsy in haemophilia.* Br J Haematol, 1997. **97**(3): p. 690-1.

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28. Darby, S.C., et al., *Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV.* Blood, 2007. **110**(3): p. 815-25.

29. Weinstein, M., M. Makris, and C.A. Ludlam, *Biovigilance and pharmacovigilance for haemophilia.* Haemophilia, 2010. **16** Suppl 5: p. 17-21.

30. Khan, M.M., et al., *Hepatitis C infection and outcomes in the Scottish haemophilia population.* Haemophilia, 2013. **19**(6): p. 870-5.

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

189) My responses to Questions 26 and 27 address this question. In summary my actions included;

a) Attempting to be well informed about viruses that might cause hepatitis

b) Monitoring individuals for hepatitis so as to be aware of its extent in patient

c) Ensuring that blood products were used appropriately

d) Using desmopressin and tranexamic acid when appropriate

e) Using cryoprecipitate in preference to factor VIII concentrate for those patients likely only to require occasional therapy or small children. After the introduction of heat-treated concentrates these had the advantage of preventing transmission of HTLVIII compared with cryoprecipitate

f) When available using concentrates that were manufactured by a process likely to reduce the risk of hepatitis infection

g) Arranging for susceptible patients to be offered vaccination against hepatitis A and B viruses

h) Collaborating with others and other organisations to develop and assess new concentrates and assess their safety from hepatitis

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

Hepatitis B

190) In individuals with haemophilia, most who became infected developed immunity and cleared the virus from their circulation. A small percentage did not clear the virus and these individuals continued potentially to have inflammation in their liver and be at risk of cirrhosis and liver cancer. These individuals were at risk of hepatitis D infection which could cause an exacerbation of hepatitis and can also form chronic infection.

NANBH

191) This was a condition very incompletely understood in the 1970s and 1980s particularly because the cause(s) were unknown and it was a diagnosis of exclusion. There was evidence that it might be due to more than one virus [1, 2]. The clinical spectrum appeared very varied; some of those affected appeared to clear the infection (in that their liver function test abnormalities lasted less than six months), while others continued to have chronically or intermittently abnormal liver function test results. There was considerable uncertainty as to the liver pathology in those who had chronic NANBH and whether the pathology was static or progressive. The reports during the period 1975 – 1984 demonstrated a spectrum of pathology and with uncertainty about its propensity to be progressive.

192) The situation became clearer in 1985 with the study from Sheffield demonstrating a range of pathology including histology which in other settings was associated

with more severe and progressive liver disease, e.g. chronic active hepatitis. The report also revealed that in some patients who had had two biopsies there was progression of the histology from mild to more severe inflammation [3]. The conclusion of these reports was supported by two subsequent reports, one from North America and one from Germany [4, 5].

193) Following the report from Hoofnagle in December 1986 [6] that interferon therapy appeared to be effective in a proportion of patients with NANBH, an extensive collaboration was established with Dr Peter Hay (hepatologist) who oversaw the assessment and treatment of patients with hepatitis at a regular clinic within the Haemophilia Centre. This led to a very active programme in which patients were assessed and treatment options considered and offered. Following the identification of the hepatitis C virus, this process dovetailed well with the virology assessment techniques for this virus that were being established by Dr Simmonds.

194) The findings of the assessments and responses to treatment of the patients have been reported and they reflect a spectrum of pathology and responses.

195) I have provided a list of references in response to Question 27. These reflect how my understanding grew or changed over time.

Hepatitis A

196) That hepatitis A appeared to be transmitted by clotting factor concentrates was first reported in 1992 from several centres in Europe. Infection resulted in episodes of worsening hepatitis. Although it appeared that this was a self-limiting infection, it was an assault on the liver which was already compromised from active hepatitis C infection.

References in respect of Question 29

1. Craske, J., N. Dilling, and D. Stern, *An outbreak of hepatitis associated with intravenous injection of factor-VIII concentrate.* Lancet, 1975. **2**(7927): p. 221-3.

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3. Hay, C.R., et al., *Progressive liver disease in haemophilia: an understated problem?* Lancet, 1985. **1**(8444): p. 1495-8.

4. Aledort, L.M., et al., *A study of liver biopsies and liver disease among hemophiliacs.* Blood, 1985. **66**(2): p. 367-72.

5. Schimpf, K., *Liver disease in haemophilia.* Lancet, 1986. **1**(8476): p. 323.

6. Hoofnagle, J.H., et al., *Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report.* N Engl J Med, 1986. **315**(25): p. 1575-8.

30. A witness who worked at the Centre between 1973 and 1975 has described in a written statement to the Inquiry a list that was kept in a drawer at the Centre listing the names of patients who had NANB hepatitis. One of the witness's roles was to update the list after samples taken from patients had been tested. The witness states that patients were not aware of the list. Were you aware of the existence of a list of this kind? If so provide full details.

197) I do not have any knowledge of such a list.

HIV and AIDS

31. What was your knowledge and understanding of HIV (HTLV-III) and AIDS and in particular of the risks of transmission from blood products? How did your understanding develop over time?

198) I should like to respond fully and in detail to this question, but time available, and to some extent my memory, does not allow me to do so as fully as I should wish. In my response to Question 21, I have set out my initial activity in response to the appearance of AIDS. Rather than setting out my present memory of 'knowledge and understanding of HIV and AIDS' some of my publications of the 1980s and 1990s (cited below) provide a fuller reflection of the changing situation as I viewed it in these decades. In addition, 'Long Term Safety Monitoring in Edinburgh' sets out in some detail the local arrangements which developed in the 1980s and 1990s [PRSE0002404].

199) The question also asks as to how my 'understanding' developed over time. This is addressed in the reviews cited below and also in my response to Question 21. The efficacy of various viral inactivation processes in relation to HIV, particularly from 1984 until 1990, was the subject of intense concern and although many processes were successful there were reports where the procedures appeared to fail (reviewed by Mannucci and Pierce [1, 2]).

200) The following is a selection of my references (1983-2010) in relation to development immune changes in haemophilia and HIV/AIDS demonstrating my developing understanding.

1. Ludlam CA, Carr R, Veitch SE, Steel CM. Disordered immune regulation in haemophiliacs not exposed to commercial factor VIII. Lancet 1983; 1(8335): 1226.

2. Carr R, Veitch SE, Edmond E, et al. Abnormalities of circulating lymphocyte subsets in haemophiliacs in an AIDS-free population. *Lancet* 1984; **1**(8392): 1431-4.

3. Ludlam CA. Treatment of the haemophilias. In: Das PC, Smit Sibinga CT, Halie MR, eds. Supportive therapy in Haematology. Boston: Martinus Nijhoff; 1985: 167-74.

4. Ludlam CA, Tucker J, Steel CM, et al. Human T-lymphotropic virus type III (HTLV-III) infection in seronegative haemophiliacs after transfusion of factor VIII. *Lancet* 1985; **2**(8449): 233-6.

5. Tucker J, Ludlam CA, Craig A, et al. HTLV-III infection associated with glandular-fever-like illness in a haemophiliac. *Lancet* 1985; **1**(8428): 585.

6. Cuthbert RJ, Ludlam CA, Brookes E, McClelland DB. Efficacy of heat treatment of factor VIII concentrate. Vox Sang 1988; 54(4): 199-200.

6. Ludlam CA. Effects of alloantigens in blood products on immunity. *Semin Hematol* 1988; **25**(2 Suppl 1): 3-7.

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8. Steel CM, Ludlam CA, Beatson D, et al. HLA haplotype A1 B8 DR3 as a risk factor for HIV-related disease. *Lancet* 1988; **1**(8596): 1185-8.

9. Cuthbert RJ, Ludlam CA, Rebus S, et al. Human immunodeficiency virus detection: correlation with clinical progression in the Edinburgh haemophiliac cohort. *Br J Haematol* 1989; **72**(3): 387-90.

10. Balfe P, Simmonds P, Ludlam CA, Bishop JO, Brown AJ. Concurrent evolution of human immunodeficiency virus type 1 in patients infected from the same source: rate of sequence change and low frequency of inactivating mutations. *J Virol* 1990; **64**(12): 6221-33.

11. Cuthbert RJ, Ludlam CA, Tucker J, et al. Five year prospective study of HIV infection in the Edinburgh haemophiliac cohort. *Bmj* 1990; **301**(6758):

956-61.

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13. Peutherer JF, Rebus S, Barr P, Ludlam CA, Watson HG, Steel MC. Confirmation of non-infection in persistently HIV-seronegative recipients of contaminated factor VIII. *Lancet* 1990; **336**(8721): 1008

14. Simmonds P, Balfe P, Ludlam CA, Bishop JO, Brown AJ. Analysis of sequence diversity in hypervariable regions of the external glycoprotein of human immunodeficiency virus type 1. *J Virol* 1990; **64**(12): 5840-50.

15. Simmonds P, Balfe P, Peutherer JF, Ludlam CA, Bishop JO, Brown AJ. Human immunodeficiency virus-infected individuals contain provirus in small numbers of peripheral mononuclear cells and at low copy numbers. *J Virol* 1990; **64**(2): 864-72.

16. Willocks L, Ludlam CA, Welsby PD. Polycythaemia and HIV infection. *Lancet* 1990; **336**(8718): 812-3.

17. Simmonds P, Beatson D, Cuthbert RJ, et al. Determinants of HIV disease progression: six-year longitudinal study in the Edinburgh haemophilia/HIV cohort. *Lancet* 1991; **338**(8776): 1159-63.

18. Simmonds P, Zhang LQ, McOmish F, Balfe P, Ludlam CA, Brown AJ. Discontinuous sequence change of human immunodeficiency virus (HIV) type 1 env sequences in plasma viral and lymphocyte-associated proviral populations in vivo: implications for models of HIV pathogenesis. *J Virol* 1991; **65**(11): 6266-76.

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20. Batchelor A, Steel CM, Ludlam CA. Enhancement of human T cell responses to allogeneic stimuli by factor VIII concentrates. *Br J Haematol* 1992; **82**(1): 94-8

21. Cuthbert RJ, Ludlam CA, Steel CM, Beatson D, Peutherer JF. Immunological studies in HIV seronegative haemophiliacs: relationships to blood product therapy. *Br J Haematol* 1992; **80**(3): 364-9.

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43. Weinstein M, Makris M, Ludlam CA. Biovigilance and pharmacovigilance for haemophilia. *Haemophilia* 2010; **16 Suppl 5**: 17-21.

References in respect of Question 31

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2. Mannucci PM, Colombo M. Virucidal treatment of clotting factor concentrates. Lancet. 1988;**2**(8614):782-5.

32. How and when did you first become aware that there might be an association between AIDS and the use of blood products?

201) I first became aware in 1982 that there was a possibility that AIDS might be acquired by the use of blood products. I cannot now remember exactly when or how, but I eventually was able to read the original MMWR report of July 1982 which described three individuals with haemophilia who had developed AIDS. At the time this publication was taken by the Medical School Library, but the copy arrived by mail sometime later in the year. My attention must have been drawn to this report because MMWR was not one of the specialist journals that I aimed to read regularly [1].

Reference in respect of Question 32

1. *Pneumocystis carinii pneumonia among persons with hemophilia A.* MMWR Morb Mortal Wkly Rep, 1982. **31**(27): p. 365-7.

33. What steps did you then take in light of that awareness?

202) Keeping up to date with new publications on the topic – this was less easy than today, being before the days of the internet.

203) Discussing the developing situation with haemophilia and other colleagues including:

a) Local haematology colleagues

b) Virologist Dr John Peutherer (with whom I was collaborating on hepatitis B investigation in haemophilia)

c) Colleagues in SNBTS locally and nationally

d) UKHCDO colleagues, meetings and collaborating in initiatives to understand the developing situation

e) Continued to participate in the UKHCDO Hepatitis Working Party which was given the responsibility to monitor the developing situation of AIDS in haemophilia

f) Participation in regular meetings with Scottish Home and Health Department along with SNBTS and Haemophilia Directors in Scotland and Northern Ireland

g) Discussions within regular Haemophilia Director Meetings for Scotland and Northern Ireland

h) Liaised with Communicable Disease Surveillance Centre to monitor reporting of AIDS cases in Scotland

204) In conjunction with Dr Steel established tests to assess immune function in those with haemophilia in early 1983.

205) Continued to make available Haemophilia Society Bulletins and Haemofacts AIDS leaflets in the Haemophilia Centre Waiting Room (which patients could take away)

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

206) My responses to Questions 31 and 33 have also addressed this question.

207) In summary, shortly after the initial cases of AIDS were described there was much uncertainty.

a) Although it was quite possible that the cause of AIDS was a new, or an existing virus that had mutated, e.g. hepatitis B virus, there were many other possible causes being considered. Even in 1992, some people had difficulty accepting that AIDS was due to a virus, see Ludlam [1].

b) The prevalence of AIDS in the general population in the US was greater than in the UK or mainland Europe.

c) In those with haemophilia, the risk of developing AIDS appeared to be greater in the US than the UK or mainland Europe.

208) Having established the urgent need for greater information I undertook the following investigations to assist with optimising treatment decisions:

a) Established assessment of immune status of people with haemophilia in early 1983 and continued this in a wide range of recipients of blood products [2-4]

b) Established with SNBTS a batch 'dedication' system to reduce the exposure of users to different batches of factor VIII concentrate

c) Assisted SNBTS with the assessment of heat-treated factor VIII concentrate development

d) Established at the earliest opportunity to assess individuals for anti-HTLVIII in late 1984 which identified that some individuals had been exposed to HTLVIII [5]. This led to the setting up of the meeting in London on 10th December 1984 at which the decision was made to recommend heat-treated concentrates in preference to non-heated ones [HCDO0000394_117].

e) In December 1984, offered all appropriate patients heat-treated SNBTS concentrate and for those on home treatment exchanged their non-heat-treated product at home for heat-treated.

f) Continued to monitor all in receipt of blood products for anti-HTLVIII and immune function.

References in respect of Question 34

1. Ludlam CA. AIDS: the alternative view. Lancet. 1992;**339**(8808):1547-8.
2. Cuthbert RJ, Ludlam CA, Steel CM, Beatson D, Peutherer JF. Immunological studies in HIV seronegative haemophiliacs: relationships to blood product therapy. Br J Haematol. 1992;**80**(3):364-9.
3. Carr R, Veitch SE, Edmond E, Peutherer JF, Prescott RJ, Steel CM, et al. Abnormalities of circulating lymphocyte subsets in haemophiliacs in an AIDS-free population. Lancet. 1984;**1**(8392):1431-4.
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35. What, if any, actions did you take to reduce the risk to your patients of being infected with HIV?

209) The actions which I took to reduce risk have been described in the responses to questions 31, 33, and 34. These included;

a) Assume that AIDS might be caused by a transmissible agent.

b) Avoid use of blood product if possible. Considered whether desmopressin may be appropriate. Following the publication by Mannucci of its use in haemophilia in 1977, I had undertaken some research which demonstrated its use in treatment of patients [1] including surgery. To highlight its use, I was invited to give a lecture on the topic at the UKHCDO Annual Scientific Meeting in Glasgow in 1980.

c) Use tranexamic acid to inhibit fibrinolysis – particularly useful to help haemostasis following dental surgery.

d) Continued the use of cryoprecipitate for those individuals who might not need much blood product support. This was existing policy for reducing the risk of hepatitis.

e) Continued to promote the use of SNBTS products because they were derived from a population with an apparent low risk of AIDS.

f) With SNBTS introduced a batch dedication system for clotting factor concentrates to reduce recipient exposure to different batches.

References in respect of Question 35

1. Ludlam CA, Peake IR, Allen N, Davies BL, Furlong RA, Bloom AL. Factor VII and ibrinolyticresponse to deamino-8-D-argenine vasopressin in normal subjects and dissociate response in some patients with haemophilia and von Willebrand's disease. Br J Haematol. 1980;**45**(3):499-511.

36. Did you continue to use blood products to treat patients, after becoming aware of the possible risks of infection of HIV? Why?

210) It is not clear which time period is being considered by the question. It appears to concern risks after the identification of HIV (as the cause of AIDS). In an attempt to be most helpful, I am assuming that the question is directed at whether I continued to use blood products to treat patients, after becoming aware of the possible risks that a transmissible virus might be the cause of AIDS. My response to that concern is:

211) I continued to use blood products after it became apparent that AIDS in 1982 might be caused by a transmissible virus for the following reasons:

a) Initially, there was no definitive evidence that AIDS could be caused by a transmissible agent, apart from the reports of AIDS being reported in a few individuals with haemophilia.

b) The cause of immune disturbance in many asymptomatic individuals with haemophilia was not understood, but it appeared that use of blood products, independently of AIDS risk, was causing demonstrable abnormalities.

c) The clinical presentation of AIDS in haemophilia appeared different from that in other individuals, e.g. absence of Kaposi's sarcoma in those with haemophilia. This raised the possibility that the cause of AIDS in those with haemophilia might be different. The interpretation of observations referred to in (b) above had to be considered.

d) At a time when two cases became apparent in the UK in 1983 (out of 5,000 individuals with haemophilia), there was still an appreciable risk of dying in the UK due to bleeding [1, 2] even with the use of blood products.

e) I assessed that the risk of Edinburgh patients becoming infected with a putative virus was low because of the absence of AIDS cases in the general population in Scotland and because of the efforts of SNBTS to encourage individuals in 'at risk' groups to refrain from blood donation.

f) Although it was clearly possible that there was a transmissible aetiological agent, there was also a possibility it might be inactivated, diluted or neutralised during the manufacture of a blood product.

g) As I was able to maintain most patients on SNBTS blood products, I considered the risk of patients being infected by a putative virus was small.

h) UKHCDO guidance was to continue to use NHS products as previously (guidance from meeting in May 1983).

i) In other countries, where AIDS in both the general population and in those with haemophilia was more common that in the UK or Scotland, the guidance was to continue to use clotting factor concentrates, e.g. advice from the National Haemophilia Foundation in the US.

j) Part of continuing to use blood products was to establish from early 1983 onwards an active programme to monitor the immune status of those with haemophilia.

k) UKHCDO established arrangements to monitor nationally the occurrence of clinical features that might indicate infection with a putative virus.

l) I tried to keep myself well informed about developments and collaborate with local, national and international colleagues.

References in respect of Question 36

1. Rizza, C.R. and R.J. Spooner, *Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976-80: report on behalf of the directors of haemophilia centres in the United Kingdom.* Br Med J (Clin Res Ed), 1983. **286**(6369): p. 929-33.
2. Rizza, C.R., R.J. Spooner, and P.L. Giangrande, *Treatment of haemophilia in the United Kingdom 1981-1996.* Haemophilia, 2001. **7**(4): p. 349-59.

Response to Risk

37. Did you take steps to ensure that patients were informed and educated about the risks of hepatitis and HIV? If so what steps?

212) There was a broad range of ways in which patients and their families were informed about the risks of hepatitis and HIV.

a) Reminding patients about the risk of viral infection from using blood products was part of the routine arrangement for patients and was evident with the standard blood tests at review clinics and feedback of the results of these at subsequent clinics. I was always ready to respond to specific inquiries about various risks of infection by any virus [PRSE0002404; PRSE0003787; PRSE0003062].

b) At meetings of the patients' Scottish Haemophilia Group and the Edinburgh patient group the issue of viruses was considered. I remember being invited to speak at the Scottish Haemophilia Group in the early 1980s on desmopressin and this would have included its advantage in some patients of reducing the risk of virus infection. I was also invited by the UK Haemophilia Society to speak at their meetings on the topic.

c) In the very early 1980s all patients were issued with a small information sheet for inclusion with their Haemophilia Card requesting that if they attended another Haemophilia Centre and required treatment that they receive an NHS product if possible. This was to reduce the risk of patients being exposed to non-UK viruses and the reasons for this was explained when the patients were given this small sheet.

d) Patients commencing home treatment signed a consent form in which it was made explicit that there was a risk of hepatitis from the treatment. There was a protocol outlining arrangements for initiation of home therapy. These documents are attached as WITN3428006.

e) Patients were aware that I had a special interest in the safety of blood products and that we were actively researching the topic. As an example, I

have appended [WITN3428007] a copy of a letter which was sent out in 1986 to obtain consent for the use of a stored blood sample for family members.

f) Hepatitis B vaccine, after it became available was offered to susceptible patients.

g) After the recognition that hepatitis A could be transmitted by blood products in 1992, those patients who were susceptible were offered hepatitis A vaccine.

h) More broadly, Scottish Haemophilia Directors provided to the Penrose Inquiry a document describing general arrangements in Scotland by which patients were informed about hepatitis [PRSE0003869].

i) The developing situation in relation to AIDS in the early 1980s was very difficult and confusing because of a lack of any diagnostic test. Even when the initial research anti-HTLVIII test results were available, there was considerable uncertainty about the interpretation of the results. In the document entitled 'Information about HIV available to patients and families' [PRSE0000660] which I offered to the Penrose Inquiry, I summarised the developing availability of information.

