Witness Name: Prof. Edward Tuddenham
Statement No.: WITN3435002
Exhibits:
Dated:

INFECTED BLOOD INQUIRY

SECOND WRITTEN STATEMENT OF PROFESSOR EDWARD TUDDENHAM

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 15 July 2020.

I, Professor Edward Tuddenham, will say as follows: -

Section 1: Introduction

1. Edward George Denley Tuddenham.

   At an address known to the inquiry.

   Date of Birth GRO-C 1944

   MBBS. MD. FRCP. FRCPath. F Med Sci

2.

House Officer Posts:	1.	Surgery:	Queen Mary's Hospital, Roehampton, London. May to November 1968. I was continuously on call 24/7 for an acute medical surgical team for 6 months with two weekend breaks.

	2. Medicine:	Royal Victoria Infirmary Bournemouth January to September 1969. I was continuously on call for an acute medical firm for 6 months. After this I decided on a career in Pathology.
SHO & Registrar Posts:	Pathology:	(Rotating through all 4 sub specialities) United Liverpool Hospitals October 1969 December 1971 A most educational experience with lots of laboratory work in all subspecialties of pathology. Encountering David Weatherall during this period convinced me to choose Haematology as my speciality for higher training.
Lectureship:		In Haematology at the Welsh National School of Medicine, University Hospital of Wales, Cardiff March 1972 to December 1975 As a lecturer I performed all the duties of clinical and laboratory work for higher speciality training. I was particularly inspired by the work of Arthur Bloom, who was my main mentor in the choice of haemostasis for future career. His pioneering work on the relationship between haemophilia A and Von Willebrand Disease put me on the path

	to purifying factor VIII and all that followed.
Research Associate:	Department of Medicine, Division of Haematology, University of Connecticut, School of Medicine, Farmington, Connecticut, USA. January 1976 to December 1977. It was here that I got started on purifying factor VIII using antibodies to separate it from Von Willebrand Factor. I learned about setting up ultra-sensitive immunoradiometric assay techniques, which were crucial for later characterisation of factor VIII protein.
Locum Consultant	
Haematologist/co Director:	Royal Free Hospital, Haemophilia Centre. January 1978 to July 1978. Katharine Dormandy who set up the haemophilia centre at Royal Free Hospital, at first in a caravan outside the Lawn Road Hospital, had become terminally ill and a locum position was advertised. The purpose-built centre in the new Royal Free Hospital was empty awaiting occupancy. The service was being run by Dr Eleanor Goldman with a senior nurse Miss Patricia Lilly. They informed me about the practices that had been developed under Katharine and which initially continued unchanged.

Senior Lecturer: In Haematology and co Director of The Katharine

Dormandy Haemophilia Centre & Haemostasis Unit,

Royal Free Hospital School of Medicine

September 1978 to October 1986.

After Katherine retired, shortly before she died, I was appointed to her post and began the move into the new centre. I had a free hand to start organising a comprehensive care programme with regular out-patient clinics held for haematology consultation and orthopaedic management. Some of the adult patients were treating themselves at home using cryoprecipitate. We were gradually moving the patients with severe haemophilia A from cryoprecipitate to concentrate prepared at Elstree. Young children with haemophilia A were treated on demand at the centre with the Elstree concentrate. Notably there were no new cases of inhibitor development in previously untreated patients (PUPS) over a period of 10 years with this low intensity low purity treatment approach. Soon Peter Kernoff joined as my co-director in a newly created NHS consultant post. He had a strong interest in the problem of hepatitis. He gradually took over most of the clinical running of the centre as I focussed more and more on my main research project of purifying factor VIII, building a team and obtaining research grants and industry collaboration. I continued with on-call work and outpatient clinics, but as will be noted below, took no part in the sourcing of factor VIII concentrates, leaving that to Peter. The factor VIII purification and cloning research reached successful conclusion in 1984. But I continued work on spin off projects until 1986. Peter Kernoff preferred to lead all the clinical work, leaving me with the basic research. But it

became clear that to pursue research with the new tools of molecular genetics I needed to retrain.

Visiting Research Fellow:

Department of Molecular Biology, Genentech Inc.,

San Francisco – June to September 1985.

I started on the first project to identify mutations causing haemophilia and on development of polymorphic DNA markers for carrier detection. Both published in Nature.

On return from Genentech I had decided to leave the Royal Free for a different life in New Zealand. I went to Northwick Park to give my last lecture on Factor VIII. Elizabeth Simpson and James Scott asked about my plans and when I told them asked me to apply for a group with MRC located in the MRC clinical sciences centre. This I did and was offered the chance to set up my own group. Before that it was decided to send me to the MRC centre in Mill Hill for more training in molecular biology. There I joined the Laboratory of Molecular Embryology, under Robert Krumlauf at the National Institute of Medical Research from November 1986 to June 1987, where I cloned an embyo pattern forming gene (Graham A, Papalopulu N, Lorimer J, McVey JH, Tuddenham EGD, Krumlauf R. Characterization of a murine homeo box gene, Hox 2.6, related to the Drosophilia Deformed gene. Genes and Development 1988; 2:1424 1438.)

MRC Clinical

Scientific Staff:

Director, Haemostasis Research Group at MRC Clinical Research Centre Northwick Park Hospital, Harrow November 1986 to June 1994 then at MRC Clinical Sciences Centre

July 1994 to December 2005.

With my new research group, I started to expand our knowledge of the molecular pathology of haemophilia and other bleeding and thrombotic disorders. I had no clinical duties involving direct care of patients with haemophilia for the next 20 years. I did see some patients with thrombotic presentations in collaboration with the Northwick Park thrombosis unit of Dr Tom Mead. My clinical contacts supplied the samples we needed for the genetic research. Among other highlights we solved the structures of tissue factor and of factor VII.

Professor of Haemostasis:	Imperial College London, Faculty of Medicine. April 1994 to December 2005
Hon. Cons. Haematologist:	Hammersmith Hospital June 1990 to December 2005

Katharine Dormandy

Professor of Haemophilia:	Royal Free Hospital and University College Hospital Medical School January 2006 to July 2011
Consultant Haematologist:	Royal Free hospital January 2006 to July 2011

Honorary Consultant Haematologist: Royal Free Hospital
August 2011 to the present

3. From 1978 when I was appointed co-director of the Royal Free Hospital haemophilia centre, until I left to join the Medical Research Council at the end of 1986 I was a de facto member of the UKHCDO and attended as many of their meetings as possible. The meetings were either for all centres or for reference centres – Royal Free being a reference centre meant that I could and did attend both types of meeting. My role as a member was to contribute to discussions and work on subcommittees. The latter included a subcommittee on von Willbrand's disease, which mainly addressed issues of diagnosis and particularly tests used to categorise the various subtypes of the condition. I had an interest in the basic science of the structure and function of von Willebrand factor, related to my interest in the basic science of factor VIII. I do not now recall contributing to discussions on selection of factor VIII or factor IX concentrates for treating patients.

3(a) I was also a member of the advisory panel of the Haemophilia Society. These were informal gatherings where the Chairman Reverend Tanner and the secretary raised issues of the day for discussion and comment. I was mostly asked to comment on scientific aspects of haemophilia diagnosis and the biochemistry of clotting.