38. In your statements to the Penrose Inquiry you state that there were concerns about moving to heat-treated products. What concerns did you have, and why?

213) I did have a concern about the move to heat-treated products because in the heating process the factor VIII molecule structure might be altered. It is well known that heating a protein may alter its structure. The recipient's immune system might recognise the changed molecule as a 'foreign' protein and develop an inhibitory antibody against it. Such an antibody would inhibit the activity of the infused heat-treated factor VIII making therapy ineffective. Additionally, there was a possibility that the inhibitory antibody might cross react with native, or unheated, factor VIII also rendering conventional therapy ineffective in these patients. Many of the issues are set out in Chapter 23 of the Penrose Report.

214) As background information, it should be borne in mind that about one third of small children with severe haemophilia develop these inhibitory antibodies in response

to standard factor VIII. Factor VIII is a large protein and is particularly prone to stimulate antibody production.

215) As evidence that my reservations were of concern to others, I draw attention to the views expressed in the Lancet by an immunologist and a blood transfusion expert following the decision made at the meeting on 10th December 1984 to recommend use of heat-treated factor VIII concentrate [1].

216) In my evidence to the Penrose Inquiry I reported that I had collaborated with SNBTS in assessing heated factor VIII concentrate by giving test infusions to patients during 1984. I was very careful to follow up infusion with samples to assess for the development of an inhibitory antibody. Following the small number of infusions, no inhibitory antibodies were detected, but this was not evidence that when given to a large number of patients some increase in antibodies might arise.

217) At this time, in the early 1980s, commercial factor VIII manufacturers were investigating heat treatment, but there was very little knowledge in the wider community of this work because of the commercial secrecy associated with the developments.

218) My concern that small changes in the manufacturing process for factor VIII concentrate might alter the factor VIII molecule was unfortunately borne out by two subsequent instances where this was reported to have occurred [2, 3].

219) As it turned out, it was fortunate that heat treatment, even at higher temperatures than were being considered at the end of 1984, did not appear to result in the development of an increased risk of anti-factor VIII antibody development [4].

220) My further concern about the use of heat treatment is that because it reduced the yield of factor VIII during manufacture this might reduce the amount of treatment available for patients. This was a relatively minor concern compared with the very important one of trying to reduce risk of virus transmission.

References in respect of Question 38

1. Bird AG, Codd AA, Collins A. Haemophilia and AIDS. Lancet. 1985;1(8421):162-3.

2. Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermylen J. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. Thromb Haemost. 1993;69(2):115-8.

3. Peerlinck K, Arnout J, Di Giambattista M, Gilles JG, Laub R, Jacquemin M, et al. Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII concentrate. Thromb Haemost. 1997;77(1):80-6.

4. Cuthbert RJ, Ludlam CA, Brookes E, McClelland DB. Efficacy of heat treatment of factor VIII concentrate. Vox Sang. 1988;54(4):199-200.

39. What considerations did you give to the use of heat-treated products prior to the meeting of UKHCDO Reference Centre directors on 10th December 1984 [HCDO0000394_117]? Did you agree with the recommendations to use heat-treated concentrates?

221) The initial endeavours to heat treat blood products were aimed at reducing the risk of transmission of hepatitis. The heat treatment strategies that were being considered had to demonstrate that they were effective against unidentified virus (es) that caused NANBH and that they did not damage the clotting factor molecule in the therapeutic product. No available concentrates with these proven characteristics were available in 1984, and therefore it was not appropriate to have considered their use for routine treatment of patients.

222) I was aware that SNBTS was very actively considering various heat treatment strategies that might be appropriate to reduce the risk of hepatitis transmission. To assist in this, I assessed a sample of pasteurised factor VIII concentrate in 1983 in a single patient (who had been informed and had given consent) who had experienced repeated reactions to the product.

223) The situation changed at the end of October and beginning of November 1984 when it was evident both that some patients in Edinburgh had seroconverted to HTLVIII as a result of receiving SNBTS factor VIII concentrate, and that initial reports showed that HTLVIII appeared to be heat sensitive to dry heating at 68 degrees centigrade. The aim then became heat treatment to reduce the risk of HTLVIII infection (rather than that of hepatitis).

224) As a result of these observations, SNBTS dry heated samples of its factor VIII concentrate at 68 degrees for 2 hours. I was invited to assess it in patients. This I did, so far as I can recall, in a small number of informed and consenting

individuals. There were no reactions, recovery of the factor VIII in the circulation was as anticipated, and no inhibitory antibodies were detected subsequently.

225) At the meeting on 10 December 1984 there was a long discussion about the potential risks and benefits of heat treatment [HCDO0000394_117]. Although I had reservations about heat treatment, I agreed that, on balance, it was appropriate to proceed to recommend such products. In doing so at this time there was minimal evidence of the 'necessary' heating arrangement to prevent HTLVIII transmission. In subsequent studies the apparent efficacy of 68 degrees for 2 hours heating was demonstrated in Scotland, but it became clear that a higher temperature for a longer period would offer a higher degree of protection.

40. Do you consider that heat-treated products should have been made available earlier? If not, why?

226) I do not think it would have been appropriate to introduce heat-treated products as routine therapy earlier than December 1984. It would have been appropriate to consider heat-treated products earlier under a clinical trial arrangement, but to do so would have required evidence that the manufacturing process was likely to have led to a product that did not transmit NANB hepatitis.

227) The original aim of heat treatment was to prevent clotting factor concentrates from transmitting the causative virus (es) of NANB hepatitis. The history describing the difficulties and attempts to prevent NANB virus (es) transmission was recorded in considerable detail in Chapter 23 of the Penrose Report. It was unclear in the 1980s how many viruses might be responsible. There was no specific test for the presumed agent(s). The only way to test safety was by assessment in previously untreated patients by serially measuring liver function tests over six months as set out in the ISTH guideline [1]. There was no evidence that any of the available techniques could prevent NANB hepatitis in recipients at this time [2].

228) The situation changed at the end of 1984 when initial evidence emerged that retroviruses and HTLVIII were heat sensitive [3, 4]. The immediate priority at this time was to reduce the risk of further batches of concentrate transmitting HTLVIII rather than to prevent NANB hepatitis transmission. It was therefore appropriate to introduce a heating regimen which had been reported to inactivate the virus. It was essential to monitor recipients of such products for evidence of HTLVIII

infection [5, 6] and the development of inhibitory antibodies against the clotting factor.

References in respect of Question 40

1. Schimpf K, Mannucci PM, Kreutz W, Brackmann HH, Auerswald G, Ciavarella N, et al. Absence of hepatitis after treatment with a pasteurized factor VIII concentrate in patients with hemophilia and no previous transfusions. N Engl J Med. 1987;316(15):918-22.

2. Colombo M, Mannucci PM, Carnelli V, Savidge GF, Gazengel C, Schimpf K. Transmission of non-A, non-B hepatitis by heat-treated factor VIII concentrate. Lancet. 1985;2(8445):1-4.

3. Levy JA, Mitra G, Mozen MM. Recovery and inactivation of infectious retroviruses from factor VIII concentration. Lancet. 1984;2(8405):722-723.

4. MMWR. Update: Acquired Immunodeficiency syndrome (AIDS) in persons with hemophilia. MMWR Morb Mortal Wkly Rep. 1984;33:589-91.

5. Rouzioux C, Chamaret S, Montagnier L, Carnelli V, Rolland G, Mannucci PM. Absence of antibodies to AIDS virus in haemophiliacs treated with heat-treated Factor VIII concentrate. Lancet. 1985;1(8423):271-2.

6. Cuthbert RJ, Ludlam CA, Brookes E, McClelland DB. Efficacy of heat treatment of factor VIII concentrate. Vox Sang. 1988;54(4):199-200.

41. In your evidence to the Penrose Inquiry [PRSE0003026] you stated that during the period December 1984 to June 1986 it was necessary to assume that all concentrates could transmit the causative agents for NANB hepatitis. What steps did you take to reduce the risk of your patients being exposed to NANB hepatitis in light of that assumption? Did you inform patients of this assumption?

229) The aim of introduction of heat treatment of factor VIII concentrate in December 1984 was to attempt to reduce the risk of infection by HTLVIII. There was never the expectation that 68-degree heating for 2 hours would be effective against the virus (es) that were thought to cause NANB hepatitis. Up to December 1984, the policy was to use desmopressin, tranexamic acid, and cryoprecipitate where possible to reduce the risk of NANB hepatitis in patients who might only require a few treatments. Therefore, after December 1984, the risks of NANB hepatitis transmission by cryoprecipitate and concentrate did not change. The risk of HTLVIII infection was reduced by heating concentrate. Blood donor screening for anti-HTLVIII was not introduced until October 1985 and therefore cryoprecipitate before this date could transmit HTLVIII.

230) I did not specifically inform patients after December 1984 that the risk of NANB hepatitis was likely to continue after this date, because there was never the

suggestion that it would be reduced significantly by the heating regimen that was introduced. Because there had been no change in the perceived risk there was therefore no need to inform patients. Any patients who had inquired would have had the situation explained.

42. Do you have anything further to add to the evidence you provided to the Penrose Inquiry about heat treatment and the availability of heat-treated products after 1984?

231) Thank you for the invitation to provide further evidence in relation to the availability of heat-treated products after 1984.

232) I provided extensive information to the Penrose Inquiry and have nothing further to add to that material.

43. Do you consider that your decisions and actions and those of the Centre 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.

233) Under the existing circumstances, and with the then current state of knowledge, I consider that the decisions and actions taken at the Centre were reasonable and appropriate and in line with national guidelines and recommendations.

234) The second part of Q 43 is a very broad question and one that has to take into account the evolving state of medical knowledge on all infective agents, the then current legislation, ethical and professional guidelines. The response to the question as to what *might* have been done differently very much depends on what information was available to make the decisions. To clarify this, I have set out some examples of decisions and actions that were possible.

235) The question asks if 'decisions and actions' '**could** have been done differently'. There are things that could have been done differently in relation to HIV including:

a) Stopping the use of all blood products – this would have prevented all new infections from any cause. Any effects of changes in therapy would depend upon when those changes were introduced.

b) Reducing or stopping all concentrate use but continuing with cryoprecipitate and fresh frozen plasma. Any change in risk of infection would likely be different for different infectious agents.

c) Reducing or stopping the use of all imported concentrates.

d) Heat-treated concentrates could have been made available earlier.

e) Once it was apparent that the Scottish plasma supply had become contaminated with HTLVIII, Scotland could have switched to the use of commercial heat-treated concentrates.

f) Patients could have been regularly asked at each review clinic if they wished to continue with their current treatment.

g) Patients could have been invited to regular meetings and given an update on the latest AIDS information nationally and internationally.

236) The question also asks if 'decisions and actions' '**should** have been done differently'. Is this part of the question seeking suggestions based on the historic (i.e. then current) information, or on information that was subsequently and/or is now available?

237) Based on the **then** current level of knowledge:

The view has been expressed by patients to the present Inquiry that they should have been informed about the risk of AIDS from blood products in 1983 and 1984. Whilst I was aware from the Haemophilia Society that there was anxiety in UK patients expressing concern and seeking information (particularly about the use of imported concentrates), as I have recorded elsewhere, I do not recall such inquiries from patients in Edinburgh. I think this was probably because patients were being treated with local NHS prepared therapy. Had I been asked by them, I would have explained the current information in relation to AIDS and indicated that it was possible that an infective agent might get into the blood supply, but that I considered the risk to be small. I would not have recommended any change of therapy.

238) Based on the **now,** current level of knowledge:

a) If it had been known in 1978 that clotting factor concentrates could transmit HIV, and that HIV was an almost universally fatal infection, the importation of concentrates should have been ceased at this time. Any such information should then have been made available to patients at the time.

b) It would have been essential to review the use of all UK blood products after 1978.

c) UK sourced heat-treated concentrates should have been introduced prior to the end of 1984.

d) Further information would have affected the discussion about whether it was appropriate to move away from UK blood products in 1997 to reduce the risk of vCJD.

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

239) The only way to prevent infections by the use of "infected blood products" was to stop using all blood products. In the 1980s there was no way of being certain that a blood product would not result in an infection. Even after the introduction by 1988 of what appeared to be adequate viral inactivation steps to prevent transmission of HIV and NANB hepatitis, there was still evidence of transmission of other viruses, e.g. hepatitis A and parvovirus.

45. 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 in patients with bleeding disorders? What, if any, do you consider could or should have been done differently by these others?

240) These are very broad questions and appear to relate to any infection which might be transmitted by blood or a blood product. I do not know of all the circumstances in which other individuals or organisations were operating and therefore it is difficult for me to propose what could or should have been done differently by them.

46. Do you consider that greater efforts could and/or 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 not?

241) I do not have any knowledge about efforts that were considered prior to 1980 to inactivate viruses in blood or blood products. This is a technical question which would be better addressed by manufacturers. From my perspective, as I have set out in my other responses, it was a major challenge to attempt to inactivate unidentified viruses in clotting factor concentrates whilst preserving the integrity and activity of potential unstable individual clotting factors. One of the major considerations was whether heat-treated blood products would readily solubilise, as such processing tended to make a therapeutic material difficult to dissolve. This was more likely to be a problem with relatively low purity products, as was more characteristic of concentrates in the 1970s. One reason that viral inactivation became possible in the 1980s was because of technical advances resulting in the development of purer products.

Section 5: Treatment of Patients and Edinburgh Royal Infirmary

Provision of information to patients

47. What information did you provide or cause to be provided to patients with a bleeding disorder (and to patients who did not have a bleeding disorder but were treated with blood products for other conditions) about the risks of infection in consequence of treatment with blood products prior to such treatment commencing? Please detail whether and if so how this changed over time.

242) There was information from a wide variety of sources about the risk of hepatitis and HIV infection by blood products used for treating people with congenital bleeding disorders. About 10 years ago, I summarised them for the Penrose Inquiry and I think they are likely to be more accurate descriptions than what I could compile now.

243) The relevant documents are:

a) Information about HIV available to Patients and Families [PRSE0004704]

b) Response to request of 16th November from the Penrose Inquiry about Topic C5 (NANBH) by Professor Ludlam [PRSE0003062]

c) Information available for Patients about Hepatitis Risk (prepared by Haemophilia Directors in Scotland) [PRSE0003869]

244) I do not have details of information which might have been provided to patients without bleeding disorders who were treated with blood products such as red cells.

48. What information did you provide or cause to be provided to patients about alternatives to treatment with factor concentrates? Please detail whether and if so how this changed over time (*sic*).

245) The alternative option to treatment with a blood product was desmopressin. I would have explained to a patient why I was recommending this therapy, its mode of action and why it was recommended. I would have explained about potential side effects which included nausea, flushing, and water retention. The latter was potentially the most serious complication and was due to its anti-diuretic property which could last up to 24 hours. In an adult, water retention might result in a headache. Following desmopressin therapy patients were advised to restrict oral fluid intake for 24 hours and if a headache developed to stop drinking completely and to contact the Centre. As a result of patients restricting fluid intake I do not recall any patient reporting a headache. Desmopressin is contraindicated in small children because fluid retention can result in convulsions. If it is used, this should be with great caution.

246) The initial preparation of desmopressin was for intravenous use. The manufacturers developed a higher potency preparation which could be given subcutaneously. It should be used with caution in individuals with cardio-vascular disease. A further high potency nasal spray version was also manufactured.

49. What information did you provide or cause to be provided to patients before they began home treatment /home therapy?

247) Patients only start on home therapy after they have been treated in hospital, usually for a considerable period of time and therefore they were able to learn about how therapy should be given. In the days when the majority of patients were not on home treatment and required therapy in hospitals, very many were very proficient at setting up intravenous infusions of cryoprecipitate and knew of the safety precautions that were necessary. They were only enabled to start on home therapy when individual patients were assessed as being competent to do so.

248) With the appointment of a Haemophilia Sister, the arrangements for the initiation of home therapy and its monitoring became one of her principle responsibilities. She would teach patients and parents about when and how to give therapy. Safety precautions would be explained and a sharps bin provided for disposal of needles and syringes. A fridge was necessary for storage of the concentrate.

249) In June 1982, the Haemophilia Sister proposed training for those undertaking home treatment. I have attached her handwritten notes on what would be covered at those sessions which were carried out by her. I agreed that these seminars were a very good way of alerting patients as to how home treatment would be carried out [WITN3428008].

250) At paragraph 37, I referred to the protocol for home treatment and the consent form which was signed before home treatment could begin.

50. When did you first discuss AIDS or HIV (HTLVIII) with your patients?

251) I have addressed this question in my response to Question 47 and the accompanying documents. I hope these provide the information sought.

51. In your evidence to the Penrose Inquiry [PRSE0001664] you discuss interactions with Dr Richard Tedder in 1984-1985. Please describe these interactions, in particular as regards testing of samples from Edinburgh patients.

252) My interactions with Dr Tedder were described, as best I remembered them, in my report to the Penrose Inquiry [PRSE0001664]. The evidence I gave on that subject was on Friday 17 June 2011 and begins at page 83 of the transcript for

that day [PRSE0006035]. The details are set out in the final Report in paragraphs 33.181 to 33.198. Both the reporting of the evidence in the final Report and the evidence I gave orally are more detailed than I would be able to recall almost another 10 years later. If there are further queries I am happy to try and recall events.

52. How were patients told that they had been, or might have been, infected with HIV? What information was given to them about the significance of a positive diagnosis? Did you tell patients to keep their infection secret?

253) When the results of anti-HTLVIII testing became available at the end of 1984 from Dr Tedder's laboratory, all patients initially learned that they could find out more about HTLVIII and AIDS if they attended the open meeting to which all patients, parents and partners were invited in December 1984. In the letter of invitation to the meeting ([WITN3428009] those patients or parents who were unable to attend were invited to make contact with me if they wished to learn more about HTLVIII and AIDS. Subsequently, all patients were written to letting them know that a result might be available, and that if they wished to know the result, they should make an appointment to see me in person. Enclosed with the letter was an information sheet about AIDS giving the same safety advice to all patients irrespective of their anti-HTLVIII result [PRSE0002785].

254) At that time, only approximately 1/100 to 1/500 individuals who were anti-HTLVIII positive had developed AIDS. The interpretation of an anti-HTLVIII result was therefore not straightforward.

255) For an interpretation of an anti-HTLVIII result, I make reference to my document 'Long term safety monitoring for transfusion transmitted infections' submitted to the Penrose Inquiry [PRSE0002404] paragraphs 23 and 24 which set out the possible interpretations of a positive and negative result. This issue is also further considered in the response to Question 54 below. This information was made available to patients who inquired about their result.

256) I suggested to patients that they should consider carefully whom to inform of their result, particularly for those who were anti-HTLVIII positive. I did not tell them to keep the information "secret". I have addressed this further in my response to Question 63 (v) below.

53. Please provide full details of a group meeting which was held with patients (your evidence to the Penrose Inquiry [PRSE0001664] suggested that the meeting took place on 16 December 1984) to discuss HTLVIII. What was the purpose of the meeting? Who was invited to attend? What is your recollection of what happened at the meeting? What information was provided to individuals?

257) The Penrose Inquiry Final Report paragraphs 33.221 to 33.274 contain a full description of the background to the meeting and what happened during it. There is a good contemporaneous record of information given in paragraph 33.238. This contemporaneous note [PRSE0002471] was taken by one of the attendees and I cannot improve on that record.

258) I gave evidence on this subject on Friday 17 June 2011, and I cannot improve on that now. The evidence begins at page 108, and at page 109 of the transcript, I am asked about the purpose of that meeting. I go on to set out the background to the meeting and then the purpose is addressed at page 111. I also noted my recollection at that time was that we wrote to all the patients with haemophilia in Scotland. I cannot improve on that evidence at this remove.

54. In your evidence to the Penrose Inquiry [PRSE0001664] you stated that "there was a lot of discussion at the time about whether clinicians should or should not tell patients." Please provide details of those discussions and who they were with. What reasons were considered and discussed for informing or not informing people about their HIV results?

259) There was much consideration when the results of initial anti-HTLVIII testing from research investigation became known as to how the information should be made available to patients. Should patients be given the information directly or should they have the opportunity to consider whether would wish to know the result? At this time there was uncertainty about the interpretation that should be put on a positive and a negative result (see below). From a practical point of view there was no specific treatment or recommendations for those who were anti-HTLVIII positive, and the same safety advice, including condom use, was given to all patients irrespective of anti-HTLVIII result.

260) I discussed the issue of how to make the information available to patients with a number of colleagues, including those in blood transfusion and virology.

261) I was influenced by a lengthy discussion on this subject at the meeting of UKHCDO Reference Centre Directors with blood transfusion and virology colleagues on 10th December 1984 [HCDO0000394_117]. The minutes of the meeting record that during that lengthy discussion there were several differing views expressed. The eventual conclusion was that each clinician would make up their own mind, based on the facts of each individual case. In general, it was agreed that if patients asked for information then it was to be provided.

262) There were also important local discussions with my close colleagues Mrs Iona Philp (Haemophilia Sister) and Mrs Geraldine Brown (Social Worker) about how we should proceed with making the information available to patients. We agreed that all patients should know that results were available. This information was conveyed at the open meeting in December 1984 and all patients were written to in January to ensure that they knew this. Enclosed with the letter inviting them to make an appointment was an information sheet about AIDS and Haemophilia which contained important safety information [PRSE0002785]. All patients, irrespective of anti-HTLVIII result, were informed about risk of sexual transmission and requested to use condoms. These were discretely made available at the Haemophilia Centre and given out routinely with all home treatment supplies of concentrates. When patients attended the Haemophilia Centre, if judged appropriate, patients were reminded that results were available. The haemophilia team held weekly meetings to keep the HTLVIII patients' situation under review.

263) I also discussed the situation with Professor Forbes, and my recollection is that he intended to let patients know that results were available and that they could request their result. Years later, I learned that he changed his view and decided to proactively invite anti-HTLVIII positive patients to his clinic.

264) As a result of the then current situation, the Haemophilia Team's view was to allow individuals to request their anti-HLVIII result. This arrangement for patients worked well, with the vast majority of them requesting an appointment in the succeeding 1-3 months. There was a small number who did not wish to know their result.

Interpretation of an anti-HTLVIII result

265) A positive anti-HTLVIII result was interpreted as the patient either having been exposed to HTLVIII, or that it was a false positive. Additionally, we did not know whether a true positive result indicated a previous or current infection with HTLVIII. The working premise was that a positive result should be interpreted as reflecting a current infection, but this was not certain. For most viral infections the antibody neutralises and clears the virus and the patient becomes non-infectious, e.g. as with the flu virus, but we now know that HIV is unusual in that the virus and antibody co-exist. Furthermore, there was some uncertainty as to whether the patient had been exposed to live virus, or whether the antibody could have arisen in response to 'non-infectious' virus antigen in the clotting factor concentrate (in a similar way to vaccination). Another possibility was that the antibody could have been acquired from the clotting factor concentrate, as passive 'immunity'.

266) A negative anti-HTLVIII could be interpreted in a number of ways. The most straightforward was that the individual not been exposed to HTLVIII. He could, however, have been exposed and produced an antibody below the level of detection by the test. Alternatively, the patient had produced an antibody that was not detected by the test (i.e. a false negative). Another interpretation is that the patient had not produced any antibody in response to exposure, but he might still be infected. It subsequently became apparent that this occurs during the 'window period' in all individuals; this being the period between exposure to HTLVIII and the development of detectable antibody. In the case of HTLVIII, this can be many months. It is pertinent that in December 1984 a publication from the USA reported several patients from whom the virus could be isolated, but who were anti-HLVIII negative [1].

267) At the end of 1984 and 1985, only approximately 1/100 to 1/500 individuals who were anti-HTLVIII positive had developed AIDS. It was therefore unclear what the risk was of an antibody positive person developing AIDS.

References in respect of Question 54

1. Salahuddin, S.Z., et al., *HTLV-III in symptom-free seronegative persons.* Lancet, 1984. **2**(8417-8418): p. 1418-20.

55. In your evidence to the Penrose Inquiry you stated that, following the December 1984 meeting referred to above, letters and information sheets were sent to patients [PRSE0001664]. What information was contained within the letters and information sheets? Were they sent to all patients or only some?

268) Following the meeting on 19 December 1984, all registered patients and parents were written to and sent the information sheet [PRSE0002785]. There was an accompanying letter which encouraged patients to make an appointment if they would like further information or discuss their individual situation. For completeness, a copy of a letter to all patients' GPs is also reproduced [WITN3428010].

56. What was the Centre's/your policy in relation to testing partners/family members of people known or suspected to be infected with HIV? Under what circumstances were the tests carried out?

269) The policy was to ensure that those who might be infected with HIV appreciated that the infection could be spread both by blood and sexually, and how this risk could be reduced. The potentially infected person should discuss this with their partner. Our policy was that partners should be offered counselling prior to testing. If after counselling the individual wished a test, the blood sample would usually be taken at the Haemophilia Centre; the result would be made available to the individual as soon as it was available. Non-sexual partners were not at significant risk of infection, and this was explained to patients and members of the household. Routine testing was therefore not usually recommended.

270) All patients were warned of the risk of infection and condoms were freely available within the Centre and were also discreetly given out with home treatment. Additionally, the patients and their families were very aware that they need to clear up any blood spillages carefully.

57. What, if any, information or advice did you provide to partners or family members of people that were at risk of infection with HIV or infected with HIV?

271) This question has been addressed in my responses to Questions 37 and 55 which refer directly to patients. The families of the Centre's patients had access to the same material.

272) Partners and family members were always welcome with or without an appointment at the Haemophilia Centre. They were seen by an appropriate member of staff who discussed their individual situation and offered relevant information and counselling.

273) The document PRSE0003787 discloses more detailed information about what was available to patients and families.

58. At a special meeting of Haemophilia Reference Centre Directors on 13 May 1983, at which you were present [HCDO0000003_008], it was suggested that there was a need for haemophilia centre directors to discuss what should be done with regard to the surveillance and reporting of suspected cases and the management of patients". What decisions and actions did you take following that meeting, with regard to surveillance and reporting of suspected cases and the management of patients?

274) This meeting on 13 May 1983 was to appraise those present of the then current situation in the UK in relation to AIDS in patients with haemophilia and in the general population.

275) The then current policy in Edinburgh was to use cryoprecipitate and NHS clotting factors in preference to commercial ones, as considered at the meeting and the existing local policy was therefore continued. The Centre's policy was already in agreement with the guidance that was issued on 24th June after the meeting [1].

276) In the spring of 1983, I had already established arrangements for monitoring immune function in patients and these were continued after the May meeting.

277) My recollection is that there no patients with clinical stigmata of AIDS or AIDS-related complex and therefore no patients to report.

Reference for Question 58

1. UKHCDO, *Acquired Immune Deficiency Syndrome*. 24 June 1983.

59. Were patients infected with hepatitis B informed of their infection and if so how? What information was provided to patients with hepatitis B about their infection, its significance, prognosis treatment options and management?

278) Many patients in the 1980s had evidence of past infection with hepatitis B and the majority had cleared the infection as evidenced by the appearance of anti-HBs in their blood. All patients were given the results of their hepatitis B investigation at clinic visits and told of their significance.

279) Patients were regularly monitored for hepatitis B to ensure that there was continuing evidence of immunity in those previously infected; for those at risk, if there was evidence of acute infection they were immediately contacted and reviewed.

280) For the small percentage of patients who did not have evidence of having cleared hepatitis B, they were reviewed and offered individual advice related to their circumstances. This was provided by a hepatologist, Dr Peter Hayes, who counselled these individuals and offered appropriate investigation and management.

60. Were patients with NANB hepatitis informed of their infection and if so how? What information was provided to patients with NANB hepatitis about the infection, its significance, prognosis, treatment options and management?

281) At routine follow up clinic visits patients would be updated about their most recent liver function test results and, if these were suggestive of NANB hepatitis, patients would be told of these. It was often referred to as hepatitis, but would have been distinguished from hepatitis B.

282) Patients were given up to date information about NANB hepatitis as it developed over the years both by Haemophilia Centre staff, but particularly by Dr Peter Hayes who led the review of patients. The changes in the understanding of NANB hepatitis and its management over the years has been outlined in my responses to Question 26 to 29.

61. When did the Centre begin testing patients for hepatitis C? How were patients informed of their diagnosis of hepatitis C? What information was provided to patients infected with hepatitis C about their infection, its significance, prognosis, treatment options and management?

283) Following the identification of the hepatitis C virus in 1989, we continued our virologic studies with Professor Simmonds who established the initial laboratory techniques for assessing the virus and its specific antibody. As a result of our initial investigations, it became clear that there were shortcomings in the first-generation antibody and that second-generation assay results were more reliable.

284) Patients were given results of investigations when we were confident that they were accurate and informative. They were informed that what had previously been referred to as 'hepatitis or NANB hepatitis' was now identified as hepatitis C. It was not a new diagnosis, but rather a renaming of the condition.

285) The overall management of patients' hepatitis was by Professor Peter Hayes. He generously attended the Haemophilia Centre to see patients. This had the advantage that review of their hepatitis could occur concurrently with review of their haemophilia. It also allowed good and effective communication with patients and the Haemophilia Centre staff.

286) In addition to the information described previously that has been made available over the years to patients about hepatitis, a specific hepatitis C patient information sheet was developed and given to all relevant patients. To help ensure that all patients were appropriately managed, a check-list was used for each individual being considered for interferon therapy which was filed in their case notes These documents are appended as WITN3428011.

62. Were the results of HIV and 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.

287) In general, I was keen that patients received the results of all investigations. For example, knowledge of known hepatitis investigations was usually given at the subsequent patient review clinic. There were occasions when it might be appropriate to inform a patient of a result sooner; an example would be evidence of a new infection of acute hepatitis, especially of hepatitis B, because of the risk to spread of infection to other individuals. In this instance, the patient would be contacted and their situation discussed. Another example was that after it was reported that hepatitis A could be transmitted by 'virally inactivated' concentrates in 1992, stored blood samples were analysed to ascertain which patients were at risk of infection. Those who were susceptible were contacted and offered hepatitis A vaccine to protect against infection.

288) In relation to HIV, in the situation that evolved in the mid-1980s, patients were given autonomy to decide when they would like to know the result of the then anti-HTLVIII antibody test which had been established by Dr Tedder as a research investigation. This was a very difficult time for people with haemophilia, because of all the uncertainty that surrounded the issue of AIDS in general and specifically for those with haemophilia. I have set out previously the difficulties in interpreting an anti-HTLVIII result and in knowing of the prognosis of those who were positive.

289) In December 1984, all patients were written to, letting them know that new information in relation to AIDS had become available [WITN3428009]. They were invited to an open meeting at the Royal Infirmary to which they could bring a partner. The letter invited individuals to seek an appointment with me if they wished more information, and particularly if they could not attend the meeting. At the meeting patients were told that anti-HTLVIII testing was possible and that results were available on some patients. All present were invited to make an appointment to see me if they wished to know their own result. Patients were informed of the safety precautions that all patients should observe, irrespective of their anti-HTLVIII result. In January 1985, all patients and parents, irrespective of an anti-HTLVIII result, were sent an information sheet about AIDS, anti-HTLVIII testing and safety precautions that all patients (irrespective of their anti-HTLVIII

result) should adopt. This was sent with an accompanying letter encouraging patients to make an appointment to see me to learn of their anti-HTLVIII result, if they wished to know it [PRSE0002785].

290) It was important to allow patients to reflect upon the situation and not to feel pressurised to ask for a result. Very shortly after the December 1984 meeting, many patients were in touch and made appointments to see me. If they wished to know the result, I would inform them of it (if known) and I would offer an interpretation of it. I would offer to retest individuals at that time to confirm the initial result.

291) The vast majority of individuals made contact early in 1985 and were seen by me or one of my colleagues. Each week our haemophilia team met to review patients and review some of the difficulties that were presenting. This was a way of monitoring the unfolding situation and to support staff in helping patients. This was a very difficult period, made harder by the uncertainty about the consequences of an anti-HTLVIII positive result.

292) There were a few individuals who did not get in touch as a result of the invitations. There were two patients, both with close relatives with haemophilia, who were at the December 1984 meeting and who were sent the AIDS information leaflet along with a letter inviting them to see me if they wished to learn more. All patients had free access to condoms and these were also discreetly issued with home treatment supplies of factor VIII/IX. At this time, there was no specific treatment recommended for individuals who were anti-HTLVIII positive. As after two years neither of these two individuals had inquired about their antibody status we considered it appropriate to invite the patients and ask if they would like to know the result. As they indicated they then wished to know, they were given the result.

293) There were, in addition, a very small number of patients who were anti-HTLVIII positive, and when asked if they would like to know to result were adamant that they did not wish to know. I considered it essential that these individuals were aware of the safety precautions that were appropriate. Subsequently, when therapy was developed that would be of benefit, I had further discussions to encourage patients to know their status, because they could potentially benefit from therapy.

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

294) There appear to be at least two aspects of the public health implications of these viral infections.

295) Firstly, the resources that were required to treat patients with these viral infections. I considered that one of my responsibilities was to request and try to ensure the availability of resources that were necessary to ensure patients that received the best treatment that could be made available.

296) Secondly, there were the public health implications for the community including family members. For the individuals in the patient's immediate household, it was important that sexual partners were being protected where they were at significant risk of infection; this was by recommending condom use by all individuals treated with a clotting factor concentrate to protect against the virus causing AIDS. For close contacts of patients who were hepatitis B antigen positive, and therefore possibly infectious, hepatitis B vaccine (after it became available in the 1980s) would be offered to family members on the advice of a virologist.

297) The further public health considerations were very wide ranging and were considered on a case by case basis. For example, schools were anxious about children known to have haemophilia. To address some of the generic issues I had meetings at the Scottish Home and Health Department and the Scottish Education Department. It was a standard arrangement that the Haemophilia Sister would visit all schools, in conjunction with relevant parents and children, so they knew about haemophilia and how pupils should be looked after.

298) There was also the public health issue of a very negative community view of AIDS and especially of those who might be infected. There was the terrible stigmatisation of some individuals and families of people with haemophilia irrespective of their anti-HTLVIII status. Patients and families required much support because of the hostile environment many lived in, and because often patients were known in their community to have haemophilia. When someone is

physically disabled (from haemophilia) it is difficult to conceal this – thus many were readily identifiable. This was one of the reasons that we cautioned patients about passing on information about their anti-HTLVIII status especially if positive, as described in response to Question 52 above.

64. What information was provided to patients about the risks of other infections?

299) Patients with haemophilia were also at risk of other non-hepatitis viral infections from clotting factor concentrates including parvo B19, hepatitis G, TTV, parv4, as well as bacterial infections. Those with HIV were at risk of opportunistic infections (see (iv) below).

300) In general, patients were not informed about the risk of parvo B19 as most individuals became infected as children probably from community acquired infection. Hepatitis G, TTV, and parv4 are probably not pathogenic and are already widespread in the community. The evidence is that virally attenuated concentrates do not transmit hepatitis G virus or TTV.

301) Individuals with long-line indwelling catheters used for giving concentrate infusions are at risk of these lines becoming infected. This complication was well discussed with patients in advance of long-line, e.g. Hickman line, or portacath, insertion, as meticulous sterile precautions were required each time the line was accessed to give concentrate or draw a blood sample. This situation mostly, but not exclusively, arose in small children because of the difficulty of venous access.

302) Individuals who were HIV positive were at risk of 'opportunistic' infections. These were infections that were in the environment and were able to colonise patients as their immune function declined. Common was pneumocystis carinii and patients were offered monthly pentamidine inhalations (a very unpleasant experience) prior to the efficacy of oral daily cotrimoxazole tablets as offering equal protection. The other common infection was candida of the mouth and oesophagus – nystatin and ketoconazole were offered to reduce the risk of and to treat infection. Patients were informed about these two infections and offered preventive therapy. There were a number of much less common opportunistic infections that patients might have been told about, but they would most only been mentioned if the clinical circumstances suggested one by be a clinical possibility, e.g., cerebral toxoplasma

303) Some of the lymphomas arising in those with HIV are Epstein-Barr (EB) virus driven. Many individuals in the general population have been exposed to EB virus and the individual's immune system suppresses the infection which becomes quiescent, but in a few individuals with HIV when their immune systems decline the EB virus replicates and can lead to the development of a lymphoma. Patients would not normally be offered this information, as the chance of developing a lymphoma was considered small and there was no action that was known to reduce the risk.

Consent

65. What information was given to patients about the purposes for which blood samples were being taken? Did you obtain patients' informed consent to the storage and use of those blood samples?

304) Patients were informed that the blood samples were being taken to monitor their medical condition and for research with respect to their haemophilia. With this knowledge, patients agreed to allow blood samples to be taken. I have explained elsewhere about the range of investigations that were undertaken and the purposes of the investigations [PRSE0002404]. Patients were also made aware that samples might be stored.

305) I obtained two letters from former colleagues in 2006 to assist with a complaint made about me to the GMC. Dr Carr and Dr Tucker set out their recollections in those letters which were then sent to the GMC as examples of evidence of my openness with patients and the arrangements for their care. Copies are provided at WITN3428012. Dr Tucker's letter was referred to in the Penrose Report (chapter 33.137).

66. Were patients under your care treated with factor concentrates or other blood products without their express consent? If so how did this occur? What was your approach to obtaining consent to treatment?

306) My policy was that patients should be informed about the potential benefits and known likely side effects of blood products that were recommended. I would explain the nature of the proposed therapy and its potential benefit and point out the possibility of transmission of infection and the potential consequences, for example,

hepatitis, and the real potential for a factor VIII inhibitor to arise. For the vast majority of patients, they were appropriately informed and knowledgeable. The patient's verbal consent was taken as evidence that the patient agreed to the treatment.

307) There were rare occasions when newly diagnosed patients were treated in emergency situations when the immediate clinical priority was to alleviate the patient's distress, and it is possible that in these circumstances the patient may not have been informed of possible adverse effects of treatment.

67. The Inquiry has heard from witnesses who say that they were not in a position to give informed consent to treatment with factor concentrates, because they were not given sufficient (or any) information about the risks of treatment or about alternatives to treatment. Do you accept this? If not, explain the basis on which you say that your patients did give informed consent to treatment with factor concentrates.

308) My response to this Question (67) has been in part set out in my response to Question 66 above. In addition, in the early 1980s, it was well established that there were risks of hepatitis and anti-factor VIII antibody development with factor concentrates. My policy was that these risks should be explained and understood by patients. Agreement to the therapy was taken as evidence of consent. It is possible that patients may not recollect exactly what they were told, particularly with the passage of many years.

309) Patients often commenced concentrate therapy when home treatment was initiated, having previously been treated with cryoprecipitate for a prolonged period of time. At this time, they were invited to sign a consent form on which it was explicitly stated that they accepted the risk of hepatitis. I have referenced that consent form in paragraph 37, WITN3428006.

310) The perceived risks of infection varied and evolved over time, starting initially with hepatitis B, followed by other viruses, through to the possibility of vCJD transmission. In addition, the risks in some situations diminished, e.g. following introduction of viral reduction technologies. I have set out details of ways in which patients were informed about the risks of therapy over time and how these were available to patients [PRSE0003787, PRSE0003062, PRSE0002404, PRSE0004704 and PRSE0003869]. In relation to vCJD, patients were sent information.

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

311) As I have set out previously, when I took up my appointment in 1980, patients were offered routine blood tests at clinics to monitor the medical consequences of haemophilia and its treatment. The purpose of this was to monitor them for infection by identified specific viruses as these became known, e.g. antibody and other tests for hepatitis B and later hepatitis A. In addition, non-specific assessments of possible viral infections were undertaken, such as liver function tests and assessment of immunity. My approach was summarised in the document 'Long term safety monitoring for transfusion transmitted infections (with particular reference to HBV, non-A non-B hepatitis and HIV) 1974-1989' [PRSE0002404].

312) The patient's awareness that the blood tests were to monitor their medical situation and their agreement to have blood taken was considered as consent for the investigations.

313) At the end of 1984, when limited anti-HTLVIII testing became available as part of Dr Richard Tedder's research, some patients were tested without their consent. As has been described elsewhere, the results were made available to patients. I do not have any recollection of any patient at the time being critical of this testing.

314) After December 1984, it was made very clear to all patients that there was routine monitoring for anti-HTLVIII, as they were potentially at risk of exposure to the then identified virus.

315) Following the GMC Guidance about consent for HIV testing issued in 1988 [WITN3428013], every effort was made from that time to get explicit consent and to record this in patients' case notes.

69. You referred in your evidence to the Penrose Inquiry to "implied consent" [PRSE0001664] – what did you mean by this? Did you consider at the time that this was sufficient basis for testing and/or treating patients? On what basis did you reach that view?

316) My policy was that patients should understand the probable or possible risks of treatment, and that they would be offered monitoring for these risks by blood tests at the clinics. If the patient gave verbal agreement to the treatment and agreed to give a follow-up blood sample at clinic visits, I considered this to be "implied consent".

317) The patients were seen by me and haemophilia staff on a regular and routine basis. I did not ask for consent in respect of each and every test I carried out after I had explained the tests we did routinely [PRSE0002404].

318) When new products became available on a formal assessment basis, an information sheet was provided along with a consent form.

319) As evidence of our open policy with patients I have produced as WITN3428012 two letters from medical colleagues.