3(b) I was co-opted to attend the Advisory Committee on the Virologic safety of blood when that was formed, but only recall attending one or two meetings. I remember advising that the new test for hepatitis C be used to screen all donors but would need to see the minutes to refresh my memory of what else was discussed and what if anything I contributed.

4. I provided expert advice to the Penrose Enquiry. I have not been involved in any other enquiries, investigations, criminal or civil litigation in relation to human immunodeficiency virus, hepatitis B virus or variant Creutzfeld-Jakob disease in blood or blood products in the UK. I provide evidence for an individual case of a patient residing in Republic of Ireland, who had been

infected with HIV and had attended Royal Free. It was clear that the infection had originally occurred while he was in Dublin before he came to our care. I have also given responses to complaints from two individual patients of the Royal Free Haemophilia centre relating to hepatitis C infection. These have been settled through the Hospital legal advisors. For the Penrose enquiry I attended one meeting and responded to questions about my involvement with haemophilia care in the 1980s. The questions and my responses were of a general character as the record will show.

5. I note the request that in answering the following questions I should where relevant include reference to earlier and later experience preceding and following my time as a Director of the Royal Free Hospital haemophilia centre; in particular concerning my subsequent research and interactions with the trusts and funding thereof.

Section 2: Decisions and actions of those treating patients with bleeding disorders at the Katharine Dormandy Haemophilia Centre

6. The history of the KDHC (as it is now known) is graphically summarised in a display time line at the centre itself, installed in 2015 on the 50th anniversary of its founding by Katharine Dormandy, spanning its first incarnation as a caravan in the car park of the Lawn Road Hospital to its current status. I took over from Katharine in 1978,as noted above, just before the centre moved into its current location in a separate purpose built facility on the ground and second floor of the South East Corner of the New Royal Free Hospital building in Hampstead. The hospital and medical school had moved to Hampstead from its historic location in Grey's in Road, the year before. In effect I had a blank slate on which to start a new enterprise of comprehensive care for our haemophilic patients in brand new surroundings. I had the experience of working with Arthur Bloom in Cardiff to guide me. We started formal regular review clinics for all patients. Helping me were Dr Elinor Goldman and Sister Patricia Lilley, who had been with Katharine for several years and knew the patients and their management intimately. We had orthopaedic special help from Mr Colin Madgewick, who was strongly engaged with the service. The first permanent appointment I succeeded in making was of the family

counsellor and psychosocial worker Mrs Riva Miller. Riva with Elinor Goldman established a pioneering partnership in family therapy as a holistic approach to our patients in the setting of their families, so obviously a feature of a genetic disease, but one that had been neglected until they showed the value of this approach (see J Haem Pract 2015; 2(2): 22-23. doi: 10.17225/jhp00056 www.haemjournal.com22 An approach that puts the family at the centre of haemophilia care). To begin with obtaining supplies of treatment materials, cryoprecipitate, plasma, NHS concentrates of factor IX or factor VIII, and commercial factor concentrates was handled by Dr Goldman. As soon as Dr Peter Kernoff arrived as my co-director in mid-1978, he took that over. I never during my period as co-director of the centre took any part in selecting or ordering therapeutic materials. This may seem unusual but, as senior lecturer, I focussed on the teaching and research aspects of my position, while NHS colleagues dealt with most of the more service-oriented matters. I was however fully involved in patient diagnosis and management when running outpatient clinics and on call services. The service grew organically as more patients arrived by referral and of course as previously untreated newly diagnosed infants. Dr Kernoff, with his research interest in blood transmitted hepatitis instituted a plasma/serum bank of stored frozen samples, taken regularly from patients attending for treatment. I do not know if patients consented explicitly for storage of their samples and their subsequent analyses. He also presciently stored bottles of concentrate from each batch used for later testing. These were an invaluable resource for research on the transmission and development of hepatitis and HIV in our cohort of patients, giving rise to many important research results published over the next 30 years. The work was carried on by his successor after he sadly became incapacitated following a heart attack. For my part I started on my major goal of purifying factor VIII to homogeneity as soon as I was able to form a small research group with funding from the Royal Free Hospital trustees. I took over empty space on the second floor, where the coagulation laboratory was also located, and where I located my office to be near the research and the clinical laboratory. The clinical/laboratory interaction is central to the practice of academic haematology. Other laboratory-based departments with which we had close collaboration were immunology and virology. The centre developed

along lines of increasing the width of our comprehensive care, successively engaging more specialist nurses, physiotherapists, genetic counselling with carrier testing, orthopaedic management. Home therapy had been initiated by Katharine based on cryoprecipitate and provision of small home freezers. This was replaced by freeze dried concentrates as they became available. We had regular meetings with the laboratory staff to discuss new case diagnosis and monitoring of treatment. We also developed many new assays, in which I had a strong interest during my time at the centre.

7. Dr Peter Kernoff. NHS consultant haematologist and Co-director of the centre. Main interest in transmissible hepatitis in haemophilia. He was also a pioneer in developing computerised data management for the national data collection and for clinical research. He became the main organiser of routine clinical care for our haemophilic patients.

Dr Elinor Goldman. Associate clinical specialist. Developed with Riva Miller the family therapy model of haemophilia care. Provided the genetic counselling service and kept meticulous family records for all our patients.

Mrs Riva Miller. Family therapist.

Senior Nurse Patricia Lilley. Was the longest serving member of our nursing staff with a wealth of practical experience.

Mr David Bone was the chief medical laboratory scientist at the time I joined, having worked with Katharine Dormandy from the early days of the centre.

Dr Ronald Hutton. Principal Biochemist. An expert on platelet function who had described the first cases of platelet release defect. A prime resource for teaching haemostasis to doctors and technicians.

8. In the early days of my work at the centre from 1978 to 1979, Peter and I shared responsibilities for clinical care. But as my research group enlarged and the project of purifying factor VIII took shape, I handed over most of the organising of clinical care to Peter and focused my time and energies more and more on basic research. By 1982 we had achieved a scalable batch

process to make pure factor VIII in collaboration with Speywood Ltd. We then partnered with Genentech Inc to clone the factor VIII gene and make possible genetically engineered protein. This became my major occupation for the next two years. The completion of the project by 1984 led on to the work which established genetic mutational diagnosis for haemophilia A, carrier determination with polymorphic markers and accurate antenatal diagnosis. By 1986 I had completed this stage of clinical research and decided to move to an institution where molecular biology was more developed and could support the next stage of my research ambitions.

9. This is a matter of record, of which there are excellent ones in the archives of the centre and of the National Haemophilia Database. From memory I think we had about 200 patients with bleeding disorders registered at the centre when I started in 1978, of which about 100 with haemophilia A, 20 with haemophilia B, 30 with von Willebrand disease and the rest with factor XI deficiency, a range of platelet function defects and a few with rare bleeding conditions like factor VII deficiency. We always had many patients with factor XI deficiency because of our location in North Central London with its large Jewish community. For exact figures please refer to the KDHC where Mr Pankaj Morjaria will be able to access the old records.

10. I had no part in the decisions and actions taken or the policies formulated at the centre regarding selection, purchase and use of concentrates. I had no part in the formulation and application of any such policies.

11. I believe that Dr Kernoff took on the responsibility for deciding on product sourcing.

    11(a) I do not know how he made the decisions.