320) I thought at the time that this was a sufficient and reasonable approach but looked at in 2020, and for a number of years now, I accept that patients and the law would now expect more information to be provided.

Research

70. Please detail all research studies that you were involved with during your time as director of the Centre. In relation to those research studies that could be relevant to the Inquiry's Terms of Reference, please:

a. Describe the purpose of the research;
b. Explain the steps that were taken to obtain approval for the research;
c. Explain what your involvement was;
d. Identify what other organisation or bodies were involved in the research
e. State how the research was funded and from whom the funds came;
f. State the number of patients involved;

g. **Provide details of steps taken to inform patients of their involvement and to seek their informed consent; and**
h. **Provide details of any publications relating to the research.**

Introduction

321) For over 30 years as director of the Centre, I have been participated in a wide variety of 'service evaluations', 'audits', and 'research activities' in the field of haematology, many in relation to haemostasis and especially haemophilia, and other heritable and acquired coagulation disorders. The question seeks information about 'research' and this term may only be applicable to a small proportion of my various activities. Many more of them would be more properly termed as 'service evaluation' and within the scope of 'usual practice (in public health including protection'. I shall try and provide, however, information about my work which has attempted to shed new light on a number of aspects haematology and, in particular, the safety of therapy for haemophilia. There were in addition research activities not related to blood infection safety, and I shall give a brief outline of the general topics along with a list of publications.

322) Whilst gathering information together to respond to the above questions, and in particular trying to further understand the different ways investigation of patients and diseases could be classified and for which areas of activity Research Ethical Approval is required, I found a recent NHS Health Research Authority (HRA) web site useful (http://www.hra-decisiontools.org.uk/ethics/). Although this is current guidance, it also offers a way of assessing work that was undertaken 30-40 years ago. Guidance that it offers about how investigations should be considered is suggested in four categories as outlined and defined below:

a) **Research: '**The attempt to derive generalisable or transferable new knowledge to answer questions with scientifically sound methods including studies that aim to generate hypotheses as well as studies that aim to test them, in addition to simply descriptive studies.'

b) **Service Evaluation: '**Designed and conducted solely to define or judge current care.'

c) **Clinical/Non-financial audit:** 'Designed and conducted to produce information to inform delivery of best care.'

d) **Usual Practice (in public health including health protection):** 'Designed to investigate health issues in a population in order to improve population health. Designed to investigate an outbreak or incident to help in disease control and prevention.'

323) The recommendation is that Research Ethical Approval from the HRA is normally only required for 'Research', but it is not required for the other three categories.

324) The web site also states that Post-marketing surveillance in not usually considered research.

325) The majority of my work should be categorised as Service Evaluation, Usual Practise and Post-marketing surveillance as outlined above. While some of the data generated, however, from Service Evaluation might be 'generalisable or transferable', e.g., the 1983 lymphocyte immune studies, was not undertaken with this intention.

Assessment of infections arising from use of blood products.

326) In relation to the infective safety of blood and blood products, virtually all the investigations have been to monitor the actual and potential risks of infections. This was my responsibility as the physician with the remit of trying to provide the highest level of safe care for patients with haemophilia. To do this, it was necessary to assess patients for potential perceived risks. The nature of these risks changed markedly from 1980 onwards and necessitated therefore a changing schema of appropriate investigations.

327) My responsibility was to help develop the programme of investigations, raise resources so that patients could be appropriately investigated, and seek ethical approval when required. It was important to ensure that individual patients were aware that their medical condition was being comprehensively investigated and monitored and that they were in agreement with this. I had a policy of being very open with the patients about our activities. When patients attended review clinics,

they were asked if an additional small sample could be taken and stored for 'research purposes.' Those who asked for additional details were given further information by the medical staff. Some patients were interested to learn to which laboratories the samples were sent and the type of investigations being undertaken. This information was always provided. Many patients were being seen regularly for review and these occasions gave patients regular opportunities to learn about how our understanding was developing. It was well known amongst patients that I had a keen interest in the assessment of blood safety and that storing small blood samples would assist in monitoring this. This was also considered good laboratory practise because, at very least, it allowed the opportunity to subsequently check an individual laboratory result. The amount stored was less than half a teaspoonful (approximately 1-2ml). I do not recall any patient expressing a reservation about giving blood samples because they might be used, not only for their individual benefit, but also because they might be used to gain wider knowledge to the benefit of the wider haemophilia community.

Hepatitis A and B

328) From the initial hepatitis B studies undertaken prior to 1980, and those after this date, monitoring of hepatitis B infection enabled knowledge to be gained about the actual risk of hepatitis B infection. This might be considered as a safety assessment and thus viewed as best practice and the responsibility as a prescriber of such blood products. The results demonstrated that despite screening of blood donors for hepatitis B, clotting factor concentrates were still infectious. The immediate benefit of this knowledge was to emphasise the importance of offering hepatitis B vaccine when it became available to protect susceptible patients. This clinically very relevant safety investigation might appropriately be viewed as 'service evaluation' or 'usual practice (in public health including health protection) or it could be viewed as research because the results were generalisable to a wider population. When it became apparent that hepatitis A could be transmitted by clotting factor concentrates in 1992, we were able quickly to assess, from stored samples, who was at risk and to offer protective vaccination.

Developing AIDS situation

329) As I have set out elsewhere [PRSE0002404] my concern about the developing AIDS situation in the early 1980s led to the setting up of techniques to assess immunity in patients, as this was the only way to investigate the immunological effects of clotting factor concentrates on patients in Edinburgh; the results of similarly designed investigations were being reported from elsewhere in the world. Again, as for hepatitis A and B assessments, this immune evaluation was 'service evaluation' responding to a developing situation.

330) Following identification of anti-HTLVIII positivity in Edinburgh patients, the only way to begin to adequately investigate the situation, particularly in relation to those presumed to have been infected by the 'implicated batch' of concentrate, was to seek resources to establish the necessary investigations, as these were not available within the NHS. This was relatively quickly achieved with research funding from SHHD, and subsequently the MRC, to monitor the consequences of infection and assess the efficacy of measures to reduce further infections. The very least that was owed to the patients was that those infected, and those at risk of infection, should be monitored as comprehensively as was reasonably possible.

Hepatitis C

331) With the identification of HCV in 1989, we were keen to establish locally laboratory tests which would accurately diagnose current or previous infection in patients. The initial 'first generation' test appeared to be relatively insensitive, and we evaluated further 'second generation' techniques which were considerably more accurate. This assessment was helped by patients responding to brief hepatitis questionnaires. During the late 1980s and early 1990s, Professor Peter Hayes was able to offer patients a broad range of investigations and treatments which he personally arranged and some of which he carried out. As part of our service evaluation, for the benefit of the haemophilia and broader hepatitis community, we published our experience. Professor Simmonds' evaluation of patient genotypes demonstrated that the genotype in patients reflected the products patients received, and that there were differences between those who received local NHS derived concentrates compared with those who received concentrates derived from US donors.

Variant CJD

332) Although I was instrumental in raising the issue as to whether blood and blood products might transmit vCJD, I did not undertake any laboratory studies as there were no reliable markers. I did however, with colleagues, help establish arrangements for monitoring possible infection and for managing the perceived public health risk.

333) Details of the work undertaken was set out in the publications arising from the investigations that are listed at the end of this statement. The other individuals, and their affiliations, who participated in the work were co-authors of the publications.

Other Topics

334) Other haemophilia areas of research have included studies on the molecular biology of factor VIII, effect of coagulation factor concentrates on immune function in vitro, and the responses to desmopressin infusion. Under the auspices of the Coagulation Factor Working Party for Scotland and Northern Ireland investigations were undertaken to assess new SNBTS clotting factor concentrates. Studies have been undertaken to assess the efficacy and safety of surgery with recombinant VIIa in patients with anti-factor VIII antibodies.

335) I have had research activities in other areas of blood coagulation and other aspects of haematology and these are included in the list of publications.

Responses to the above questions.

a. Describe the purpose of the research;

336) The overall purpose of the investigations has been set out above and while a small proportion of the investigations might be properly classified as 'research', the majority were carried out for the purposes of Service Evaluation and to maintain Usual Practice (in public health including health protection), as defined above.

b. Explain the steps that were taken to obtain approval for the research;

337) Ethical approval was sought from the then current appropriate committee. The South Lothian Ethics Committee came into existence in about 1985. Prior to this, the Royal Infirmary Physicians Committee provided guidance. Projects for which external funding was sought usually required evidence of ethical approval as a condition of funding.

c. Explain what your involvement was;

338) My responsibility was to help oversee the overall arrangements for the assessment of the patients.

d. Identify what other organisation or bodies were involved in the research

339) The other bodies involved in supporting the activities included Lothian Health Board, University of Edinburgh, funders as set out below and small contributions from charities and pharmaceutical companies, as outlined elsewhere (response to Question 125).

e. State how the research was funded and from whom the funds came;

340) Funding of investigations was from a variety of sources:

1. Lothian Health Board and University by way of supporting teaching hospital activities

2. Lothian Health Board Endowment Fund

3. External national funding organisations

    a) Medical Research Council
    b) Chief Scientist, Scottish Home and Health Department
    c) Wellcome Trust
    d) Scottish National Blood Transfusion
    e) Pharmaceutical companies
    f) British Heart Foundation

g) Chest Heart and Stroke Association

h) Haemophilia Society

4. Peter Palmer Trust

f. State the number of patients involved;

341) Virtually all registered patients under long term follow-up may have contributed to the investigations. Some of the studies were on non-haemophilia subjects – details are in the publications below.

g. Provide details of steps taken to inform patients of their involvement and to seek their informed consent; and

342) It was well known amongst those with haemophilia that there were infective risks arising from the use of blood products and that I was active in trying to monitor and assess this on their behalf. When blood samples were being taken for routine surveillance investigations, patients were usually asked if a little extra could be taken for 'research' and for storage. For some of the studies, individual written consent was sought, e.g. hepatitis studies in 1986. For other cardiovascular studies, which involved drug administration the details of the studies, medicines to be given and potential side effects were carefully explained, information sheets provided and written consent forms.

h. Provide details of any publications relating to the research.

343) Reports of studies which were predominantly 'service evaluations' or 'usual practice (in public health including health protection)'.

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3. Carr, R., et al., *Abnormalities of circulating lymphocyte subsets in haemophiliacs in an AIDS-free population.* Lancet, 1984. **1**(8392): p. 1431-1434

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18. Simmonds, P., et al., *Human immunodeficiency virus-infected individuals contain provirus in small numbers of peripheral mononuclear cells and at low copy numbers.* J Virol, 1990. **64**(2): p. 864-72.
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Source of Grants

Medical Research Council

Clinical, immune and virological investigation of haemophiliacs with particular reference to HIV infection. C.A. Ludlam, J.F. Peutherer, C.M. Steel.

1st August 1989 - 31st December 1992

Virological and immunological determinants of liver disease in haemophiliacs infected with hepatitis C virus. C.A. Ludlam, P. Simmonds, J.F. Peutherer.

1st October 1992 - 30th September 1995.

Scottish Office Home and Health Department

Study of immune function and HTL VIII infection on haemophiliacs treated exclusively with NHS factor VIII/IX concentrate. C. A. Ludlam, J. F. Peutherer.

1st April 1996 ~ 31st March 1989

The contribution of immunogenetic factors to variation in rates of disease progression among HIV infected subjects. C.A. Ludlam, J.F. Peutherer, R.J. Prescott.

1st January 1994· 1st January 1996

Treatment of Haemophilia in Scotland: Does Clinical Outcome Relate to Usage of Coagulation Factor Concentrate Therapy. C. A. Ludlam, G.D.O Lowe, R.J. Prescott and Haemophilia Directors for Scotland.

1st January 1995 - 30th June 1996

The contribution of a novel flavivirus, hepatitis G virus/GBV-C in the aetiology of acute and chronic hepatitis. C. A Ludlam, P. Simmonds, Dr. P. Hayes.

Wellcome Trust

A study of the immune response to HIV: Analysis of susceptibility, pertaining to the

major histocompatibility complex and t cell receptor repertoire. C.A Ludlam, AG. Dalgleish,
1st January 1993 - 1st January 1994

Scottish National Blood Transfusion Service

Clinical studies on new coagulation factor concentrates. C.A Ludlam

Other Grants

British Heart Foundation

Platelet Volume and Haemostatic Markers In Unstable Angina. KAA Fox, C.A Ludlam, T. O'Malley. 1st September 1993 - 31st August 1995

Cell Adhesion Molecules, Chronic Infection and Cardiovascular Disease. G.S. Hillis, C.A Ludlam, KAA Fox and others. (1999-2000)

Endothelial Function and Endogenous fibrinolysis in the coronary and peripheral vascular beds, D.E. Newby, C.A Ludlam and KAA Fox and others. (1998-1999)

Haemophilia Society

Regulation of expression of coagulation factor VIII gene. C.A Ludlam, D. Stirling. 1st December 1993 - 31st November 1994

Chest, Heart and Stroke Association

The influence of prolonged testosterone administration on the haemostatic system. C.A Ludlam, F.C.W. Wu, R.A Anderson. 1st January 1991 - 31st December 1992

71. What do you understand by the ethical principles that should guide research? Did you apply those principles to the research studies referred to above and if so, how? If not, why?

346) This is a very broad question. The question does not give a definition of 'research' and I have alluded to the various ways the assessment of patients can be viewed in my answer to Question 70. There are laws, governance requirements, and codes of practice for the conduct of research, which should be adhered to, but which develop and therefore are changed over time. For interventional research, in which the individual is subjected to an invasive investigation or procedure, or a trial medicine, it is important that the subject understands the risks, and in addition, if a patient, the potential benefit, of the intervention.

347) The Medical Ethics Group Report prepared for the Inquiry offers a broad and historical count of ethical issues in relation to patients participating in research and I agree with its overall approach.

348) Having responsibility for a group of patients, it is necessary to ensure that they receive the best care that can be offered. To do this there is a need to be curious about each patient's condition and the many factors that may influence it. To do so requires an understanding as to whether the environment is changing, and if so, how as this will influence investigations. Furthermore, there is a requirement to have an up to date knowledge of how treatment may potentially effect patients and to monitor, so far as is possible, the effects of their therapy. It is important patients are told how this is being attempted. I believe patients attending the Edinburgh centre understood that there was an active monitoring for infectious agents. Thus the way patients are investigated must change with developing knowledge; to do otherwise would breach the GMC guidance.

349) Where new therapy has been developed and needs to be assessed in a formal clinical trial for acceptability, I have ensured the project had received approval from the appropriate ethical committee, that patients received written information, had an opportunity to discuss the proposal, and they were only enrolled into the project it they had signed a consent form.

350) I have always been very keen to ensure that any patient who experiences harm as a result of participating in a trial would be readily and appropriately

compensated. As an example, at my instigation, I went to considerable lengths to ensure that recipients of new NHS-derived clotting factors would receive ready and appropriate compensation if they were materially harmed (described in Penrose Preliminary Report from Para 11.350 onwards.

72. Were patients involved in research studies without their expressed consent? If so how did this occur?

351) Patients should have an understanding about why blood tests are being suggested in a particular clinical context. Thus, in haemophilia, the blood tests will relate to the diagnosis or monitoring laboratory tests that are relevant. What is clear in the haemophilia situation, is that the risks of side effects of treatment change with time, e.g. with newly considered viral infections, and with the sensitivity of the laboratory tests. For this reason, small aliquots of samples were stored and this was considered good laboratory practice. On occasion, these were used at a later date to investigate the patient further or review a previous observation. In Edinburgh, it was well known by patients that I had a particular concern about viral safety of treatment and that I had an active programme for surveillance. When blood was being taken for routine surveillance patients were asked if a little extra could be taken for 'research'/ ongoing studies. I was always happy to explain our monitoring process to patients and the staff regularly reminded patients of our activities. Thus, when patients were asked if a little extra blood could be taken, although it was described as being for 'research', much of the activity would more correctly be classified as 'Service Evaluation' and Public Health Monitoring. As patients were informed as to the purpose of the extra sample, and agreed to the small extra sample, that this was taken as evidence of consent.

352) The extent of information provided to obtain consent depends upon the potential benefits and risks of the research. For example, in my studies in Cardiff in the late 1970s to assess platelet kinetic parameters for patients who might receive ex vivo radiolabelled platelets, I explained in great detail what was involved and the risks, e.g. infection of the platelets during the radiolabelling process, as part of the process of informing patients about the study. I do not recall it being appropriate at that time to offer information sheets or written consent forms in Edinburgh, for the skin tests we undertook in patients with haemophilia, these were considered as research, and the nature of the test and why we were inviting them to participate

was carefully explained. There was also a commitment for the patient to return two days later for the skin test result to be read.

353) For studies that were non-interventional and were observational, the amount of information given routinely might be less. For example, patients registered at and attending the Centre were told that long-term safety monitoring was part of the routine and patients were aware of this.

73. Was patient data (anonymised 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?

354) Patient data is used for a whole range of arrangements from providing appointments to overall service provision including its assessment in Audit, Service Evaluation and Public Health Assessments. There is the implied agreement when being a patient in the NHS that patient data is used for a whole range of processes but that the data is handled 'confidentially' and on occasions anonymously.

355) When involved in either research or service evaluation as set out above in response to Questions 70 and 72 I am very clear that any patient data (i.e. results of tests) were handled confidentially. I have always been very mindful to preserve my patients' anonymity which was an even more acute situation in haematology with all the issues we faced in the 1980s. I am aware that it has been suggested elsewhere that I did not anonymise sufficiently in publications to prevent one particular individual identifying a patient in an article. This individual was able to identify information about a patient because of their pre-existing knowledge of personal information about the patient. The identity of the patient would not be possible by a member of the general public. I now appreciate this situation and appreciate that more could have been done to conceal the details of individuals.

74. Was patient data (anonymised or otherwise) shared with third parties (e.g. UKHCDO or Oxford Haemophilia Centre) without their express consent? If so how and why did this occur, and what information was provided to whom?

356) When patients were diagnosed with a congenital bleeding disorder they were systematically registered with the Haemophilia Centre. Part of the registration process involved their inclusion in the National Haemophilia Database (NHD), and they would be issued with a Haemorrhagic States Card (or Haemophilia Card) giving details of their diagnosis as a 'passport' to getting treatment at other Haemophilia Centres.

357) The initial attempts to understand the extend of haemophilia by developing a record of patients started in the mid-1950s with a card index box in the Medical Research Council in London. This developed more formerly into the National Haemophilia Database in 1969 when UKHCDO was established. The arrangement was pioneering, and it has been emulated now in many countries throughout the world. The UK data was held within the NHS at the Oxford Haemophilia Centre and later, when computerised, on a Wessex NHS server. The NHD moved to Manchester where the data is now held in a secure NHS computer facility. UKHCDO was requested by the Departments of Health to maintain the database. Over the years, with developing governance regulations, the NHD has been very careful to abide by the needs for both confidentiality and transparency in its operation. The database is overseen by the UKHCDO Data Management Working Party whose members comprise, as well as several haemophilia directors, representatives of the Haemophilia Society, and an individual patient, Haemophilia Nurses Association, Haemophilia Physiotherapists Group, and a Health Service Commissioner. A leaflet explaining the database, periodically updated, is made available to patients who can request copies of their individual data. The database is an essential component of the overall arrangements for providing haemophilia care in the UK. Patients have the option to request removal of their data, but this has happened exceedingly rarely. The amount of data held has gradually increased over the years and details are given in the patient information leaflet and on the UKHCDO website.

358) The Royal Infirmary Blood Bank (part of SNBTS) was given a listing of known patients and their recommended treatments – patients would not routinely have

been informed of this. This was to ensure patients each received the correct treatment.

359) In 1983/4, at the beginning of the AIDS era, there was a request to send to the Public Health Laboratory Service (PHLS) in Colindale details of any patients having any of the features of 'AIDS-related complex'. There was much discussion nationally about this because of the issues of patient confidentiality. This was at a time before any blood tests were available for HTLVIII, and it was a public health attempt to monitor whether there might be affected individuals in the population. My recollection is that a compromise arrangement was established where details of patients would be reported to the Oxford Haemophilia Centre and cumulative summary information would be forwarded to the PHLS. So far as I recall, I did not have any patients with relevant features (of 'AIDS-related complex') and therefore none were reported.

360) With the development of national purchasing of commercial clotting factor concentrates, it is possible that *anonymous* details of a small number of patients may have been made available to National Services Scotland without individual patient consent. The information provided would be the diagnosis and the required treatment, thus ensuring that appropriate treatment would be available.

75. Please provide details of any articles that you have published insofar as relevant to the Inquiry's Terms of Reference.

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PUPS

76. Detail all decisions and actions taken at the Centre by you and with your involvement with regard to a category of people referred to as 'previously untreated patients' (PUPS).

361) Individuals referred to as PUPS were those who had not received treatment with blood, blood products, or clotting factor concentrate.

362) This category of patient began to be considered, principally in the early 1980s, as individuals particularly vulnerable to infection. If a blood derived product was indicated, the one that would be recommended was one which was available and which, in the clinical circumstances, offered the lowest perceived risk of serious infection. The perceived safest product(s) changed over time and depended upon the perceived chances and consequences of infective and inhibitor risks.

363) In the early 1980s, for a new patient requiring only occasional treatment, cryoprecipitate would be recommended. As has been set out elsewhere, a patient likely to have required repeated treatment would relatively quickly become exposed to NANB hepatitis.

364) By 1988, evidence had accumulated that the then available virally inactivated concentrates were probably safe from transmitting the NANB virus (es). At this point the concentrates were perceived as the treatment of choice for PUPS, with NHS concentrates probably being considered safer than commercial ones.

365) When SNBTS solvent-detergent treated concentrates became available in the early 1990s, these were offered to patients including to PUPS. All patients PUPS were invited to participate in a follow-up study to assess the viral safety of the new concentrates.

366) When recombinant factor VIII and IX became available in the mid-1990s, these were perceived as being safer than plasma-derived concentrates with respect to infections and became recommended for PUPS.

77. Did you use the term PUP or PUPS when speaking or referring to any of your patients? If so what did you mean by the use of the term?

367) PUP was an abbreviation for 'previously untransfused or untreated patient'. The term was used within the haemophilia team as a short-hand description. Patients who had been so identified would very likely have had the abbreviation explained to them.

Treatment of patients who had been infected with HIV or Hepatitis

78. How was the care and treatment of patients with HIV/AIDS managed at the Centre? What steps were taken to arrange for, or refer patients for, specialist care? What treatment options were offered over the years to those infected with HIV? What information was provided to patients about the risks and benefits of specific treatments and side effects?

368) For those with haemophilia the Centre had provided for many years a 'general practitioner' and medical service. (Patients were reluctant to see their GP with medical complaints because of the possibility that their presenting problem was possibly due to their bleeding disorder). There was the expectation that the Centre should continue to provide this first line service.

369) Initially the patients who were anti-HTLVIII positive were managed medically by the Haemophilia Centre staff and in the Royal Infirmary in-patient ward. At this time, as there was no specific recommended therapy, patients were monitored as described elsewhere. In 1985, the Haemophilia Centre was viewed locally by some as being the expert 'AIDS Centre' and some non-haemophilia patients were referred for investigation and management.

370) The principal clinical risk to patients was the development of opportunistic infections, e.g. candida and pneumocystis carinii. In haematology, we had considerable experience in preventing and managing patients with opportunistic infections, because these are common in patients undergoing therapy for leukaemia and lymphoma. When it became appreciated, in about 1988, that regular inhaled pentamidine reduced the risk of Pneumocystis carinii pneumonia (PCP), we arranged for this to be available to appropriate patients in a room adjacent to the Haemophilia Centre. (Specialist ventilation of the room was necessary because of the toxicity of pentamidine). This was superseded in around 1989 by daily oral cotrimoxazole which was equally effective and much more acceptable to patients.

371) When the zidovudine MRC trial was established in 1988, we applied to be able to offer participation in it to patients. Our application was successful and it was offered to patients.

372) With the development of other AIDS management expertise in Edinburgh, I was keen to draw on this expertise. The other centres of developing experience were in genitourinary medicine and at the infectious diseases unit at the City Hospital.

373) As the HIV service developed at the City Hospital, I wanted the specialists in the infectious diseases to take over management of affected patients, but haemophilia patients were very reluctant and wished to continue to be seen solely at the Haemophilia Centre. Dr Ray Brettle, the leading HIV consultant at the infectious diseases unit, was very willing to help and initially he visited the Haemophilia Centre regularly. We discussed each patient's progress in detail and as a result they were able to benefit from his expertise. When further anti-HIV drugs became available in the late 1980s and 1990s, I considered that the patients really should receive their HIV care primarily at the infectious diseases unit, as I did not have the expertise fully to manage their therapy. Eventually patients agreed to have their HIV care transferred to the infectious diseases unit, which had meanwhile moved from the City Hospital to the Western General Hospital.

374) My recollection is that patients were told about the pentamidine and cotrimoxazole prophylaxis by the medical and nursing staff. Full explanation was necessary because inhaling pentamidine for 20-30 minutes is a most unpleasant experience.

375) An information sheet about zidovudine was provided by the MRC for those who were considering entering the trial.

376) Information about subsequent anti-HIV therapy would have been provided by the infectious diseases unit.

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

377) As described in the response to Question 78, patient follow-up was initially at the Haemophilia Centre, but subsequently it was conducted at the infectious diseases unit. As I had secured external financial support to establish laboratory testing, we were able to monitor the immune and viral status of patients and the results of these investigations were available to the infectious diseases unit. Hence patients did not need to specifically visit the infectious diseases unit for necessary tests, but could have these carried out when they attended the Haemophilia Centre. There was good communication between the two units and this partnership of care worked well.

80. How was care and treatment of patients with hepatitis B managed at the Centre? What steps were taken to arrange for, or refer patients for, specialist care? What treatment options were offered over the years? What information was provided to patients about the risks and benefits of specific treatments and about side effects?

378) All patients were assessed regularly for hepatitis B infection. Hepatitis immunity was regularly checked by measuring anti-HBs levels. For the very small number of patients who had active hepatitis B, their investigation and management was overseen by Professor Hayes, or one of his senior colleagues. I do not have further information about treatment options offered or about information provided about risks and benefits or side effects.

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

379) The arrangements for monitoring these very few patients with active hepatitis B was under the guidance of a senior hepatologist.

82. How was the care and treatment of patients with NANB hepatitis managed at the Centre? What steps were taken to arrange for, or refer patients for, specialist care? What treatment options were offered over the years? What information was provided to patients about the risks and benefits of specific treatments and about side effects?

380) Prior to the discovery of the hepatitis C virus, regular monitoring of liver function tests was routinely provided from the 1970s. When it became clear that some patients might develop significant liver disease, I sought the advice in 1986 of Dr Peter Hayes, Hepatologist, at the Royal Infirmary. He generously agreed to conduct combined clinics at the Haemophilia Centre where he reviewed the patients, discussed their individual situation with the patients and haemophilia staff, and arranged agreed investigations, treatment, and its monitoring. Treatment with interferon, and later with ribavirin, was offered by Dr Hayes who explained about the potential benefits and side effects of these therapies. An information sheet was prepared and given to patients. A detailed check list was used for each patient to ensure appropriate counselling and investigations had been arranged.

381) Other information available to patients has been outline in response to Question 37.

83. How was the care and treatment of patients with hepatitis C managed at the Centre? What steps were taken to arrange for, or refer patients for, specialist care? What treatment options were offered over the years? What information was provided to patients about the risks and benefits of specific treatments and about side effects?

382) The clinical arrangements established for assessing NANB hepatitis, as described in the above response to Question 82, were continued after the identification of

hepatitis C virus as a cause of NANB hepatitis. Arrangements were in line with national guidelines

383) It was necessary to establish reliable hepatitis C laboratory tests and Professor Peter Simmonds set about assessing the initial first generation test when available which had shortcomings. With his expertise, HCV genotyping, quantitation and reliable second-generation antibody tests became available for evaluating patients.

384) The range of investigations and the responses to treatment is summarised in a series of papers [1-14] describing the clinical service offered to patients and the response to therapy.

385) Information made available to patients is described in the response to Question 37. Patients were given a locally prepared information sheet about hepatitis C and a check list of information provided and investigations was filed in the case notes [WITN3428011].

386) My involvement with hepatitis C arrangements ended prior to the introduction of more recent anti-HCV therapy.

387) To document our care arrangements, we described our assessment and management of hepatitis C in a series of papers [1-14].

1. Simmonds, P., et al., *Hepatitis C quantification and sequencing in blood products, haemophiliacs, and drug users.* Lancet, 1990. **336**(8729): p. 1469-72.
2. Watson, H.G., et al., *Use of several second generation serological assays to determine the true prevalence of hepatitis C virus infection in haemophiliacs treated with non-virus inactivated factor VIII and IX concentrates.* Br J Haematol, 1992. **80**(4): p. 514-8.
3. Jarvis, L.M., et al., *Frequent reinfection and reactivation of hepatitis C virus genotypes in multitransfused hemophiliacs.* J Infect Dis, 1994. **170**(4): p. 1018-22.
4. Hanley, J.P., et al., *Treatment of hepatitis C infection in haemophiliacs: the Edinburgh experience.* Haemophilia, 1995. **1 Suppl 4**: p. 36-8.

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6. Ludlam, C.A., *Liver Biopsies.* The Haemophilia Society Bulletin, 1995.
7. Preston, F.E., et al., *Guidelines on the diagnosis and management of chronic liver disease in haemophilia.* Haemophilia, 1995. **1 Suppl 4**: p. 42-4.
8. Preston, F.E., et al., *Heterogeneity of hepatitis C virus genotypes in hemophilia: relationship with chronic liver disease.* Blood, 1995. **85**(5): p. 1259-62.
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14. Makris, M., et al., *Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia.* Haemophilia, 2001. **7**(4): p. 339-45.

84. What follow-up arrangements and/or ongoing monitoring was arranged in respect of patients who were infected by Hepatitis C?

388) The follow-up and monitoring of patients was under the direction of Professor Peter Hayes and mostly took place in the Haemophilia Centre. Patients were also assisted and reviewed by the Hepatitis C Sister who provided information and helped with the therapy and its monitoring.

389) The arrangements are described in the papers cited in the response to Question 83.

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

390) The Haemophilia Centre in Edinburgh has always looked after both children and adults in a seamless service. Children with haemophilia were looked after by me initially when I took up my appointment, but I passed on their care to the Dr Angela Thomas after she was appointed as a consultant paediatric haematologist in 1993. Children were monitored for hepatitis, in the same manner as adults, at regular review clinics. With respect to HIV in the 1980s, we had two teenagers with haemophilia and HIV whom I looked after; their medical management was similar to that for adults.

86. What if any arrangements were made to provide patients infected through blood products with counselling, psychological support, social work support and/or other support.

391) The development of services for people with haemophilia after 1980 has been described in some detail in PRSE0002404.

392) In the early 1980s, I was keen to obtain support for patients and my initial priority was to obtain funding for a haemophilia sister post, which was achieved in 1982. This post-holder provided a receptive access to haemophilia advice (including about hepatitis and HIV) and continuity of care for patients. I also obtained social work support from the Royal Infirmary Social Work service – this had the great advantage in being based in the hospital. Mrs Geraldine Brown was appointed in 1984 prior to our identification of anti-HTLVIII positive patients. I was subsequently able to ensure that a major part of her time was available to support patients and families of all patients, irrespective of their infection status. With the increased clinical needs in early 1985, two clinical assistant medical posts were created to undertake much of the routine patient review. These individuals (who both had experience of general practice) worked as a team with the social worker, haemophilia sister, and nursing staff to support the patients. To enhance the range

of support, I along with other colleagues, raised funding for, and participated in the appointment of, a clinical psychologist, Dr Alison Richardson who joined the team.

393) We provided an open access service, including being open on Saturday morning, so that patients could be seen at almost any time. The staff also visited patients and families at home.

394) This team worked well together to help patients. Giving support was stressful in many different ways, not least because so little was known initially about the uncertain consequences of being anti-HTLVIII positive. Weekly meetings were held to discuss difficulties and support the staff. We greatly benefited from the involvement of Dr George Masterton, Consultant Liaison Psychiatrist, who reviewed and managed patients we referred, and supported our team at times of particular stress. He gave a witness statement commenting on our service to the Penrose Inquiry [PRSE0004379]. In addition, he provided me with a letter to assist in responding to a GMC investigation in 2006. This is attached as WITN3428014.

395) Mrs Geraldine Brown was the Haemophilia Centre social worker from November 1984. She also gave a witness statement to the Penrose Inquiry which fully assessed the services we delivered to counsel and support patients [PRSE0003013]. She was also asked to give evidence to that Inquiry which she did on 16 June 2011.

Records

87. What was the Centre's policy as regards recording information on death certificates when a patient had been infected with HIV or hepatitis?

396) When a death certificate is completed, it is important it contains correct and accurate information. As the death certificate is a public document its contents may reveal information about an individual which was not previously available. In relation to HIV and hepatitis, this is information which might well not have been known beyond the immediate family and could have implications for the family if it became more widely known. This was a topic of concern to patients and families and was something that we considered carefully for all individuals. If a patient

raised it and expressed a view, it was noted and we did our utmost to adhere to their wishes.

397) Separate from the issue of a patient's medical condition being confidential (as above), there was the public health requirement to know the number of individuals dying with HIV. My recollection is that it became possible for the ONS to be informed of such information on a confidential basis and that this would not appear on the public record.

88. What were the retention policies of the Centre in regards to medical records during the time you were director?

398) My policy was that the medical records should be retained as close as possible to where a patient might attend in an emergency. In 1980, the Medical Records Department was keen to keep the medical case notes in their central store which delayed access. Subsequently, it was agreed that they could be stored in the Department of Haematology office. This was located at the far side of the hospital campus from Ward 23 and the Haemophilia Centre where the patients attended with acute bleeds etc. Following my arranging for this facility to be subdivided into a reception area/ waiting room and consulting room, the most recent volume of case notes was stored in filing cabinets in the waiting room. This had the duel advantage that the case notes were immediately available when a patient presented and it was possible for a record of the episode to be recorded contemporaneously.

399) In relation to the long-term retention of records, I was very keen that all medical records were retained indefinitely. This was a recommendation of the Royal College of Pathologists in relation to patients with a genetic disorder. This policy, however, met with some resistance from the Medical Records Department. In addition, I considered there was a very important need to retain permanently medical records for all those who had died from HIV because of the seriousness of this infection. To arrange for case notes to be retained indefinitely, I had to personally sign individual labels to this effect which were each placed inside the front cover of each volume of the patient's medical record.

89. Did you maintain separate files for some or all patients? If so, why; where were those files located; and where are they now?

400) The following are records that were held:

a) Principal medical records – held in Haemophilia Centre

b) Haemophilia Register, (containing basic information about the patient and their underlying bleeding disorder) – held in Haemophilia Centre

c) Short clinical summaries for discussing HIV patients with Dr Brettle (mostly single pages). At the time they may have been stored in the pocket at the back of the most recent medical case notes folder. I am not sure if these still exist, they might be in archive.

d) Short note recording some patient views in early 1985 (as to whether they wished to know their anti-HTLVIII status in response to December 1984 meeting and letter sent in January 1985) – was stored in locked confidential file in my office. Some were subsequently filed in the patients' principal medical records and other were destroyed when I retired.

e) Computer records mostly of laboratory results – computer server in Royal Infirmary.

f) Treatment records of individual infusions, issues of home treatment and treatment forms retuned by patients – held in Haemophilia Centre and later computerised.

g) Family pedigrees (details of family trees for registered patients) – held in Haemophilia Centre.

h) Genetic files (details of causative genetic variant and other relevant data, including copy of consent form for genetic testing) -- held in Department of Haematology.

i) Laboratory clotting records (individual card index file for each patient containing cumulative data) – held in Department of Haematology. Later this was computerised.

j) Annual returns to UKHCDO – held in Haemophilia Centre.

k) Records by social worker and clinical psychologist – held by these departments.

l) Psychiatrist records – held by Department of Psychological Medicine.

401) I retired from the NHS in 2011 and I do not know the current whereabouts of the above records.

90. Did you keep records or information (e.g. information being used for the purpose of research) about your patients at home? If so, why, what information and where is that information held now?

402) I did not keep records or information about patients at my home, except in very limited circumstances as follows:

403) The only information that I held about patients for a period was information I sent to the GMC in response to complaints. The GMC had sent copies of case notes to my home address – I did not request these. Subsequently I transferred them to the Royal Infirmary and they were destroyed. Recently the Medical Defence Union has returned to me information it has made available to the Inquiry, and some patient material is contained therein.

404) I have had access to medical reports from time to time when recruited to advise in respect of litigation against NHS Lothian.

405) Occasionally I was asked to provide an expert report for a Fatal Accident Inquiry or for civil litigation and for these purposes I would have a copy of the relevant medical records. It is likely I took these home in the evening. Subsequently they were either returned to the sender or destroyed.

91. Do you still hold records or information about any of your patients? If so, explain why and identify the records or information that you still hold.

406) I do not hold any records or information about my former patients, except as outlined in response to Question 90.

92. You have already been asked, in Rule 9 requests dated 20 June 2019, 15 August 2019, 7 October 2019 and 18 November 2019 to respond by way of separate statement(s) to specific criticisms by former patients and/or the family member of former patients. The statements which the Inquiry has received so far concerning individuals who were treated at the Royal Infirmary of Edinburgh raise some issues on which the Inquiry also seeks your response more broadly:

a. Whether you told patients to avoid the use of factor concentrates not manufactured in Scotland, and if so, why?

407) Prior to my taking up my appointment at the beginning of 1980, my predecessor, Dr S H Davies, had a policy of treating patients with haemophilia with blood components and products produced by SNBTS. One of the reasons for this was to limit exposure to donors who might be infected with viruses not endogenous in the population in Scotland. Furthermore, local patients might have a degree of immunity of locally prevalent community infections which might also be transmitted by blood.

408) This seemed to me to be a sensible policy, and one I was keen to try and to continue to implement. When Edinburgh registered patients required treatment locally, I did my best to arrange this with locally produced products. Patients, however, often travelled and could present to other Haemophilia Centres in the UK requiring treatment. I was concerned that at other Haemophilia Centres they might receive concentrates prepared from blood collected outwith the UK (because of the relative shortage of NHS manufactured concentrates). To try and prevent this, I gave each patient a short printed 'note' to present with their Haemophilia Card when visiting other Haemophilia Centres. This requested that the patient be treated, whenever possible, with an NHS product. It was suggested that this short 'note' be kept folded inside their Haemophilia Card. As NHS products were much valued by Haemophilia Directors, I offered to 'reimburse' other centres with SNBTS concentrate.

409) When I took up my post, the principal concern was for viruses that caused hepatitis. Whereas a certain amount was known about hepatitis B, the cause of hepatitis that was characterised by usually intermittent rises in liver enzymes was unclear. It was thought to be probably due to one or more viruses characterised as 'non-A non-B virus(es)', although there was also a view that the hepatitis might be an 'allergic' reaction to infusions of blood products. When I gave the 'note' for inclusion with their

Haemophilia Card to the patients, I explained that I was principally concerned about the possible causes of hepatitis and the potential sources of causative viruses.

410) This policy had the effect of protecting patients from non-local viruses. As a result, the patients attending the Edinburgh Centre were seen within the UK as being treated differently from those attending most other Haemophilia Centres. This policy was known to, and supported by, the patients' Haemophilia Society. It offered an almost unique opportunity to assess, in the long term, whether a policy of using only local products would be beneficial to patients. One of the regrettable drawbacks of this policy was that the availability of home therapy had to be delayed.

b. Whether you told patients that there was nothing to worry about in terms of any risk from factor concentrates?

411) As is clear from the above statement, I was concerned in 1980 about infections transmissible by treatments and this was explained to patients. It was explained that we were monitoring liver tests routinely because of the presence of hepatitis. I explained that we did not understand the cause or causes of the hepatitis and that we did not know of the long-term implications.

412) There were other real and well-known risks of factor concentrates. For example, it was well known and established that patients could develop reactions to the concentrates. The most severe were anti-factor VIII antibodies. These anti-bodies could result in infused factor VIII being neutralised and treatment rendered ineffective. These antibodies were regularly screened for by routine blood tests (similarly to hepatitis assessment). From time to time, many patients experienced 'allergic' reactions to concentrates when they would feel unwell, usually at the time of the infusion, and might develop a skin rash or temperature. Such reactions were more common with cryoprecipitate, but also occurred with concentrate infusions, particularly those of lower purity.

413) Later it became clear, both from local studies and from those published in the literature, that patients had immune changes. Both the cause and consequences of these were uncertain, but they were clearly of concern.

414) In summary, as evidence of my concern about the infective risks of blood products in the early 1980s, I would cite the following:

a) The policy of trying to avoid the use commercial concentrates – see (a) above.

b) Routine monitoring of patients for side effects of treatment, e.g. hepatitis and anti-factor VIII antibodies.

c) Participating in the UKHCDO Hepatitis Working Party deliberations.

d) Small blood samples were routinely stored so that if infections arose they could be more fully investigated.

e) I initiated immune lymphocyte tests for patients in early 1983 in response to the first reported cases of AIDS in 3 people with haemophilia.

f) I set up assessment of immunity by skin testing.

g) As soon as I became aware that anti-HTLVIII testing was available in the UK, I negotiated for some stored samples to be tested.

h) Information available to patients is described in PRSE0003062 and PRSE0004704.