    11(b) I did not get involved at all with these decisions.

    11(c) The record will show that many commercial products were in use at the centre over the years as well as those coming from Elstree and from Oxford.

11(d) In view of financial limitations, cost must have played a role.

11(e) None.

12. I would be guessing if I made any reply to this question as I did not discuss the matter with Dr Kernoff or even consider it at the time. If factor was available to treat the patients, we were able to manage their condition. The risk aspect was in retrospect underestimated with the tragic consequences now under investigation.

13. No other organisation would have influenced the centre in its decisions, other than general advice and discussion taking place among haemophilia centre directors.

14. At some point a decision was evidently taken to use primarily UK sourced concentrates in children with haemophilia. I do not know how that decision was made or by whom at the Royal Free. Interestingly a consequence of that seems to have been a very low incidence of inhibitors in our patients, as published.

15. Alternative treatments included plasma, cryoprecipitate and for mild haemophilia and von Willebrand disease, DDAVP. Patients with rare deficiencies like factor VII deficiency could be treated with a concentrate, when that became available. The prothrombin complex concentrate containing factors II, VII, X was used in patients who had those rare deficiencies. And there was a fibrinogen concentrate for afibrinogenaemia. Also factor XIII concentrate was available for the deficiency cases. We used platelet concentrates for patients with platelet function disorders.

16. If UK self-sufficiency had been achieved in blood products, so that we had no need to import commercial blood products, then the incidence of HIV would have been significantly reduced, not eliminated. Hepatitis C would not have been reduced. Nor would risk of CJD, which would have been increased.

At KDHC we began using DDAVP as soon as it was available. It is not always effective, depending on the underlying genetics and other less well understood variation, and it cannot be used for more than a few days.

17. We like other haemophilia treating physicians regarded cryoprecipitate as a treatment that was being used as a stop gap until it could be replaced with higher purity products containing the specific factor needed, in other words factor VIII in haemophilia A and Von Willebrand factor for Von Willebrand disease. Until concentrates were developed for von Willebrand disease it was the treatment of choice for those patients as it is rich in von Willebrand factor. When VWF rich factor VIII concentrates were available these became the treatment of choice in severe and moderate von Willebrand disease. I am not aware that we had difficulty in obtaining supplies of cryoprecipitate.

18. Katharine Dormandy had introduced cryoprecipitate-based home therapy before I was appointed. This was replaced with concentrates of factor VIII as soon as they became available. The policy was to introduce home treatment to every patient with severe haemophilia if they were able to manage the self-infusion, or in the case of children, their parents could be taught to carry out the procedure. We never used home treatment in very small children, only on demand until they could be infused by parents.

19. Prophylactic treatment was not introduced during my time at the KDHC from 1978 to 1986. When I returned there in 2006 it was almost universal for severely affected patients.

20. Factor concentrates from UK source were used in children when I arrived there in 1978. It must have been Katharine's policy.

21. Before DDAVP was in use the mild and moderate patients with haemophilia A might have received cryo-precipitate or concentrate depending on what was available. The Oxford factor IX concentrate was available by the time I started so Haemophilia B patients were treated with that concentrate or the Elstree concentrate.

22. I am not aware of any other viruses or infections that were transmitted by concentrates other than the theoretical risk of CJD by concentrates made from UK plasma batches known to contain plasma from individuals who later developed CJD. This theoretical risk mainly affected patients with factor XI deficiency who received the UK concentrate.

23.

23(a) I was a lecturer in the clinical role that would now be described as STR. I rotated through the sub-specialities in training. During my time in the haemophilia centre I saw patients in the out-patients for diagnosis and follow up. Also, I went on ward rounds with Arthur. He soon appreciated my interest in bleeding disorders and gave me some research projects as well as clinical advice. He was a mentor to whom I frequently went for advice and guidance on clinical and research questions.

23(b) I was in Cardiff as a lecturer from 1971 to 1975. The risk of Hepatitis B and its detection with the Australia antigen test was well established. So that could be prevented by screening. Knowledge of another entity that we called non-A non-B (NANB), had just emerged in 1975. I was not aware of any detailed discussion about policies for use of concentrates. I recall making up cryoprecipitate and giving concentrates, but not what they were, whether domestic or commercial. The provision of information to patients is also a matter of which I had no knowledge or any recollection about how it was done. I know Arthur had a close connection with the patients personally.

Section 3: Knowledge of, and response to, risk

24. When I first began to treat people with haemophilia at Liverpool Royal Infirmary in 1969, my senior registrar told me the tragic story of a patient with severe haemophilia A who had resisted being treated with cryoprecipitate because of fear of hepatitis. He had come in with severe bleeding and my colleague convinced him to have cryoprecipitate infusions. They controlled the

bleeding, but the patient developed hepatitis and died. From that time, I was well aware of the potentially fatal consequences of treating haemophilia with blood products and that the risk increased with donor exposure. During my time at the Cardiff centre, screening for hepatitis b and later development of a vaccine reduced or eliminated the risk from hepatitis B. Then the new agent, at first called non A non B was detected in patients treated with multiple donor concentrates. However it seemed to be quite mild compared to Hepatitis B, without the dreaded fulminant hepatitis that occurs with Hepatitis B.

When I started at the KDHC in 1978 there was a developing awareness that NANB hepatitis was common after a first concentrate product infusion. I recall Peter Kernoff establishing that every previously untreated patient given concentrate developed elevated liver enzymes. Some patients then recovered normal liver function, but some continued with chronic hepatitis. The severity of this complication was being monitored by many centres, including at the Royal Free by Peter, whose major interest was in this problem. With advice from the large and busy liver unit established by Sheila Sherlock, liver biopsies were carried out to track the progress of the liver damage. However one patient who had a highly abnormal reaction to infusion of concentrate, probably allergic, developed uncontrollable bleeding after a percutaneous liver biopsy and died. After that fewer or no biopsies were carried out in our patients. It was clear that the chronic inflammation associated with NANB was causing fibrosis and declining function in some patients. However it would be a decade before the full long term risk of NANB would be clear. My knowledge of the risks of blood product infusion was therefore increasing with the emergence of the evidence, from a perception that the risk was fairly low, certainly when weighed against the clear evidence of progressive damage to joints of untreated haemophilia and the more than occasional major bleeding event with risk to life and limb. I knew that severely affected haemophiliacs- if untreated, rarely reached their third decade. Any bleed, especially an internal one, can progress to fatality if untreated so we continued to weigh the risk benefit ratio against a changing body of evidence. Especially as it emerged that the new disease of AIDS was affecting people with haemophilia.

25. I am not aware of any formal decision-making structure in place at KDHC during the period 1978 to 1986. If there was one it was in the knowledge and judgement of my colleagues, especially Peter Kernoff. He was certainly as well informed as anyone about these risks through his work on NANB. That may have had an inherent misleading bias when applied to Hepatitis C as contrasted to HIV, since all NHS concentrates were infected by hepatitis C, but - as it later transpired, far fewer were infected with HIV.

26. During my time at KDHC 1978 to 1986 I did not think there was a difference. I knew that commercial donation was the norm in US products but had no idea of the low standard of screening donors. My experience in the UK included running donor sessions in prisons, but as they were volunteer sessions and because needle using drug addiction was still uncommon the UK in the early 1970s, my perception of the type of donor recruited in the US was optimistic to say the least.