415) For the above reasons, I would never had said 'there was nothing to worry about' when much of my concern and actions were in response to the potential for harm from treatment.

c. Why it was not until December 1984 that you provided any information to patients about the possibility of infection with HIV?

416) I recall some of the publicity in the press about AIDS arising in individuals with haemophilia in 1983. The Haemophilia Society had clearly received inquiries from concerned patients. I do not recall patients who attended the Edinburgh Haemophilia Centre asking about the risk of AIDS. This did, however, surprise me. I did not spontaneously raise the possibility of infection with them for a number of reasons. In 1983, the risk of AIDS in patients with haemophilia in the UK appeared to be small; there being one possible case in a population of about 5,000 individuals. Although it was likely that one of the causes of AIDS was a virus transmitted by blood and blood products, the extent of this was unknown. At this time, patients in

Edinburgh were treated with NHS concentrates derived from donors in Scotland where there were no reported cases of AIDS. There were very clear and appreciable benefits from the use of blood products in treating and preventing bleeding, particularly in enabling patients to treat themselves at home. Moreover, despite the availability and use of blood products, approximately 5-10 patients were dying annually in the UK from haemorrhage.

417) Had I been asked about the risk of transmission of a putative AIDS virus in Scotland, I would have explained the difficulty in estimating the risk, and that I considered the risk to be smaller than the US and elsewhere in the UK. Individuals in the general population with AIDS had been diagnosed in England. We were already treating patients in accordance with UK national recommendations. As I recall the situation, I think that Edinburgh patients, knowing the local preference for locally sourced therapeutic products, also probably considered the risk to be small.

418) If a patient had expressed concern about the risk of AIDS, I would have explained my considered view of the situation. I would have discussed the possible therapeutic options. I would not have agreed to the use of a concentrate produced outwith the UK. A patient could have been treated with cryoprecipitate, but this would have required them to relinquish treatment at home; there was no certainty that this would reduce the risk of AIDS, and they would have been at risk of allergic reactions which occasionally were very serious. If the patient wished to discontinue treatment, I would have accepted this view and made arrangements for assisting and assessing them with individual bleeding episodes, e.g. resting splints and analgesia. I would also have required to know, in advance, their wishes about treatment if they presented in future with a life-threatening bleed, e.g. a major gastrointestinal or intracranial haemorrhage.

d. Whether patients were informed promptly about their test results (for HIV and/or hepatitis) and if not, why?

419) My policy has always been to make available to patients all results of investigations. I would also interpret the results for the patient.

HTLVIII

420) What is now known about a current anti-HIV result, its validity, and its implications is very different from the situation at the end of 1984 and in 1985 regarding the initial anti-HTLVIII results and their interpretation.

421) In the context of the initial anti-HTLVIII results which were reported by Dr Tedder, who had set up the assay as a research project, there was a difficulty in interpreting both a positive and negative result.

422) A positive test result was evidence of exposure to HTLVIII, but not necessarily that the individual was actively infected. In the majority of viral infections, the finding of an antibody to a virus indicates past (not present) infection, e.g. an antibody to a strain of flu virus indicates previous infection with that strain. Furthermore, if the individual had been exposed to an 'inactive' virus, they might develop an antibody, e.g. as in a vaccination procedure. Additionally, it was unclear what the false positivity rate was for the anti-HTLVIII test, i.e. whether the test is positive in the absence of true anti-HTLVIII antibody.

423) A negative result might occur because the patient had not been exposed to the virus. It might be negative because the assay was not sufficiently sensitive to detect the antibody, i.e. the antibody was present at a low concentration and below the level of sensitivity of the assay. Furthermore, a negative result did not necessarily indicate that the patient was not infected with HTLVIII, as after infection there is a period of several months before the anti-HTLVIII antibody becomes detectable. There is also the possibility of the test result being a false negative, i.e. the patient has the antibody, but it is not detected by the assay.

424) Thus at the end of 1984, the interpretation of an anti-HTLVIII test was not straightforward. At that time, only about 1/100 to 1/500 people who were anti-HTLVIII positive had AIDS, and along with the above caveats, this made it very difficult to explain to patients the significance of a positive or negative result.

425) At the December 1984 meeting in the Royal Infirmary, to which all patients were invited, I stated that we had anti-HTLVIII results on some patients and that these would be available to individuals along with an interpretation. All patients were also written to and told that they could learn of the result of their own blood test. As a

safety precaution, because of the uncertainty of interpretation of the anti-HTLVIII result, all patients were given information about safe practises, including condom use. Very many patients made an appointment to see me to ask for their results, some shortly after the meeting, and many in early 1985.

426) As a result of the newspapers and press highlighting the AIDS situation in general, and particular the fact that some patients with haemophilia in Edinburgh had been exposed to HTLVIII, the local situation was well known and highly publicised. As a consequence of community hostility to AIDS, some patients wanted time to reflect on whether they wished to learn of their anti-HTLVIII status. Aware that in the immediate future there was no treatment that could be offered, after discussion, we decided that we should allow patients the autonomy to decide when and whether they would like to know the result.

427) There were a very small number of patients who did not request to know their anti-HTLVIII result. Some were very explicit that they did not wish to know the result and this view persisted for some considerable period of time. We kept the situation under review and were aware of which patients had not requested their result and we considered each on an individual basis.

Hepatitis

428) The question seeks information about making results available about hepatitis in general. In the context of haemophilia, this relates to the results of routine and regularly assessed blood tests of liver function. At review clinics, patients were told of their results in general terms, but also in detail if they wished to know. They would have been given an update on their hepatitis B status; many patients were anti-HBs positive, because of previous exposure to the hepatitis B virus. A very small number of patients were actively infected with hepatitis B and this was routinely monitored and the patients were very conversant with their situation.

Hepatitis C

429) Shortly after the hepatitis C virus had been characterised and published in 1989, tests to detect it and the antibody to the virus were developed in the virology department in Edinburgh and elsewhere. There were difficulties with the 'first

generation' of antibody tests and the techniques for its assessment were refined. With a reliable antibody test it was possible to identify patients who had been exposed to the hepatitis C virus, and with the PCR test, to identify those who were still actively infected with the virus. It became accepted that the majority of non-A non-B hepatitis was due to hepatitis C and that, in effect, this longstanding condition was renamed. There was therefore no clinical urgency to inform patients of this awareness and change of name and each would usually be informed at their following routine review clinic visit. If the patient had not previously seen our hepatologist, Professor Peter Hayes, an appointment was made at one of our frequent combined liver/haemophilia clinics in the Haemophilia Centre.

Hepatitis A

430) In 1992, when it became apparent that hepatitis A virus could be transmitted by 'virally inactivate' blood products, we proactively quickly assessed patients, using stored blood samples, and wrote to and offered protective vaccine to those at risk of infection.

e. Whether you underplayed the seriousness of NANB hepatitis/hepatitis C when patients were told of their infection.

431) Our understanding of the cause(s) of NANB hepatitis and its significance changed over time. In the early 1980s, both I and the patients were aware of irregularly raised liver tests reflecting apparently mild inflammation, but there was a paucity of evidence that it was potentially a long-term serious condition. At this time I would have indicated that the patient had evidence of hepatitis, that it might be due to one or more viruses, and that its significance was uncertain.

432) By the mid-1980s, it was becoming clearer that some patients who had long-standing chronic NANB hepatitis, had on liver biopsy histological evidence of inflammation, and in some there was evidence of progressive disease. Following the publication of the paper by Hoofnagle[1] at the end of 1986, demonstrating potential benefit to patients of interferon therapy, I discussed the situation of our patients with haemophilia with Professor Peter Hayes. As a result, we established a regular combined liver/haemophilia clinic at the Haemophilia Centre to offer to assess the liver status and inform patients of their situation, offer advice and, if appropriate, interferon therapy. I was therefore aware of the potential seriousness

of chronic NANB hepatitis, was prepared to tell patients of the latest information, and to offer the assistance of an experienced hepatologist with a particular expertise.

433) This NANB hepatitis response at the Haemophilia Centre in the early 1990s greatly benefited from the hepatitis C antibody and RNA test results and enabled Professor Hayes to offer more specific and useful advice. Patients were offered new therapies for the condition as these became known and available.

References for Question 92

1. Hoofnagle, J.H., et al., *Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report.* N Engl J Med, 1986. **315**(25): p. 1575-8.

93. Some witnesses have described you as lacking in empathy, being unsympathetic, delivering information in an insensitive manner and/or being resistant to answering questions. Please comment, to the extend you feel able to, on these descriptions.

434) I was sorry to learn that I had been remembered by some patients and their families in the way that is stated.

435) I always tried to provide a personalised service for all patients. Being particularly aware that it is the only service available to them locally, it should therefore be as flexible, responsive, and accessible as possible. I always was very conscious of the many and changing difficulties that have been experienced by patients and their families, and I endeavoured to respond in a personal way to these as well to ensure a wider service response. As a chronic heritable condition, haemophilia affects not only the patient, but all members of his family. The painful nature of bleeds, the uncertainty of crises in both their onset and outcome, the continual re-experiencing of trauma with each episode of bleeding, and the difficulty of being obliged to be continually dependent on medical care, present the patient and his family with life-long anxieties and losses. Working in this field requires dedication and sensitivity to all that patients bring. I therefore saw interactions with patients *and* family members as being particularly important, not only because of the patient's individual needs, but because other members of the family may be affected by the condition, or potentially implicated as a carrier of the condition.

436) In the early 1980s, I got to know many patients well because of their relatively frequent attendance for treatment of acute bleeds (some several times per week). This was when the Haemophilia Centre was in ward 23 and before there were other medical and nursing staff who were dedicated solely to haemophilia. In addition, we effectively ran a general practitioner service for patients, when they presented with other non-haemophilia medical difficulties. With the appointment firstly of a haemophilia sister in 1982, and subsequently a further two doctors and additional staff nurses, a small integrated team exclusively for haemophilia was established. This team provided frontline care for both acute episodes and regular review arrangements. As we were a small team, there was the opportunity for patients to meet more regularly with different staff to address their specific current need. My responsibility as team leader was to ensure the team worked effectively and responsively to patients.

437) As I knew the patients relatively well, because of their frequent attendances, I was the more able to respond empathetically to their situation. If a patient asked to see me in particular, I would try to do so at that clinic visit. I acknowledge that as I had a wide range of other responsibilities and commitments, occasionally, this was not always possible; in that event, I would always arrange another time to meet with the patient. To increase availability to patients, I initiated an evening clinic and we opened the Haemophilia Centre on Saturday mornings to make it as easy as possible for patients to be seen.

438) In addition to the impact of this condition on patients, I am very conscious that having a long-term life-threatening chronic condition poses particular demands on the staff providing the service. Staff members develop longstanding and close professional relationships with patients, and when these come under strain, extreme disappointment may be felt on both sides. I understand this to be an expected part of the impact of chronic, painful, illness. In reviewing some of the Rule 9 statements by patients, and other associated information that has come to light, it is clear that patients have not received appropriate information in the past, or that they have drawn inaccurate assumptions from the information they have or remember. For example, because the GMC did not send a copy of my detailed response to a patient, this effectively left that person without any reply to the criticisms raised. Furthermore, the way in which some complaints have been handled has prevented an opportunity for the patient's concern to be appropriately addressed. It probably led to them feeling that they had not been heard by, and even as if they had been

dismissed by, me. In my view, this has significantly added to some patients' sense of grievance. This absence of information has, understandably, led to inaccurate and damaging speculation about what had happened. This has not been helped by the fact that the processes for considering these matters have been attenuated over many years during which memories have had to be held, kept alive, and therefore re-experienced.

439) In relation to being 'resistant to answering questions', I should like to state that I have always tried to be open and to offer as much information as I have available. I aimed to respond fully to questions and continue the discussion for as long as a patient wished.

440) While my personal approach needed to be sensitive to patients and families, it was also important that the haemophilia team as a whole was also welcoming. As evidence that I personally offered appropriate response and effectively led the haemophilia team, I present the following:

a) Submission by the Haemophilia Social Worker, Mrs Geraldine Brown, to the Penrose Inquiry [PRSE0007002] and her oral evidence on 16th June 2011.

b) Submission by Dr George Masterton, Consultant Psychiatrist, to the Penrose Inquiry [PRSE0004379].

c) Letter by Dr Masterton, for onward transmission to the GMC, describing the functioning of the haemophilia team [WITN3428014].

d) External Audit reports from 1991 onwards (when the process was initiated in Scotland, prior to being rolled out in 1994 in the UK). Part of the assessment was by confidential and anonymous patient questionnaire returned to the external auditor. Latterly, audits were undertaken by a team consisting of a haemophilia director, haemophilia nurse, and a patient. The audit reports provide evidence of a high level of patient satisfaction with the haemophilia service. Copies of these reports are available.

Section 6: Self-sufficiency

94. In December 1974 the Department of Health announced additional funding with the primary aim of making the NHS self-sufficient in Factor VIII blood products within two to three years.

a. Were you aware of this announcement at the time?

441) In December 1974, I was an honorary medical registrar and MRC Junior Research Fellow with only clinical duties to assist with in-patient treatment of those with congenital bleeding disorders. I was working in Scotland. I do not recall the Department of Health announcement at that time.

b. What role, if any, did you play in any arrangements made in the centre in which you worked at the time, or subsequently in any organisation, in response to that announcement?

442) The Department of Health announcement related to matters in England. I have never worked at a Haemophilia Centre in England. After 1980, I was present at some UKHCDO meetings where issues related to the supply of NHS manufactured Factor VIII concentrate were being discussed. I did not have any role in this matter.

95. What did you understand the term "self-sufficiency" to mean in 1974/1975? In particular, did you understand it to mean self-sufficiency in providing Factor VIII blood products prophylactically, or solely in response to bleeding incidents?

443) I do not recall in 1974/1975 being aware of the issue of self-sufficiency.

96. Did your understanding of what "self-sufficiency" meant change at any time? If so when and why?

444) I only became involved with the issue of "self-sufficiency" when I took up my appointment in 1980 in Edinburgh. My understanding was that it principally related to the provision of factor VIII and factor IX concentrate of an appropriate quality for treating patients with haemophilia from the population from which the plasma was

derived. It included use of factor VIII/IX to cover treatment of acute bleeds and surgery, and later prophylaxis. It did not include provision of 'activated' concentrates or other products which were used to treat patients with anti-factor VIII antibodies. My understanding did not change over time.

97. What was your understanding of how others defined "self-sufficiency"? Please answer by reference to (i) those involved in the supply of plasma, (ii) those involved in the production of blood products, (iii) clinicians prescribing blood products, (iv) patients using blood products (and their families), and (v) those responsible for managing health authorities and bodies.

445) Whilst I appreciate the importance of the above questions, my recollection relates primarily to the discussions in which I participated within Scotland. It is my impression that all the above groups considered "self-sufficiency" as being defined as I have done in my response to Question 96. As a consequence of my emphasising the desirability of using only NHS products, I think patients in Edinburgh understood this as aiming at "self-sufficiency." My memory is that the Haemophilia Society viewed "self-sufficiency" in the same way as I have outlined in my response to Question 96.

98. What, if any, efforts were made to ensure that all of the groups mentioned in the previous question shared a common understanding of what "self-sufficiency" meant?

446) Please see response to Question 97.

447) I do not recall any discussion about whether different groups had different understandings of "self-sufficiency" and I therefore do not recall there having been any need to reach a 'common understanding.'

99. Insofar as it is with your knowledge and experience, how were estimates made of how much factor VIII blood product would be required for use (i) in Scotland, (ii) in England and Wales and/or (iii) in the United Kingdom. In particular.

a. What was your role in making such estimates, and how did this change over time?

b. What was the role of UKHCDO and how did this change over time?

c. What assumption would underpin the estimates (including assumptions as to how the blood products would be used)?

d. How would estimates be made (e.g. by whom were they made, when and through what process)?

e. How were estimates shared with other interested parties?

f. How did any of these processes change over time?

448) My responses are as follows:

a) After 1980 I, along with haemophilia colleagues in Scotland, senior SNBTS personnel, and officials at Scottish Home and Health Department considered this issue at the regular meetings. I was not involved in any equivalent discussions for England and Wales.

b) "Self-sufficiency" was considered at UKHCDO meetings, but the detailed discussions with blood transfusion services and health authorities were on a country (not UK-wide) basis.

c) In Scotland, the estimate included use for treating acute bleeds, surgery, and prophylaxis. It was based on the then current and anticipated future use.

d) In Scotland, Professor Cash, in 1981 developed a paper proposing a factor VIII requirement of 2.75 IU/head of population for Scotland. Its proposals were considered to be reasonable for planning purposes. That paper along with accompanying explanatory notes was submitted to the Penrose Inquiry [PRSE0001108 and PRSE0004724].

e) I do not recall how Professor Cash's paper was shared with others, apart from within SNBTS, Haemophilia Directors in Scotland and Northern Ireland, and SHHD.

f) The manufacture and use of factor VIII concentrate in Scotland was kept under review at regular meetings with Haemophilia directors, senior SNBTS personnel, and SHHD.

449) I do not have information about estimates for requirements in England and Wales.

450) UK estimates would be based on projecting national UK use forward.

100. How were annual figures derived for how much Factor VIII blood product has used in the course of a year?

a. What was your role in providing such figures, and how did that change over time?
b. What was the role of UKHCDO and did this change over time?
c. How would the calculations be made (e.g. by whom were they made, when, through what process and using what data)?
d. How were those figures broken down geographically (e.g. by country, region or any other until)?
e. How were the figures shared with other interested parties?
f. How did these processes change over time?

451) I respond as follows:

a) Arranging the provision of the annual factor VIII usage figures of the Edinburgh Haemophilia Centre was one of my responsibilities.

b) UKHCDO collated the usage statistics provided by individual haemophilia centres. Initially each Centre provided the total annual factor VIII at the Centre per product. The number of patients treated was recorded. This developed into an arrangement where the amount used per patient annually was reported. More recently greater detail about treatment of individual patients has been recorded.

c) At an individual Haemophilia Centre, the treatment doses would be summated manually and then reported to UKHCDO using a pro forma by Centre staff.

d) Originally, only whole UK usage data was calculated, but with increasing computerisation, it became possible to more readily analyse data by country, region, and Comprehensive Care Haemophilia Centre.

e) The Annual UKHCDO factor VIII usage statistics were published in the Annual Returns. These were made available to UKHCDO members, UK Departments of Health, NHS Blood Transfusion Services, UK Haemophilia Society, and pharmaceutical companies. Annual reports are published on the UKHCDO website which contains the reports for the past 15 years.

f) Over the years the amount of factor VIII usage data collected per individual patient has increased, both because it has become logistically possible to do this with increasing computerisation, and because it was seen to be of advantage in managing individual patients, increased our understanding of haemophilia, and because funders of the service have required more granularity about expenditure. With knowledge of the spectrum of factor VIII use, it has been possible to implement national contracting with commercial suppliers resulting in a very considerable financial saving to the NHS.

101. Were there significant differences between the estimates that were made and actual use? If so, why?

452) My understanding of the estimates on a UK basis is that the use of statistics for factor VIII for each Haemophilia Centre were based on the summation of what each patient received by way of treatment in hospital or what was given as home treatment. Initially this was a very manual process and there were no doubt small numerical errors in the addition of factor VIII units. These were the best estimates of 'actual use'.

453) Statistics were available from NHS manufacturers. For any one year their manufacturing statistics would be different from deliveries to Blood Transfusion Centres or Haemophilia Centre, or use statistics, as products might be held after manufacture for many months (and into a different accounting year). Some organisations used calendar, while others used financial, years.

102. It may be suggested that Scotland was effectively self-sufficient in blood products for much of the period with which the Inquiry in concerned, in the sense that following the development of the Protein Fractionation Centre clinicians had sufficient NHS products to meet the demands for such products.

a. Is this correct to the best of your knowledge?
b. If so, when was such self-sufficiency achieved, to the best of your knowledge?
c. In which years was self-sufficiency not achieved, and why?
d. In the periods when self-sufficiency was achieved, why did clinicians in Scotland continue to use imported products?

454) I have defined my understanding of self-sufficiency in my response to Question 95. The products available must be effective, safe and usable for treating patients. There are many factors which need to be taken into account in assessing the suitability of a treatment, as I have outlined in my responses to previous questions. There is also the question as to how much treatment is required, i.e. the amount of treatment. I note the question asks whether 'Scotland was *effectively* self-sufficient'.