27. Other than only giving treatment when it was necessary to stop bleeding, none that I can recall. The principle was, 'if in doubt as to whether signs and symptoms were due to bleeding or not, treat anyway'.

28. As noted above in 1978 knowledge of NANB hepatitis was increasing rapidly, but isolation of the causative virus hepatitis C itself and a test for it were a decade in the future. The Australia antigen had been described in 1967 and its causative role in hepatitis B was well established by the time I was appointed co-director. An international effort was proceeding to define better the natural history of these infections and their transmission, along with attempts to find treatments. In the case of hepatitis B treatment that can cure the condition remains elusive but effective vaccination is widely available and the threat to human health is coming under control. For Hepatitis C highly effective therapy has only quite recently become available and may be used in eradication campaigns on a national and possibly worldwide basis. No vaccine has been developed. For HIV - eradication and vaccination are still beyond reach. However effective anti-retroviral maintenance therapy is widely available now. But back in the early 1980s knowledge was so incomplete that one could only hope for methods to prevent transmission through blood

products by inactivating the agents responsible. Progress on that front came unexpectedly from the crude and simple expedient of heating the freeze-dried product at a high enough temperature and for long enough, such that the yet uncharacterized agents of disease transmission were inactivated, but not the precious clotting factors. Unexpectedly to me, from my protein biochemistry point of view, this proved possible. The lipid envelope of these two viruses is their weak point, susceptible to simple heating. It can also be attacked with solvents and detergents, while preserving clotting factor activity. This understanding came subsequently to the empirical development of the 'pasteurization' process to inactivate them. Just as the isolation and characterisation of microbes was after Pasteur's development of heating to sterilise and prevent their activity in fermentation.

29. Very thorough and detailed treatment records, clinical laboratory records and blood samples were collected by Dr Kernoff as the basis for a ground breaking series of paper by he and his colleagues – particularly Christine Lee- which established the time of sero-conversion, its origin to a particular batch of concentrate of cryoprecipitate and subsequent evolution of the disease(s). In this way the natural history of the two infections and their interaction was established.

30. In the state of knowledge about the infectivity of different types of concentrate for the two principal infectious agents (HC and HIV) there was no rational basis for concentrate selection. Only completely withholding treatment and allowing the haemophilic bleeding to take its course for an unknown period could have reduced transmission. In practice this is what happens in countries with no effective therapy or no national policy to make it available. The consequence in for example Tanzania or PRC is a marked decrease in prevalence of severe haemophilia over the age of 10, falling to close to zero over the age of 30. This was the frying pan or fire choice facing haemophilia treaters everywhere in the early 1980s. It may be argued that reverting to single unit donations such as cryopreciptitate would have reduced transmission. But that is a retrodiction based on knowledge of the incidence we now possess but did not then. It

would not have reduced the incidence of hepatitis C. The most severe bleeding in haemophilia is not well controlled by cryoprecipitate.

31. Regular monitoring of ALT and AST was routine for all patients to detect liver damage and chronic hepatitis.

32. In the early 1980s NANB appeared to be a mild, sometimes self-resolving infection. This view began to change as evidence from liver biopsies accumulated showing progressive hepatic fibrosis.

33. Initially I had little knowledge except that in the gay community in the USA there was a new disease causing severe acquired immune deficiency (AIDS). As news came in firstly from USA of hemophiliacs dying of AIDS like illness the much greater threat of another deadly infection emerged. The first British patient with haemophilia to die of AIDS clearly transmitted through blood products, as he had no other risk factors, brought home the news that an epidemic of deadly treatment transmitted infection had arrived. The fact that infection was mostly transmitted by commercial concentrate was proved once the HTLVIII test could be applied to our stored patient samples.

    As more and more Haemophiliacs developed clear evidence of AIDS or AIDS like infections, we knew more of our patients had the condition. By the time I left the centre in 1986 already three patients had died of what in retrospect must have been AIDS due to HIV. That year we tested all the patients and had a clear picture. That was also the year that effectively pasteurized factor concentrates became available.

34. In July 1982, the Centre for Disease Control released news that three hemophiliacs had AIDS defining illness, despite having no risk factors other than treatment with factor VIII concentrate.

35. As noted above all patients of the centre were tested for HTLVIII antibody as soon as the test became available in early 1986. The results were conveyed to the patients in the context of family therapy by my colleagues Dr Goldman and Mrs Miller.

36. Between 1982 when a possible risk became apparent and 1986 when a definitive test and safe heat-treated product were developed, no changes in treatment policy were to my knowledge instituted other than continuation of preference for UK product in treatment of children. If such a policy could have been introduced on a rational basis is a matter of debate. As noted above I was not personally involved in any local discussions about such a policy.

37. Yes - because our policy was to continue treating bleeds as they arose on demand, given that we had no way of knowing which products were infective, nor what the case transmission or case fatality rates were. We did know about the consequences of not treating bleeds. At this distance in time I cannot recall which imported concentrates we used. It is a matter of record contained in the individual patient treatment records.

38. No change was made to my knowledge in treatments offered to patients. I must mention that in 1983 all the decisions relating to therapy offered to patients with haemophilia were taken by Dr Kernoff. Information about possible risk of AIDS would have been given to patients at their regular reviews. The haemophilia society were also circulating information on the progress of the AIDS epidemic as it affected people with haemophilia.

39. Individual discussions would have taken place in family therapy and annual review. I was not directly involved in any such discussions.

40. As I left the centre on a sabbatical in mid-1986 and on return began plans to move to the MRC I had no involvement with or knowledge of what steps were taken to introduced heat treated products at KDHC.

41. I do not remember attending such a meeting. Given the location, the proposed agenda and the list of attendees I think I would remember it if I had attended. I am not aware of any uniform policy about heat treated concentrates from that time. That does not mean there was not such meeting or policy, just that I do not have any memory of there being one.

42. Not to my knowledge.

43. Allowing for the fact that I was not involved in such decisions or actions at the time, I have not come across a reason to think that drastic changes in treatment policy would have been justified by knowledge and information available at the time. It is clear now that one would wish that one could have accelerated research on making concentrates safe. It is also clear that concentrates were a great advance in efficacy and convenience. The downside only became apparent gradually through the period from 1980 to 1986. By the time changes could have been made to reduce risk, by for example switching back to cryoprecipitate or limiting treatment to desperate circumstances and only UK concentrate or animal concentrates used, most of the infections had already taken place in the most heavily treated patients.

44. The single most important difference could have been made at governmental level, which was to make UK self-sufficient in blood products from volunteer plasma. This was the policy proposed and endorsed by then minister for health David Owen.

45. The failure to implement self-sufficiency in blood products was a major cause of our reliance on imported products, which brought the HIV infection to most of our patients. Most but not all. Some UK batches were HIV positive. The only secure way of preventing infection from blood products is to inactivate infectious agents. This was not fully effective until 1986. Government should have pursued a policy of self-sufficiency. The research on viral inactivation took time. Just as the research on synthetic factor took time.

46. It was going on. And it did result in safe products. There was no guarantee that it would succeed or when. Should the experience with hepatitis before 1980 have led to greater efforts to make safer blood products? Until 1980 clotting factors were a niche product with low volume. The transmitted infection of widest occurrence was Hepatitis C, which was misperceived as a mild infection, tolerable in the context of a much improved product of higher purity and greater efficacy in haemostasis. This produced a false sense of the risk benefit ratio. Once the demand for factor concentrate accelerated with more home treatment and some prophylaxis the commercial incentive to make more and sell more seems to have overwhelmed the safety issues, As these

safety aspects became more and more evident more effort went into viral (or rather disease transmission – recall the viruses had not been isolated or grown and did not even meet Koch's postulates) inactivation. That virus inactivation even succeeded for hepatis C and HIV is a fortunate result of the fact they are both lipid enveloped viruses.

47. My article of 1983 predicted several developments which came to pass in subsequent years, including use of monoclonal antibodies for purification (which became standard), recombinant factor VIII and eventually gene therapy. Should better purification methods have been taken up sooner and would they have prevented the infection transmission disaster? I think they should have and could have drastically reduced infection rates. But profit calculations come into the commercial decisions. Higher purity tends to mean lower yield and product is priced in units of activity. Without an assay for a virus or its infectivity one cannot assess removal of a virus. These difficulties prevented earlier adoption of better purification of product.

48. I am not aware of any such steps. It was left to Abbott laboratories to develop such a test.

49. I have only one memory of a meeting of an advisory committee on safety of blood at which I gave it as my opinion that whatever the cost a test for hepatitis C should be applied to all blood donations to exclude donors from single unit or pooled plasma use. What if anything happened after that I do not know.

Section 4: Treatment of patients at the Centre

50. None that I can recall. As stated above, policy on this aspect of patient management was decided by my colleague Dr Kernoff.

51. Again, none that I can recall. As DDAVP became more widely used a policy was instituted to test response in mild haemophilia A and von Willebrand disease. If a patient responded well then, he or she could be supplied with product to self-treat.

52. I was not involved with this aspect of management.

53. I personally did not discuss AIDS with any patient, except as a general risk for all patients, until we had definitive information on which patients were infected.

54. After we had tested all the patients and all the staff of the centre with the HTLVIII kit.

The samples were probably sent out for testing, but I do not know where to. The time period was only a few weeks. It would have been in 1986 or late 1985.

55. Not to my knowledge. All the counselling was post-test. The person to ask about this is either Dr Christine Lee or Dr Eleanor Goldman.

56. Patients were informed individually, or with their families by Dr Goldman and Mrs Miller.

57. The interviews were video recorded and may be consulted on application. I cannot say what they were told about the significance of a positive test result. Nor can I say whether they were told to keep it secret. I was not involved with this process.

58. I do not know. I am sure that Dr Goldman and Mrs Miller would have been active in such counselling.

59. No to all questions.

60. I do not know. I think that some wives and partners may have been tested. Dr Lee and Dr Goldman will be able to answer this question.

61. I do not know. These decisions and actions would have been taken at the time I was in process of leaving the centre.

62. a. to f. These numbers are all a matter of record and I think may have been supplied by others interviewed by the inquiry such as Dr Lee. Some of the numbers will have been published. I do not have access to the historical records, but they could be obtained from the data team at the centre under Mr Pankaj Morjaria. I think it was about half the severely affected haemophilia A patients, only a few if any of the severe haemophilia B group and only a couple

of the von Willebrand patients, those with type 3 VWD who would have been on concentrate being at most risk. It cut a swathe through the group I knew best, the young men with severe haemophilia A, with many of whom I had a close connection due to seeing them frequently when I started at the centre. By my return in 2006 they were nearly all dead. The younger children who were infected mostly survived until effective antiretroviral therapy came in 1996, so I have met them again as adults.

63. The seroconversion work was undertaken by Dr Kernoff and his associate and successor Dr Lee. It has been published in various papers. I think it showed that most infections took place between 1982 and 1985 and were from imported US sourced concentrates.

64. I cannot recall any hepatitis B infections in our patients. If there were any I do not know how or by whom they were informed.

65. I do not know. There was a joint clinic with a hepatologist, which more recently was with Dr David Patch. I do not know who would have been doing the clinic in earlier years.

66. Very few if any, but the number can be obtained from our data team.

67. Although not involved with this as Dr Kernoff and then Dr Lee oversaw such matters, I presume it was by Dr Kernoff and then by Dr Lee.

68. My colleagues were responsible for these matters.

69. Essentially every single patient who received any concentrate at any time and most of those who received more than 100 units of cryoprecipitate. Detailed records of this were compiled. Some patients recovered spontaneously clearing the virus. Some were later treated with Ribavirin and interleukin. Over 70 with type one virus had persistent infection only finally cleared by the new antiretroviral treatments. Many died of complications of long-term infection.

70. No.

71. I was not at all involved with patient management and only very occasionally called on to give advice for difficult treatment problems. Dr Laffan was responsible for patient management decisions during my time there.

72. As for Q 71 please refer to Dr Laffan for this question.

73. I believe that in nearly all cases results were very promptly relayed to patients. I know of only one case where there was a delay, due to uncertainty about a test result. A patient who had been positive for hepatis C, spontaneously cleared the virus but was not so informed for several months. A complaint was raised and an apology made by the hospital for the delay.

74. The only such advice would have related to risk of transmission to intimate partners by sexual transmission. I was not involved with supplying such advice.

75. For HIV patients the risk of any infection increased as the disease progressed and eventually a fatal infection occurred. This was only partly mitigated by use of prophylactic antibiotics. Management of HIV patients was taken over by our colleagues in the Ian Charlson Day Centre at Royal Free Hospital.

76. The sexual transmission risk was explained and was only partly mitigated by barrier conception. With the advent of highly effective triple therapy for HIV transmission risks in patients with undetectable virus is known to be low or absent.

77. As I was not involved in this aspect, I must pass the question to those who were so responsible such as Dr C. Lee. Since 2006 when I returned to the centre full informed consent was obtained for any such samples in our biobank.

78. In the period 1978 to 1986 the concept of informed consent to every type of treatment was not developed as it is today. I cannot recall getting informed consent to any treatment other than for surgery, given to any patient for a bleeding disorder during my first period at the haemophilia centre.

79. I do not know if consent was obtained as I did not arrange the testing for HIV or for hepatitis C when that became available.

80. My comments in the article were truncated from a longer interview. What I explained, when it came to light prematurely that a CJD research group were interested in the samples, was that the matter was under discussion, no samples had been transferred and we were still working on the details of how to get permission from patients, many of whom would by then be deceased. The samples were those collected by Dr Kernoff and Dr Lee. I did not know if any permission had been obtained from the patients who donated them for any subsequent use. From Dr Lee's comments I assume not, as that would not have been standard procedure during the years when the samples were collected. The idea was to use the samples to test for CJD infection. In fact there is still no such test that has been proven sensitive in blood samples.

In any case the samples were subsequently destroyed due to frequent freezer break downs over long hot weekends with deterioration. My view then and now is that, before doing a test for a condition for which there is no treatment and would be fatal, elaborate informed consent would be a necessity. Even if anonymised samples were tested that would still be an issue as then the result, if made public, would arouse unnecessary anxiety. This is similar to the situation with Huntington's disease. Up to now we know of only one case of blood born transmission of CJD in haemophilia. One must hope that it stays extremely rare in the era of recombinant therapy.