455) My understanding of the Inquiry's remit is that it covers a very long period of time extending into the present century, during which Scotland was in the lead over the use of commercial recombinant concentrates. I will, however, confine my observations to the 1980s.

a) During the 1980s, over 90% of factor VIII consumption in Scotland was sourced form NHS manufacture. The small amount of 'commercial' factor VIII in the early part of the decade was because of insufficient supply of a suitable NHS factor VIII concentrate, and in the latter part of the decade the 'commercial' concentrate statistics probably included use of porcine factor VIII concentrate (Table 21.1 Penrose Report).

b) From a practical perspective Scotland became 'self-sufficient' during 1983.

c) Prior to 1983, there was use of commercial concentrate because of an inadequate supply of a suitable factor VIII concentrate to treat all patients. This was partly an inadequate supply of volume and partly the quality was problematic for certain use, e.g. treating patients with anti-factor VIII antibodies and surgery.

d) I note the question relates to imported concentrates. I assume this relates to products imported into the UK rather than imported into Scotland. I do not currently have details of the small amount of imported concentrate used after 1983. I suspect some of the commercial concentrate use relates to use of porcine factor VIII concentrate. Although this was a commercial concentrate it was manufactured in Wales and was therefore not *imported into* the UK.

103. It may be suggested that England and Wales never achieved self-sufficiency of factor VIII products, in the sense that clinicians were always reliant on commercially imported products to meet the demands for such products.

a. Is this correct to the best of your knowledge?

b. Is so, why, in your opinion was self-sufficiency was never achieved?

c. If, in your view, self-sufficiency was achieved, when was it achieved and why it was not achieved earlier?

456) My understanding is that prior to 1972, the UK was self-sufficient in factor VIII products [1], but thereafter commercial concentrates became available for importation and were used to treat patients in the UK [2]. The largest proportion of the commercial factor VIII used will have been in England and Wales.

457) Since the mid-1990s, there has been increasing use of imported commercial recombinant concentrates for treating haemophilia A and B. (http://www.ukhcdo.org/wp-content/uploads/2019/11/UKHCDO-Annual-Report-2019.pdf).

458) There are multiple and complex reasons why self-sufficiency was not maintained in England and Wales after 1971. I was not party to the discussions and negotiations for the arrangements and therefore do not have first-hand knowledge of events.

References in respect of Question 103

1. Rizza, C.R. and R.J. Spooner, *Treatment of haemophilia and related disorders in Britain and Northern Ireland during 1976-80: report on behalf of the directors of haemophilia centres in the United Kingdom.* Br Med J (Clin Res Ed), 1983. **286**(6369): p. 929-33.
2. Rizza, C.R., R.J. Spooner, and P.L. Giangrande, *Treatment of haemophilia in the United Kingdom 1981-1996.* Haemophilia, 2001. **7**(4): p. 349-59.

104. What knowledge do you have of whether and if so when Northern Ireland achieved self-sufficiency in blood products (accepting that the plasma was fractionated in Scotland rather than Northern Ireland)?

459) At the time of writing, I only have limited access to data about clotting factor use in Northern Ireland. The first report of the Coagulation Factor Working Party for

Scotland and Northern Ireland describes use of NHS and 'commercial' factor VIII concentrate in 1987-9 [PRSE0003487].

105. It may be suggested that a significant contributory factor to England and Wales not achieving self-sufficiency (or not doing so earlier) was a failure by haemophilia clinicians to provide timely and accurate estimates of future demand for factor VIII blood products. It may also be suggested that this played a role in limiting the availability of NHS products for use in parts of Scotland. In particular, it may be suggested that haemophilia clinicians failed to identify the foreseeable increase in use of such products once they became available. How would you respond to these suggestions?

460) UKHCDO has been a world leader in its national arrangements for overseeing haemophilia care in the UK. Its annual collection of treatment data provided high quality information for many purposes, including estimating future requirements. Since 1972, it has been clear that the NHS was not able to supply all the treatment requirements in the UK. The total demand for factor VIII containing products increased linearly after 1972 and the increasing use of concentrate compared with cryoprecipitate was evident.

461) As I have stated in my response to Question 103, I was not party to discussions about future needs in England and Wales, but it is clear from the usage statistics the there was insufficient NHS concentrate to meet the demand. In Scotland in 1981, an estimate of future demand was developed which proposed a figure of 2.75 IU/head population [PRSE0001108]. At this time factor VIII use was a little over 1 IU/head population and use did not reach the 2.75 estimate until the early 1990s. In retrospect this validated the future estimate made in 1981 for the following decade.

462) I was not party to any discussions about self-sufficiency during the 1970s and I therefore do not have first-hand knowledge. Following my appointment in 1980, I was invited to attend the meetings led by SHHD to oversee production of concentrates in Scotland and Northern Ireland. These meetings considered in some detail the quality and quantity of products manufactured by SNBTS against the perceived need by clinicians. The estimate of future quantity referred to above served the planning arrangements reasonably well, bearing in mind that there was an approximate 10% increase in use annually. When it became clear that new

products were desirable, the Coagulation Factor Working Party for Scotland and Northern Ireland was established. It provided an effective forum between SHHD, SNBTS, and haemophilia directors for managing the increased quantity and enhanced quality transition to new products while maintaining self-sufficiency.

106. If self-sufficiency had been achieved in Factor VIII products in England and Wales, what, in your view and in light of the experience in Scotland, would have been the effect on the numbers of patients infected with (i) HBV, (ii) HCV, and (iii) HIV? Please comment, if you are able to, on when self-sufficiency would have needed to be achieved (in your view) in order for any material difference to have been made in respect of each of these viruses.

463) These are difficult questions to answer and I have spent considerable time reflecting upon the issues that need to be considered. A range of aspects of therapy need to be taken into consideration in addressing the questions. These include the following factors:

a) The UK appears to have been self-sufficient in factor VIII products prior to 1972.

b) Factor VIII products relate to cryoprecipitate as well as concentrates, and the risk of virus infection may depend upon the indications for their respective use.

c) The UK has, so far as I know, always been self-sufficient in cryoprecipitate.

d) The question presumably only relates to the use of products containing human factor VIII derived from human donor plasma.

e) The risk of viral infection may depend upon the number of doses of a treatment and this will vary between patients particularly those with different severities of haemophilia.

f) The risk of infection may depend upon the number of different batches of product received.

g) In considering the risks it will be necessary to consider whether patients would have been treated similarly with respect to NHS vs commercial concentrates.

h) The risks of infection will depend on the prevalence of infection of each virus in the donor population and this varied during the period in question.

i) The risk viral contamination will depend upon the ability of the donor screening process to exclude infectious donations and this varied during the period in question.

j) The risk may depend upon whether the donor at the time of donation gave a single donation or was plasmapheresed.

k) The risk of infection may be related to the size of donor pool contributing to a batch of factor VIII concentrate.

l) The risk will depend upon the fractionation process used during manufacture. Some infectious agents may be preferentially excluded or enriched in the process. A degree of dilution occurs with the pooling of donations. The fractionation process itself may lead to a degree of viral attenuation.

m) The risk of virus infectivity of a product will depend upon the viral inactivation process or processes employed during manufacture.

n) The risk of infection will depend upon the susceptibility of recipient, for example, following hepatitis B vaccination, the risk of infection by this virus will be reduced.

464) Overall and considering the above variables I would conclude as follows.

If NHS prepared concentrates had been used in place of all commercial human plasma factor VIII and IX concentrates from 1972 onwards, it is likely that the prevalence of infection by hepatitis B and C in people with heritable bleeding disorders would have been very similar to what has occurred with the use of commercial concentrates. In summary NHS concentrates were infectious for hepatitis B and C in the 1970s and 1980s although these concentrates had a lower degree of contamination than their commercial counterparts.

465) In relation to HIV the situation is much more complex and complicated by many factors, some of which I have outlined above. Currently I am not able to give a view as to whether there would have been less HIV infection if the UK had been self-sufficient in factor VIII and IX concentrates.

Section 7: Scottish National Blood Transfusion Service

107. Please set out the interactions and dealings you had in relation to SNBTS as the director of the Centre, insofar as relevant to the Inquiry's Terms of Reference?

466) I interacted with SNBTS in a number of ways:

a) At a hospital level, SNBTS provided the blood bank and store of blood and blood products. There were frequent interactions with staff over the provision of treatment for patients. The Blood Bank and Department of Haematology were geographically close and as a result there were frequent informal encounters and meetings with staff.

b) There were regular formal meetings with SNBTS at Scottish Home and Health Department along with other haemophilia directors from Scotland and Northern Ireland. These were to review arrangements for the provision of treatment for people with congenital bleeding disorders.

c) There were informal interactions and correspondence with senior SNBTS staff, including at the Protein Fractionation Centre, as necessary.

d) The Factor VIII Working Party for Scotland and Northern Ireland (later to become the Coagulation Factor Working Party) established in 1988 was an important forum between haemophilia directors, senior SNBTS staff, and Scottish Home and Health Department for developing new treatments.

e) The Recombinant Coagulation Factor Consortium for Scotland formed in 1996 was an important forum for overseeing the introduction and increasing use of recombinant concentrates in Scotland.

The Consortium was chaired and led by the General Manager for NHS Lothian (on behalf of Health Boards for Scotland) and included the following individuals:

- Mr David McIntosh (General Manager SNBTS),
- Mr Peter Croan (NHS National Services Division, Finance Director),
- Dr Harry Burns (Public Health Director),
- Professors Lowe and Ludlam (Directors of Haemophilia Centres).

The Consortium agreed arrangements for:

- The orderly introduction of recombinant concentrates in Scotland.
- Ensuring that in addition to the £1 million donated by SNBTS, as start-up funding, further SHHD support would progressively become available.
- Agreeing clinical criteria for order of priority for the introduction of recombinant concentrates.
- Monitoring the roll out of the arrangements.

108. What consideration was given to increasing production of cryoprecipitate, or producing a product with lower risk, in response to the risks associated with factor products, and what if any involvement did you have with SNBTS in relation to this?

467) In the early 1980s, SNBTS made strenuous efforts to increase the production of factor VIII concentrate, particularly so that patients could have treatment at home. At this time, there were only 6 patients on home therapy in Edinburgh and very many other eligible patients could not benefit because of the requirement for home treatment to be with concentrate. This was a major logistic challenge particularly as SNBTS was also increasing the total amount of factor VIII containing products for patients. The overall process was challenged by the fact that the yield of factor VIII in concentrate was less than with cryoprecipitate. As a result of this policy, by 1983 about 40 patients were benefiting from home therapy.

468) Consideration was given to reverting to cryoprecipitate instead of concentrate production. From the international perspective of the developing knowledge of

AIDS situation, it was unclear what the risk was from clotting factor concentrates and further if this risk would be less in cryoprecipitate if AIDS was due to a virus. The infection risk would reflect presumably the infection prevalence in the donor population. It was uncertain whether the risk would be less from cryoprecipitate compared with concentrate, as the presumed virus would be massively diluted by non-infected donations and might be inactivated during the manufacturing process. At this time there were no reported cases of AIDS in Scotland.

469) To have reverted to cryoprecipitate would have required a major change in policy and practical logistics in the processing of individual blood donations. In particular, cryoprecipitate production is a very labour-intensive process and would require centrifugation of thousands of individual plasma units as described in a paper by Professor Cash [PRSE0004724].

470) Cryoprecipitate results in a much higher incidence of transfusion reactions than following concentrate use. Additionally, the dose patients receive is vary variable and not standardised because of the very large range of factor VIII levels in the blood donor population. Had factor concentrate stopped being supplied, patients would have to be taken off home therapy and they would have to attended hospital with every bleed for treatment with cryoprecipitate.

471) There were discussions and some pilot work in Glasgow in the early 1980s to consider the possibility of producing freeze-dried cryoprecipitate. The project was discontinued because it was not seen as a viable option.

472) During 1983 and 1984, I was collaborating with SNBTS in initial clinical studies to assess SNBTS heat-treated factor VIII concentrate. This work was originally aimed at reducing the hepatitis risk.

109. What discussion or meetings or interactions did you have with SNBTS 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

473) I respond as follows to the above questions:

The issue of hepatitis, HIV/AIDS, and other virus risks have been considered in many different meetings and forums over many years with SNBTS. In the 1980s, the question of viral safety was considered at the regular SNBTS, SHHD, and haemophilia director meetings. There were meetings to consider development of heat treatment and I assisted by testing products. Studies were established to study the safety of heat-treated concentrates by ALT testing (prior to the identification of hepatitis C virus) and anti-HTLVIII, and by hepatitis C testing after its identification.

110. What involvement did you have with any decisions or actions taken by SNBTS in response to the risks arising from blood and blood products?

474) SNBTS made its decisions in relation to blood safety after taking into consideration relevant factors. I did not take part directly in their decision processes.

475) I would contribute to discussions both at formal meetings, e.g. at Scottish Home and Health Department, and in informal discussions.

476) There were areas of common concern, like the development of new concentrates, and the arrangements would be agreed in discussion, for example, at the Coagulation Factor Working Party for Scotland and Northern Ireland. When recombinant concentrates became available in 1996, a consortium arrangement was established with SNBTS and Health Boards to oversee their introduction in Scotland. This Consortium is discussed in paragraph 107 above.

111. What system was followed for keeping records of the blood or blood products used in Scotland (both in relation to source and use)?

477) Record keeping of blood products used is the responsibility of each Haemophilia Centre. Records (product, batch number, and dose) are kept of all individual hospital treatments. The same details are recorded for treatment given to patients at home. The patients are asked to complete forms recording the use of treatment, e.g. site of bleed, date, and dose.

478) Annually this data was summated by patient and forwarded to the UKHCDO National Haemophilia Database.

479) Originally the system was manual with written records, but over the years the system has become increasingly computerised, both at individual haemophilia centres and at UKHCDO nationally. Records of home treatment are now encouraged by smart phone. This has markedly enhanced the ability to help patients at home by allowing real time monitoring of bleeds.

112. Why was the Factor 8 Working Party for Scotland and Northern Ireland established and what was your role in it?

480) The Working Party was established by SHHD to bring together manufacturer and users of factor VIII concentrate in Scotland and Northern Ireland. The principal remit was "To recommend methods and strategies for the validation and testing and new factor VIII products supplied by PFC" (1st Annual Report April 1989). The remit was subsequently extended to include factor IX concentrate and the Working Party was renamed the Coagulation Factor Working Party for Scotland and Northern Ireland.

481) I was invited by SHHD to chair the Working Party on inception.

482) Membership

Professor J D Cash - SNBTS National Medical Director
Dr B Gibson - Haemophilia Director, Children's Hospital, Glasgow
Dr G D O Lowe - Haemophilia Director, Glasgow Royal Infirmary
Dr E E Mayne - Haemophilia Director, Belfast
Dr D B L McClelland - Director, South East Scotland Blood Transfusion

Dr R J Perry - Director, SNBTS Protein Fractionation Centre, Edinburgh
Dr R C C Stewart – SNBT
Dr R Skinner & Dr A Keel (Senior Medical Officer & Deputy Chief Medical Officer, SHHD)
Mr D B McIntosh (in attendance) General Manager, SNBTS

483) I provided a document to the Penrose Inquiry which contains more information and have provided a copy to this Inquiry [WITN3428018]. Copies of the minutes and the annual reports are available.

113. Have you held any positions at the Scottish National Blood Transfusion Service (SNBTS) and if so what were your role and responsibilities in any such positions?

484) I was offered an honorary consultant contract with SNBTS, in about 1986. My commitment was to respond to inquiries for advice.

Section 8: UKHCDO

114. Please describe your involvement with UKHCDO.

485) When I took up my appointment as a consultant haematologist in 1980, I was invited to be a member of the UKHCDO Reference Centre Directors group. This was the group which led activities of the organisation. In 1996, I was elected by the membership as chairman for three years, having been the vice-chair 1990-96. In 2011, when I retired from the NHS, I was made an 'honorary member'.

486) I have taken part in consideration of a broad range of issues related to the provision of services and facilities for people with heritable bleeding disorders. I have been a member of several of its working parties, e.g. Hepatitis/Chronic Liver Disease and Genetics (chairman). I was invited to lead the arrangements for compiling the therapeutic guidelines in 1996 and 2002.

487) I was invited to become a director of UKHCDO Ltd in 2013. This is a position I still hold.

115. During the period that you were involved with UKHCDO, please outline:

488) This Question covers a very wide range of topics over a 30-year period. I would commend the minutes of meetings and the issued guidelines as reliable evidence on the range of topics I helped consider.

a) The purpose, functions and responsibilities of UKHCDO, as you understood them;

489) The principal function of UKHCDO is to provide professional advice on the arrangements for treatment of patients and their families with heritable bleeding disorders in the UK. UKHCDO has never had any direct management responsibility for the provision of services or treatment. At the request of the Department of Health, it maintains a database of patients with congenital bleeding disorders.

b) The Structure, composition and role of its various committees or working groups;

490) The organisation is a registered charity. Membership is open to all doctors working in haemophilia centres. There is an elected Executive consisting of chairman, vice-chairman, secretary and treasurer.

491) The Advisory Group is the main forum for consideration of the organisation's regular business and consists of representatives of Comprehensive Care Centres; it meets every few months. There was a standing invitation for the Departments of Health to send a representative – usually a representative from the Department of Health for England attended to liaise with the other Health Departments.

492) Working Parties were formed to address specific areas of concern and some have a remit to draft guidelines (membership might include other health care professionals or patient representatives).

493) There is an annual general meeting to which all members are invited. Also, to this meeting are invited representatives of the Haemophilia Society, Haemophilia Nurses, Haemophilia Physiotherapists and Social Workers who were invited to

present reports and participate in the discussions. The Departments of Health were each invited to send a representative.

494) UKHCDO Ltd was established to undertake some of the financial arrangements for the charity and in particular to oversee the financing of the National Haemophilia Database. It is wholly owned by the charity.

c) The relationship between UKHCDO and pharmaceutical companies;

495) There was no general formal relationship between pharmaceutic companies and UKHCDO. UKHCDO was prepared to consider proposals from individual companies seeking data. For example, it is becoming increasingly common for product licences to be granted on the condition that the manufacturer arranged phase IV post-marketing surveillance. UKHCDO is prepared to consider such proposals because it provides a mechanism for detecting side effects early and allows the earlier granting of a licence. The company reimburses UKHCDO for the cost of preparing the data and a report.

496) At the AGM on some occasions there would be an accompanying scientific meeting day. At some of these occasions there would be a commercial exhibition for which the pharmaceutical companies would made a payment to UKHCDO funds.

d) How decisions were taken by UKHCDO

497) Decisions were taken after consensus was reached after consideration of an issue. There was rarely a need for a vote.

e) How information or advice was disseminated by UKHCDO and to whom;

498) Advice and information would be disseminated as appropriate. There was close collaboration with other health care professional groups and the Haemophilia Society which may well have been involved with generating the advice. The most formal advice was that issued as guidelines and the majority were published in scientific journals – they were viewed very favourably by physicians around the world. Advice in relation to arrangements for service provision, e.g. health circulars

was given to Departments of Health and the Haemophilia Alliance during the generation of the Haemophilia National Service Specifications.

f) Any policies, guidance or decisions of UKHCDO in which you were involved with related to:

i. The importation, purchase and selection of blood products;

499) There were many discussions at meetings in relation to this topic which are recorded in the minutes of the meetings. Periodically therapeutic guidelines were compiled.

ii. The manufacture of blood products

500) UKHCDO was not involved with the detail of manufacture except in so far as it related to safety and availability of products.

iii. Self-sufficiency;

501) UKHCDO was supportive of the policy of self-sufficiency.

iv. Alternative treatments to factor products from patient with bleeding disorders;

502) UKHCDO guidance was confined to discussions and recommendations in relation to heritable bleeding disorders. The Therapeutic Guidelines included recommendations on desmopressin and tranexamic acid use.

v. The risk of infection associated with the use of blood products

503) This was considered on many occasions and the deliberations are recorded in the minutes of the meetings. The Hepatitis Working Party Meetings considered issues related to NANB hepatitis and later HTLVIII.

vi. The sharing of information about such risks with patients and/or their families

504) There were many discussions about how to share information about risk of infections with patients and families and these are recorded in the minutes of meetings. One of the greatest difficulties was trying to estimate the risk, which was likely to be very different for different potential infective agents. UKHCDO was always keen to give as accurate and up to date information as possible to patients. The information was provided to the Haemophilia Society and was disseminated to members and also to Haemophilia Centres for dissemination to non-members.

vii. Obtaining consent from patients for the testing and storage of their blood, for treatment and for research.