81. I have never had to take a decision on therapy in a previously untreated patient.

82. I set up an ultrasensitive radiometric assay for von Willebrand factor by radiolabelling rabbit antibody to VWF. Then I coated tubes with the unlabelled antibody to capture VWF from sample. After washing the radiolabelled antibody was added. This works well as VWF is a polymer of multiple repeated subunits. This would enable proof that VWF could be eliminated from factor VIII activity. Next the same antibody was coated in an immobile column of Sepharose beads. This enabled whole factor VIII:VWF complex to be captured

from plasma. Then the factor VIII could be eluted with Calcium Chloride at high strength of solution. The factor VIII eluted had no detectable Von Willebrand factor. It also had extremely low protein concentration and therefore extremely high specific activity. That was as far as I got on factor VIII purification in Connecticut.

83. Much of my research at the centre was laboratory based, did not involve patients and concerned pure basic research, especially the work on purifying factor VIII. That work is detailed below in answer to question 86. Where appropriate answers to questions a. to h. are entered.

83(a) Rotblat F, **Tuddenham EGD**. Immunologic studies of factor VIII coagulant activity (VIII:C). 1. Assays based on a haemophilic and an acquired antibody to VIII:C. *Thromb Res* 1981; 21:431-445.

a. We used naturally occurring antibodies from two patients to set up immunoradiometric assays. This enabled samples from patients in the centre to be assayed for presence or absence of non-functional factor VIII. Inhibitors were the only antibodies then available which were guaranteed to be specific to the elusive factor VIII molecule itself. b. no approval was obtained as no active intervention other that drawing a blood sample was carried out in humans. c. I devised and supervised the project. d. no other body involved. e. Royal Free Trust discretionary fund. f. 20 blood samples drawn for other purposes except for the haemophilic patient who volunteered to give us a unit of plasma for the research. g. except for the haemophilic patient no steps were taken to obtain informed consent. h. this study and then numerous other studies on factor VIII such as the purification and cloning papers in Nature, where the assay was the gold standard for measuring factor VIII protein concentration independent of clotting activity.

83(b) Goodall A, Kemble G, O'Brien DP, Rawlings E, Rotblat F, Russell G, Janossy G, **Tuddenham EGD**. Preparation of factor IX deficient

human plasma by immunoaffinity chromatography using a monoclonal antibody. *Blood* 1982; 59(3):664-670.

Nonclinical study to demonstrate preparation and use of monoclonal antibodies to clotting factor proteins. These were amongst the first monoclonal antibodies to be made directed specifically to a human clotting factor.

83(c) Rotblat F, Hawkey C, O'Brien DP, **Tuddenham EGD**. Immunologic studies of factor VIII coagulant activity (VIII:C). 2. Factor VIII in selected vertebrates. *Thromb Res* 1982; 25:423-431. Nonclinical study of the presence of factor VIII antigen cross reacting with a human inhibitor antibody used in the assay in a wide range of animals from London Zoo, including Guy the famous gorilla. The fact that guinea pig blood factor VIII cross reacted completely was used in further studies on the rodent for factor VIII distribution and reactions to acute phase stimuli.

83(d) **Tuddenham EGD,** Lane RS, Rotblat F, Johnson AH, Snape TJ, Middleton S, Kernoff PBA. Response to infusions of polyelectrolyte fractionated human factor VIII concentrate in human haemophilia A and von Willebrand's disease. *Brit J Haematol* 1982; 52:259-267.

a. The first clinical study of polyelectrolyte purified factor VIII infusion. The product had very low amounts of von Willebrand factor, and thus we tested the hypothesis that normal von Willebrand factor in a haemophiliac's blood would support normal half-life of infused in his circulation. Whereas in severe von Willebrand disease the half life should be shorter due to lack of the carrier protein. This proved to be the case and was the first demonstration in vivo of the hypothesis that von Willebrand factor is necessary to survival of factor VIII in the circulation. Three patients with haemophilia A (HA) and one with type 3 Von Willebrand disease (VWD) were infused with poly electrolyte purified factor VIII free of Von Willebrand factor. The half life in HA was 12 hours but in type 3 VWD it was 2 hours. b. None that I can

recall other than explaining to the patients that we were testing a new high purity factor VIII. d. Elstree blood fractionation centre. e. There were no funds involved. f. Four patients. g. minimal and informal, as was the custom at the time. Just a short description of what we would do and why. h. This publication has been highly cited over the years as the first definitive proof of the role of Von Willebrand factor in supporting the circulatory half-life of factor VIII.

83(e) Baythoon H, **Tuddenham EGD,** Hutton RA. Morphological and functional disturbances of platelets induced by cryo-preservation. *J Clin Pathol* 1982; 35:870-874. A non-clinical study using discarded platelet rich plasma from our local blood bank. No interventions were carried out so no permission for the study was then deemed to be needed. The idea was to optimise platelet storage to preserve their function.

83(f) Rotblat F, Goodall AH, O'Brien DP, Rawlings E, Middleton S,**Tuddenham EGD**. Monoclonal antibodies to human procoagulant factor VIII. *J Lab Clin Med* 1983; 101:736-746. A non-clinical study to raise monoclonal antibodies to factor VIII. These would be key to purification and characterisation of factor VIII.

83(g) Hoyer LW, Rizza CR, **Tuddenham EGD**, Carta CA, Armitage H, Rotblat F. von Willebrand factor multimer patterns in von Willebrand's disease. *Brit J Haematol* 1983; 55:493-507. a. To analyse the polymerisation pattern of von Willebrand factor in different types of von Willebrand disease to help diagnosis and classification. b. No steps were taken as was usual at the time as no intervention occurred other than taking a blood sample for laboratory analysis. c. I obtained many samples and supervised multimer analysis in our laboratory, analysed the results and wrote the paper. d. University of Connecticut Health Centre, Oxford Haemophilia Centre at the Churchill Hospital. Royal Free Hospital Haemophilia Centre. e. No additional funds obtained. f. Samples of blood from 116 patients with and 43 family members without von Willebrand disease were analysed. g. Other

than explaining that we were studying the von Willebrand factor in their blood to help understand their condition better, no formal consent process was undertaken. h. This publication was followed by many others using the multimer analysis, which became a standard laboratory procedure for analysing and classifying Von Willebrand disease. It is relevant to prognosis and treatment.

83(h) Goodall AH, O'Brien DP, Rawlings E, Rotblat F, **Tuddenham EGD**. Affinity depletion and affinity purification of human factor IX by monoclonal antibodies. *Protides of the Biological Fluids* 1983; 30:403-406. A non-clinical study describing the use of monoclonal antibodies to purify factor IX and to deplete it from plasma to make a substrate for the one stage assay.

83(i) Kernoff PBA, Thomas ND, Lilley PA, Matthews KB, Goldman E, **Tuddenham EGD.** Clinical experience with polyelectrolyte-fractionated porcine factor VIII concentrate in the treatment of hemophiliacs with antibodies to factor VIII. *Blood* 1984; Vol.63, No.1:31-41. a. This clinical study was the first to demonstrate the safety and efficacy of a new porcine factor VIII concentrate in treating patients with antibodies to factor VIII, both congenital and acquired haemophilia. b. None that I can recall. Speywood supplied the concentrate made in their factory in Wrexham. c. I helped select the patients and monitored them clinically and helped write the paper. d. Speywood Ltd. e. I do not recall that we received any additional funds from anyone for this study. f. Eight. g. Other than explaining that this was a new high purity form of factor VIII from pig blood that we hoped would not be neutralised by their antibody and thus could stop or prevent bleeding, no formal or written signed consent was obtained. h. This publication was very influential and led to many other studies using Speywood polyelectrolyte purified porcine factor VIII.

83(j) Goodall A, Kemble G, O'Brien DP, Rawlings E, Rotblat F, Russell G, Janossy G, **Tuddenham EGD**. Preparation of factor IX deficient human plasma by immunoaffinity chromatography using a

monoclonal antibody. *Blood* 1982; 59(3):664-670. Non-clinical study to describe the production of factor IX deficient plasma using a monoclonal antibody for use in the one stage assay of factor IX activity. The first such use of a monoclonal antibody, itself the first described specific to human factor IX.

83(k) Kelly DA, Summerfield JA, **Tuddenham EGD**. Localisation of factor VIII: C antigen in guinea pig tissues and isolated liver cell fractions. *Br J Haematol* 1984; 56:535-543. Non-clinical study taking advantage of our immunoradiometric assay for factor VIII antigen to determine its tissue distribution in a laboratory animal, the guinea pig. Isolated liver cell fractions were analysed and showed the presence of factor VIII antigen mainly in the hepatocytes but to a lesser extent in endothelial cells. Later studies have found that in mice only endothelial cells produce and store factor VIII. The distribution in human liver cells is still an open question, although in our current gene therapy studies we target liver cells, where factor VIII can be highly expressed.

83(l) Wood WI, Capon DJ, Simonsen CC, Eaton DL, Gitschier J, Keyt B, Seeburg PH, Smith DH, Hollingshead P, Wion KL, Delwort E, **Tuddenham EGD**, Vehar GA, Lawn RM. Expression of active human factor VIII from recombinant DNA clones. *Nature* 1984; 312:330-337. See **Q 86** answer below.

83(m) Vehar GA, Keyt B, Eaton D, Rodriguez H, O'Brien DP,Rotblat F, Oppermann H, Keck R, Wood WI, Harkins RN, **Tuddenham EGD**, Lawn RM, Capon DJ. Structure of human factor VIII. *Nature* 1984; 312:337-342. See **Q 86** answer below.

83(n) Harper K, Winter RM, Pembrey ME, Hartley D, Davies KE, **Tuddenham EGD**. A clinically useful DNA probe closely linked to haemophilia A. *Lancet* 1984; ii:6-8.

a. One of the first linkage analyses to demonstrate utility in carrier detection. b. No steps were taken to obtain approval for the research. c. I selected suitable pedigrees for the research, helped analyse the

results and co-wrote the publication. d. Mothercare Unit of Paediatric Genetics, Institute of Child Health, London; Division of Inherited Metabolic Disease, Clinical Research Centre, Northwick Park Hospital, Harrow; Department of Biochemistry, St Mary's Hospital Medical School, London; Haemophilia Centre, Royal Free Hospital, London. e. No additional research funding. f. About hundred blood samples from normal volunteers, obligate carrier females and their family members. g. As the carriers had supplied samples for genetic counselling purposes and this study was intended to improve accuracy of the service, it was assumed they had implicitly consented to the research carried out. Clearly this would not be acceptable nowadays, but was normal in the time period when the research was carried out. h. This publication was the first of many using similar extragenic and intragenic probes for the purposes of carrier detection. The marker was of maximum utility as heterozygosity was high and there was no cross over between this marker and the factor VIII locus, which at that time had not been cloned. Intragenic markers came later (see publications 15, 17 and 31 below).

83(o) Winter RM, **Tuddenham EGD**, Goldman E, Matthews KB. A maximum likelihood estimate of the sex ratio of mutation rates in haemophilia A. *Hum Genetics* 1984; 64:156-159. It was of interest to determine when in a pedigree a new mutation appeared. About a third of cases of haemophilia A present as the first in their family due to recent de novo mutation. It most commonly occurs in male gametes due to internal inversion. We used data from pedigrees ascertained in families segregating haemophilia A who were studied at the centre for purposes of carrier determination. No additional samples were taken and only the records of our genetic counselling clinic were used in this research.

83(p) Gitschier J, Drayna D, **Tuddenham EGD**, White RL, Lawn RM. Genetic mapping and diagnosis of haemophilia A achieved through a Bcl I polymorphism in the factor VIII gene. *Nature* 1985;

314(6013):738-740. a. To demonstrate that a polymorphism within the factor VIII gene could be used to determine carrier status in relatives of an index case of haemophilia A. b. None that I can recall. The female relatives had all come for carrier testing and implicitly consented in our view to application of the new DNA methods to get an accurate answer. c. I obtained the samples from suitable kindred that we had stored. d. Royal Free Hospital Haemophilia centre. Genentech Inc. e. No additional funds were obtained for this study. f. Not stated explicitly, but numerous samples from multigenerational normal kindreds were scanned for segregation of polymorphic markers. Also samples from kindred segregating haemophilia A to test informativeness of the markers. Probably over 200 individual DNA samples were used. g. None. h. This publication established a number of important markers for linkage analysis applicable to haemophilia A. The probes used became standard in the field until the advent of mutation specific diagnosis and disease tracking based on our further work.

83(q) Gitschier J, Wood W, **Tuddenham EGD**, Shuman MA, Goralka TM, Chen EY, Lawn RM. Detection and sequence of mutations in the factor VIII gene of haemophiliacs. *Nature* 1985; 315: 427-430. a. This was the first study to determine the actual mutation disabling the haemophilic patient's own factor VIII gene causing the condition. Nowadays routinely used as part of diagnosis and family segregation analysis. b. None that I can recall. We had stored whole blood samples, isolated the DNA and carried out the analysis. This was very difficult and demanding in the days before the PCR method was invented. c. I selected the samples and isolate the DNA. I also provided the clinical details and helped write the paper. d. None. e. No specific funding. Genentech supported individual scientists to carry out original research based on their work for the company. f. 36 samples from patients were analysed, but only 4 mutations were identified. However, as a first the paper led the way for many subsequent analyses. g. No steps were taken. The samples were

anonymised to the researchers at Genentech. The results were entered in clinical records and conveyed to the patients, who were interested to learn the cause of their condition. h. as the first direct determination of mutations causing haemophilia A this work led to many other studies. The database of mutations causing Haemophilia A that I started now contains over 3,000 unique variants and is the largest such collection for any human disease.

83(r) Gitschier J, Lawn RM, Rotblat F, Goldman E, **Tuddenham EGD.** Antenatal diagnosis and carrier detection of haemophilia A using a factor VIII gene probe. *Lancet* 1985; i:1093.

a. To use an intragenic polymorphic probe to determine the mutational status of a foetus at risk of haemophilia A. b. None c. I identified the probands and families and arranged for the relevant samples to be taken and sent to my colleagues at Genentech for analysis. d. Royal Free Hospital Haemophilia Centre and Genentech Inc. e. No funding other than the employment and reagent costs carried by the institutions involved. f. Two. g. The women who carried the at-risk foetus had requested antenatal diagnosis in order to proceed to termination if found to be carrying an affected foetus. This was deemed to be consent. h. As the first analysis to use chorion villus for genetic analysis in haemophilia it led to a new approach to antenatal diagnosis that is widely used today.