505) UKHCDO did not have a policy on the storage of small aliquots of blood samples collected at routine review clinics. Guidance was provided for patient consent in relation to storage of blood samples for genetic testing; this being particularly important not only because the result of sample testing may have implications for other family members but also it allowed for both retesting and applying new investigations if appropriate(1).

viii. Heat treatment

506) The various discussions about heat-treatment are recorded in the minutes of the meetings. The principal decision to opt for heat-treatment was taken at the meeting on 10th December 1984 [HCDO0000394_117].

ix. Other measures to reduce risk

507) There have been many discussions about the risks of treatment; the risk of anti-factor VIII antibody development is a major and life-changing event which over the years has been reviewed at many meetings.

x. vCJD exposure

508) As reported elsewhere (response to Question 126) I took the lead in raising the issue of the possibility that the agent causing vCJD might be transmitted by clotting

factor concentrates. This led to a major change in therapeutic policy and very detailed information being made available to patients.

xi. Treatments for HIV and hepatitis C

509) These were considered by UKHCDO at various meetings and the deliberation recorded in the minutes. Two guidelines in relation to liver disease were developed [2, 3].

References in respect of Question 115

1. Ludlam CA, Pasi KJ, Bolton-Maggs P, Collins PW, Cumming AM, Dolan G, et al. A framework for genetic service provision for haemophilia and other inherited bleeding disorders. Haemophilia. 2005;11(2):145-63.

2. Preston FE, Dusheiko G, Lee CA, Ludlam CA, Giangrande PL. Guidelines on the diagnosis and management of chronic liver disease in haemophilia. Haemophilia. 1995;1 Suppl 4:42-4.

3. Makris M, Baglin T, Dusheiko G, Giangrande PL, Lee CA, Ludlam CA, et al. Guidelines on the diagnosis, management and prevention of hepatitis in haemophilia. Haemophilia. 2001;7(4):339-45.

Section 9: Pharmaceutical companies/medical research/clinical trials

116. 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 of the advisory or consultancy services that you provided.

510) I have tried to recall times when I have provided advice or consultancy services to pharmaceutical manufacturers of blood products prior to my retirement from the NHS in 2011. In doing so, I have not included my interactions with SNBTS over manufacture of blood products. I do not have any written records and have compiled the list below from memory which makes it possible that it is incomplete.

511) Baxter: I was invited to help to devise the programme and act as co-chairman for an international meeting, funded by Baxter, on safety of treatment for haemophilia in Minneapolis in 2004. The proceedings of this were published [1]. As a result of the discussions at this meeting an 'Interdisciplinary Group' of 45 European physicians was established to respond to some of the perceived threats to

haemophilia care. Together with Professor Mannucci I was invited to co-chair the project and meetings which resulted in publications cited below [2-4].

512) Novo Nordisk: A protocol was developed for a Novo Nordisk sponsored study on the use of rVIIa to cover surgery in patients with anti-factor VIII antibodies. I recall attending a meeting, probably in London, in relation to the project. The results of the study were published. Subsequently I was also invited to a meeting to compile guidance on the use of rVIIa in orthopaedic surgery which was published [5]. In conjunction with Axon, and with financial support of Novo Nordisk, I have led the Haemophilia Academy project 2008 - 2019.

513) Immuno: I was invited to a meeting in 1983, (perhaps at Heathrow airport), on a topic that I do not now recall.

514) Since retiring from the NHS I have been invited to provide part-time consultancy to several pharmaceutical companies. In 2012 I worked with Ipsen in Paris which was developing a recombinant porcine factor VIII concentrate and a human recombinant factor IX concentrate. This project closed at the end of 2012. The following year (until 2016) I provided consultancy to Sobi in Stockholm; it had developed extended half-life recombinant factor VIII and IX concentrates. In 2017 I provided a very limited consultancy to Roche UK in relation to emicizumab. In 2018 I was approached by BioMarin (California) to monitor the response in patients in their phase 3 gene therapy study for severe haemophilia A; I am still helping with this study.

References in respect of Question 116

1. Ludlam, C.A., et al., *Clinical perspectives of emerging pathogens in bleeding disorders.* Lancet, 2006. **367**(9506): p. 252-61.

2. Colvin, B.T., et al., *European principles of haemophilia care.* Haemophilia, 2008. **14**(2): p. 361-74.

3. Astermark, J., et al., *European curriculum for thrombosis and haemostasis.* Haemophilia, 2009. **15**(1): p. 337-44.

4. Makris, M., et al., *EUHASS: The European Haemophilia Safety Surveillance system.* Thromb Res, 2011. **127 Suppl 2**: p. S22-5.

5. Giangrande, P.L., et al., *Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven] in elective orthopaedic surgery in haemophilic patients with inhibitors.* Haemophilia, 2009. **15**(2): p. 501-8.

117. 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 provide details.

515) Further to the events referred to in my response to Question 116, I can add the following:

a) Baxter: It is likely that I received an honorarium (as well as travel expenses) for helping to organise and chair the meeting in Minneapolis. It is also likely I received an honorarium and travel expenses for co-chairing and leading the Interdisciplinary Group.

b) Novo Nordisk: The central purpose of the meeting was to consider how to assess rVIIa use in surgery. I consider it unlikely that I received an honorarium although I am likely to have received travel expenses. I think it likely that I received an honorarium and travel expenses for attending the meeting to compile guidance on use of VIIa in orthopaedic surgery. I received an honorarium for leading the Haemophilia Academy.

c) Immuno meeting in 1983: I do not think I was given an honorarium (although I think it likely that my travel expenses were reimbursed).

118. 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 and any financial or other remuneration you received.

516) Please see response to Questions 116 and 117. I do not recall participating in any other such bodies or advisory panels.

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

517) I have never received any financial incentive to use any blood product.

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

518) I have never received any non-financial incentives from pharmaceutical companies to use certain blood products. In the 1980s and possibly 1990s some pharmaceutical companies sent annual desk diaries.

121. Have you ever received any funding to prescribe, supply, administer, recommend, buy or sell any blood product from a pharmaceutic company?

519) I have never received any funding for any of the above.

122. 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?

520) On any occasion that I was asked to make a declaration about involvement with pharmaceutical companies I readily did so.

521) Within the hospital, requests for leave of absence, for example to attend a scientific meeting, required declaration of details of any external funding received. This required me to include the name of any pharmaceutical company concerned.

522) Studies or publications, for which there was financial support from a pharmaceutical company, would have this recorded in the publications, usually under the heading 'conflict of interest'.

523) UKHCDO has a system where members are asked to record potential conflicts of interest in relation to their work.

524) I always complied with any guidelines to which I was subject, in so far as I am aware.

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

525) I have undertaken evaluation of rVIIa concentrate in patients with anti-factor VIII antibodies who required orthopaedic surgery. As indicated above this was a Novo Nordisk sponsored study in which I was one of the investigators. The rVIIa was probably provided free of change. The results of the study would be reported to Novo Nordisk as the sponsors. After the start of the study it became clear that the dose of rVIIa was insufficient to maintain reasonable haemostasis in the post-operative period. This led to revision of the protocol to use a higher dose [1, 2].

526) It is possible that I have undertaken other studies but I do not recall the details of any.

References in respect of Question 123

1. Smith, M.P., et al., *Elective surgery on factor VIII inhibitor patients using continuous infusion of recombinant activated factor VII: plasma factor VII activity of 10 IU/ml is associated with an increased incidence of bleeding.* Thromb Haemost, 2001. **86**(4): p. 949-53.

2. Ludlam, C.A., et al., *A prospective study of recombinant activated factor VII administered by continuous infusion to inhibitor patients undergoing elective major orthopaedic surgery: a pharmacokinetic and efficacy evaluation.* Br J Haematol, 2003. **120**(5): p. 808-13.

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

527) Please see my response to question 123.

125. 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.

528) I do not recall details of receiving funding for medical research from pharmaceutical companies, except possibly a small amount to cover expenses in relation to assessing rVIIa in orthopaedic surgery (as described in response to Q 123). If funding was received from a pharmaceutical company, it was directed either to the Health Board, or the Health Board Endowment Fund, or the University of Edinburgh. Funds were received from SNBTS in support of assessment of new clotting factor concentrates.

Section 10: vCJD

126.When and in what circumstances did you become aware of the risks of transmission of vCJD associated with the use of blood and blood products?

529) I became aware of the possibility that vCJD might be transmissible by blood and blood products after the publication of the report by Will et al in 1996 [1]. I wrote to Dr Will to seek his view about the possibility of transmission by blood and blood products. I append a copy of my letter and his response [WITN3428015]. I became concerned because there did not appear to be an appreciation that the vCJD prion might be transmitted by clotting factor concentrates. As I had recently taken over as chairman UKHCDO, on 20th November 1997, I set up a meeting of interested parties (commercial and NHS manufacturers, representatives of the Departments of Health, representative of the licensing authority and CJD experts) along with UKHCDO Reference Centre directors, to consider the potential safety of clotting factor concentrates [HCDO0000463]. After taking evidence, UKHCDO directors discussed the situation and concluded that 'it is likely that any risk of transmission would be reduced by use of concentrates prepared from donor plasma collected in other countries, such as the USA, where there are no recorded cases of nvCJD or BSE' [2]. Although this view gave rise to controversy, the regulatory authorities moved to a position of allowing, and subsequently mandating, that pooled plasma products manufactured in the UK should only be made from plasma imported from parts of the world at low risk of vCJD [3]. Other aspects of the history are set out in a previous review [4]. The details of an individual with haemophilia in whom the vCJD prion was found in his spleen have been reported [5]. The overall history is set out in some detail [6].

References in respect of Question 126

1. Will, R.G., et al., *A new variant of Creutzfeldt-Jakob disease in the UK.* Lancet, 1996. **347**(9006): p. 921-5.

2. Ludlam, C.A., *New-variant Creutzfeldt-Jakob disease and treatment of haemophilia. Executive Committee of the UKHCDO. United Kingdom Haemophilia Centre Directors' Organisation.* Lancet, 1997. **350**(9092): p. 1704.

3. Turner, M.L. and C.A. Ludlam, *An update on the assessment and management of the risk of transmission of variant Creutzfeldt-Jakob disease by blood and plasma products.* Br J Haematol, 2008. **144**(1): p. 14-23.

4. Ludlam, C.A. and M.L. Turner, *Managing the risk of transmission of variant Creutzfeldt Jakob disease by blood products.* Br J Haematol, 2005. **132**(1): p. 13-24.

5. Zaman, S.M., et al., *The risk of variant Creutzfeldt-Jakob disease among UK patients with bleeding disorders, known to have received potentially contaminated plasma products.* Haemophilia, 2011. **17**(6): p. 931-7.

6. Millar, C.M., et al., *Risk reduction strategies for variant Creutzfeldt-Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders.* Haemophilia, 2010. **16**(2): p. 305-15.

127. What was the process at the Centre for informing patients about possible exposure to vCJD?

530) The Health Protection Agency took the lead in arranging the assessment of risk, deciding who should receive information, and in devising much of the written material that was sent to patients. In relation to concentrates produced in Scotland, there was liaison with SNBTS, SHHD, and the Banner Committee. Appropriate patients were sent the relevant information with an accompanying letter.

531) The overall UK response to issues relating to vCJD have been described in a report on behalf of UKHCDO [1].

Reference in respect of Question 127

1. *Risk reduction strategies for variant Creutzfeldt-Jakob disease transmission by UK plasma products and their impact on patients with inherited bleeding disorders.* Haemophilia, 2010. **16**(2): p. 305-15.

128. When and how were patients told of possible exposure to vCJD?

532) Patients were informed by a letter which enclosed written information. Examples of the correspondence sent out are attached at WITN3428016. There are copy letters dated 25 March 1998, a letter dated 7 February 2001, an information sheet dated 7 September 2004, and a letter dated 21 September 2004 enclosing an information sheet dated 20 September 2004.

533) There was an initial mailing of information and subsequent information was sent out explaining that some individuals had received concentrate to which there had been a donation from a donor who subsequently developed vCJD.

534) Further information was sent in 2009 [WITN3428017] to inform patients that a patient with haemophilia had died and at autopsy he had been found to have the

vCJD prion in his spleen. He did not have clinical vCJD and had died of an unrelated condition.

129. What information was provided to patients about the risks of vCJD?

535) Information about the risks of vCJD was sent out to patients by letter. I have referred to some of those letters in paragraphs (i) – (iii) of 128 (above).

536) I am aware that the form of information which was sent out in 2009 remains on the UKHCDO website (http://www.ukhcdo.org/patient-information/). It reflects the correspondence sent to patients by the Edinburgh Haemophilia Centre at that time.

130. What counselling, support and/or advice was offered to patients who were informed that they might have been exposed to vCJD?

537) All patients received an invitation to discuss their individual situation. They were asked to return a brief form acknowledging receipt of the information and to indicate whether they would like an appointment to discuss their situation further. A stamped addressed envelope was provided. Arrangements were made to see those who replied to say they would like a further consideration of the issues. A template check list was used as a record of topics that had been considered with each patient. Many of the patients attending were seen by Dr Rosie Dennis, the Associate Specialist at the Haemophilia Centre, who had overseen much of the review of the treatment records in relation to vCJD.

Section 11: Financial Support Schemes

131. Explain as fully as you can any involvement you have had in relation to any of the trust or funds set up to provide financial assistance to people who had been infected.

538) I have not been involved in any way with the establishment or workings of any of the funds.

539) My policy was that patients who were eligible for support knew of the relevant funds and how they could be contacted. Patients were assisted with applications by the medical staff and social worker.

540) At a patient's request we would supply data in confidence to support applications.

Section 12: Other Issues

132. Please explain, in as much detail as you are able to, any other matters that you believe may be of relevance to the Infected Blood Inquiry, having regard to its Terms of Reference and to the current List of Issues.

541) Thank you for the invitation to add to my response to the Inquiry. The topics listed below cover issues not addressed in my written replies to the specific questions.

The tragic consequences of viral infections

542) I want first to acknowledge the devastation wreaked by viral infections on all individuals and families and to express my sympathy and concern for all those infected and affected. As well as remembering those whom I knew to be infected, I have in mind others whose experiences may not have been brought to the attention of this Inquiry. While the thoughtful Report of the Archer Inquiry, and the detailed review by the Penrose Report of events in Scotland, have addressed some of the issues, I hope this Inquiry's Report will address the issues on behalf of all who have been caught up in the events of the past 50 years. It is important that lessons are learned, not only from the way the risks of therapy have been assessed and responded to, but also how those infected and affected were offered help and support. This matters not only as an historic issue, but because it concerns the continuing needs of individuals and their families today. Furthermore, the infective risks of blood and blood products must be kept under effective review and minimised, and anyone who suffers should receive prompt support for the unintended consequences under "no fault" arrangements.

Patient, family, and the haemophilia team as a community

543) I first met members of the haemophilia community as a medical student in 1969. Later, I treated many, in my role as the ward house officer during 1971, and as a

medical registrar 1972-75. The ward provided a 24-hour open-access service, mostly for treatment of bleeds, but also as a general practitioner service; often four or more individuals were inpatients, either as a result of bleeds or for orthopaedic procedures. When I returned to take up a consultant appointment in 1980, very few received home therapy. Consequently, I quickly became re-acquainted with those with severe and moderate haemophilia. Because of their frequent attendance at the ward I, and/or a registrar, reviewed the patients on the majority of occasions and arranged cryoprecipitate therapy. This ward-based service led to many patients getting to know one another and forming a small haemophilia community; some being from the same nuclear, or extended, family. From 1982, the establishment of a full-time haemophilia team enabled the patients to be given greater attention.

The stress of living with uncertainty

544) Over the years, the patient-staff team relationship had to encompass the many challenges presented by haemophilia. Of these, perhaps the most difficult was living with uncertainty; the uncertainty of when inevitable, unpredictable bleeds might occur and the inevitable disruption to anticipated family life. Uncertainty also existed in the risks of hepatitis, ill-defined risks of viral infections, interpretation of an anti-HTLVIII result and the possibility of developing AIDS, the uncertain efficacy of viral inactivation procedures for concentrates, and later the issues raised by vCJD. For the patients, their families, and the small staff team, addressing uncertainty was very demanding. Given the professionally close nature of the relationship between them, it was extremely distressing for everyone to have to accept disappointment when therapy did not meet expectations. This must surely have resonated with and compounded the greater devastating realisation, felt by both patients and haemophilia treaters, that the very therapy that had once appeared to offer them the prospect of a relatively normal life-expectancy, instead now risked being lethal.

Support by the wider clinical service

545) As well as the core haemophilia staff team, I should like to acknowledge a wider group of hospital colleagues, who despite risk to themselves, supported the patients. This included laboratory staff, clinicians in other disciplines, and especially those who undertook invasive procedures. Patients' dental care was

not compromised by HIV considerations, and I want particularly to acknowledge several surgeons who were ready to provide major essential, and sometimes, emergency surgery at potential risk to themselves. I should like to acknowledge the contribution SNBTS medical, nursing, scientific and technical staff have made to the care of people with haemophilia: some of whom were potentially at risk from handling of blood and blood products.

Complaints and attenuation of their resolution

546) It is only as a result of this Inquiry's investigations that I have become aware that patients appear to have been poorly served when making their complaints. I have set out in greater detail in reply to a specific Rule 9 request, how I responded in 2005 to a complaint originally made in 2003 to the General Medical Council (GMC). My understanding was that my response to the GMC, including supporting documentation, was forwarded to the patient. I have only recently learned that my response was not sent to the patient, because of the GMC's protocol for handling complaints. My patient, therefore, did not, and has not, received any response in respect of their complaint. I find it completely understandable that the patient felt aggrieved, and that this absence of information has led to speculation about what had occurred during their medical care. It is unclear to me how the patient came to be advised to complain to the GMC, rather than taking this up initially and directly with the hospital. Had that happened, there would have been an independently chaired meeting between the patient and myself, providing an opportunity to question their therapy and management and receive answers directly from me. If this had failed to satisfy the patient, they could have made a formal complaint to the NHS or the GMC. Thus my patient and I have been poorly served by the actual management of their complaints which has resulted in further extensive difficulties which have seriously compromised care. I understand that, the GMC has instituted new procedures for the involvement of Patient Liaison Officers in the managing complaints to help patients receive an informative and specific response

Responses by governments

547) It is regrettable that governments over many years have not reacted more appropriately or proactively and with greater honesty to the consequences of viral infections in people with haemophilia. I accept that there have been difficulties in

understanding evolving situations and uncertainties and in developing guidance. When I brought my regret at this lack of guidance from governments to the attention in the Penrose Inquiry, I was informed this was not a governmental responsibility. An example of inappropriate government action unhelpful to the patients was the advice, in 1989, that receipt of financial help required proof of negligence by their clinicians and others. This requirement was made despite representation by the Haemophilia Society and a number of clinicians canvasing MPs. Had those in the Departments of Health considered the impact of such a directive on life-long patient-doctor relationships, and for which there was usually no alternative clinician available?

548) At the outset, the Cosgrove (later the Penrose) Inquiry's remit, did not include consideration of financial support for those affected. The Scottish Government's 2007 decision to delay reviewing such support for patients and families pending publication of the Scottish Inquiry in 2015 was unsupportive of the haemophilia patient and family community which therefore had to wait more than 8 years for this reassessment.

549) More recently, I believe that it has not been helpful to those infected and affected to hear government ministers state categorically that infections "should not have happened". This appears to reflect, at a high level of government, an inability to understand the complexities, difficulties, and history of this tragedy. Patients, their families, and the health service deserve better.

Changes to medical practice

550) Medical care today has benefitted greatly from learning the importance of listening to patients and their families. In this, the particular experience of addressing the pandemic of HIV has proved to be a catalyst, with learning that has extended to wider medical arenas. The necessary development of multi-disciplinary approaches to care, ethical standards, and national treatment guidelines which are now indispensable are ones for which UKHCDO in conjunction with patients can be proud.

551) It is intended that a summary of the development of arrangements for haemophilia care in Scotland will be produced. This will be a broad-based description by key individuals who were responsible for the service.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed GRO-C

Dated 14/10/20

Table of exhibits:

Date	Notes/ Description	Exhibit number
September 2020	CV of Professor C A Ludlam	WITN3428002
August 2010	Letter from Procurator Fiscal	WITN3428003
September 2020	Edinburgh Haemophilia Centre Staff List	WITN3428004
September 1996 and September 1997	Recombinant Guidelines	WITN3428005
Undated	Home Treatment Agreement Form & Protocol for Home Treatment	WITN3428006
January 1986	Hepatitis Family Member Letter 1986	WITN3428007
June 1982	Home Treatment Arrangements	WITN3428008
December 1984	Invitation to Meeting	WITN3428009
January 1985	Letter to GPs	WITN3428010
Undated	Hepatitis Information Sheet & Interferon Checklist	WITN3428011
January 2006	Carr and Tucker Letters	WITN3428012
August 1988	GMC Guidance	WITN3428013
January 2006	Masterton Letter	WITN3428014

August 1996	Ludlam Letter to Dr Will	WITN3428015
1998-2001	vCJD Information for Patients	WITN3428016
February 2009	vCJD Letter to Patients	WITN3428017
June 2011	Submission to Penrose Inquiry on the Establishment of FVIII Working Party for Scotland and Northern Ireland	WITN3428018