83(s) Goodall AH, Jarvis J, Chand S, Rawlings E, O'Brien DP, McCraw A, Hutton R, **Tuddenham EGD**. An immunoradiometric assay for human factor VIII/von Willebrand factor (VIII:vWF) using a monoclonal antibody that defines a functional epitope. *Br J Haemat* 1985; 59:565-577. a. To develop an accurate sensitive test for Von Willebrand Factor antigen and activity in blood plasma. b. none. c. I helped select samples from patients with von Willebrand disease. d. Royal Free Hospital Haemophilia centre. e. no additional funds. f. 23 patients with von Willebrand disease. g. none. Samples had been stored for analysis. h. This assay became widely used after the

publication as it gave a simple quick and accurate result by comparison to the platelet based Ristocetin Co-factor assay.

83(t) Kelly D, **Tuddenham EGD**, Summerfield JA. The effect of an acute phase reaction and BCG innoculation on factor VIII in the guinea-pig. *Thromb Res* 1985; 40:445-451.

A non-clinical study.

83(u) Wion KL, Kelly D, Summerfield JA, **Tuddenham EGD,** Lawn RM. Distribution of factor VIII mRNA and antigen in human liver and other tissues. *Nature* 1985; 317(6039): 26-729.

This was a study entirely performed on tissue samples obtained at organ donation. Two organ donor's tissues were used. a. to define the sites of factor VIII messenger and factor VIII antigen in human tissues and cells. b. none. c. I designed the research and obtained the organ donor samples at time of surgical organ donation. d. Royal Free Hospital and Genetech Inc. e. No additional funds apart from a research grant supporting Dr Kelly. f. two organ donors. g. None for obvious reasons. h. This publication was highly cited as a definitive answer to the question of the site of synthesis of factor VIII. However recent research has shown that in mouse factor VIII is exclusively synthesized in endothelial cells. Although the research which proved that cannot be performed in humans, it is thought likely that factor VIII in made in endothelial cells in humans as well. However, on revisiting our data from the 1985 study I do not find any obvious errors, so the matter remains open.

83(v) Rotblat F, O'Brien DP, O'Brien FJ, Goodall AH, **Tuddenham EGD**. Purification of human factor VIII:C and its characterisation by western blotting using monoclonal antibodies. *Biochem* 1985; 24:4294-4300. A study using human plasma obtained from blood bank sources. The donors who provided the plasma were deemed to have implicitly granted permission for their blood to be used for research as well as clinical purposes.

83(w) Kelly DA, **Tuddenham EGD**, Summerfield JA, Sherlock SS. The effect of liver disease on factors V, VIII and Protein C. *Br J Haemat* 1985; 61:541-548. a. As stated in the title the effect of liver disease on the coagulation factors was investigated. b. none that I can recall. It was a laboratory study on samples already obtained for clinical monitoring purposes. c. I supervised the laboratory assays, analysed the results and helped write the publication. d. Liver and Haemophilia Units at Royal Free Hospital. e. research fellowship awarded to Dr Kelly. f. 85 patients with liver disease. g. none that I can recall. h. this publication has been cited many times in reviews.

83(x) Milton J, Hutton RA, **Tuddenham EGD,** Frojmovic J. Platelet size and shape in hereditary giant platelet syndromes on blood smear in suspension: Evidence for two types of abnormalities. *J Lab Clin Med* 1985; 106(3):326-335. a. we were interested in the rare platelet defect syndromes associated with giant platelets. We hoped to discover the cause of the increased size. b. none that I recall. c. selection of patients for study and obtaining blood samples. d. none. e. Mr Milton was a medical student on a summer studentship. He was self-funding as far as I can recall. f. 16 patients with giant platelet syndromes. g. Patients were aware that we were studying their platelets to try to understand better the cause of the defect. No formal recorded consent process was undertaken. h. This publication only.

83(y) Burroughs AK, Matthews K, Qadiri M, Thomas N, Kernoff P, **Tuddenham EGD,** McIntyre N. Desmopressin and bleeding time in patients with cirrhosis. *BMJ* 1985; 291:377-1381. a. Desmopressin had been used as a haemostatic in various conditions. We wanted to understand what effect it might have in Cirrhosis and whether it could be clinically useful in this condition. b. none that I recall. c. I supervised the laboratory assays, analysed the results and helped write the paper for publication. d. none. The company provided the drug. e. no additional funds. f. 15. g. The clinical aspect of the study was the

responsibility of Dr Burroughs (now deceased). h. This publication only.

83(z) Mannucci PM, Abildgaard CF, Gralnick HR, Hill RGH, Hoyer LW, Lombardi R, Nilsson IM, **Tuddenham E**, Meyer D. Multicenter Comparison of von Willebrand Factor Multimer Sizing Techniques* Report of the Factor VIII and von Willebrand Factor Subcommittee. *Thromb Haemost* 1985; 54(4):873-877. Non-clinical report on the status of research in the area.

83(aa) Kinnear PE, **Tuddenham EGD.** Hermansky-Pudlak Syndrome. Albinism with haemorrhagic diathesis *Br J Ophthalmol* 1985; 69:904-908. A case report. No intervention other than normal laboratory testing undertaken for diagnostic purposes.

83(bb) Mikami S, **Tuddenham EGD**. Studies on immunological assay of vitamin K dependent factors. I. Measurement of factor VII antigen by radioimmunoassay. *Br JHaematol* 1986; 62:171-181. A laboratory study to develop a new assay method. This was used in other subsequent population risk studies by colleagues in Glasgow.

83(cc) Mikami S. & **Tuddenham EGD.** Studies on immunological assay of vitamin-K dependent factors. Comparison of four immunoassay methods with functional activity of protein C in human plasma. *Br J Haematol* 1986; 62:183-193. A laboratory study. No clinical intervention other use of routinely taken blood samples for assay development.

83(dd) Mikami S, O'Brien DP, Mellars G, Goodall AH, **Tuddenham EGD.** Studies on immunological assay of vitamin-K dependent factors. III. A double monoclonal immunoradiometric assay for factor IX antigen. *Br J Haematol* 1986; 62:513-524. A laboratory study undertaken to develop a new monoclonal based assay.

No clinical intervention.

83(ee) Chand, S, McCraw A, HuttonR, **Tuddenham EGD,** Goodall AH. A two-site monoclonal antibody-based immunoassay for von Willebrand factor - demonstration that vWF function resides in a conformational epitope. *Thromb Haemost* 1986; 55:318-324. A laboratory assay development study.

83(ff) Wion K, **Tuddenham E**, Lawn R. A new polymorphism in the factor VIII gene for prenatal diagnosis of haemophilia A. *Nucl Acids Res* 1986; 14:4535. a. to establish another linkage marker for haemophilia A carrier determination. b. none. c. obtained samples from suitable kindred that had been seen in our genetic counselling service. d. Genetech Inc. f. Not stated in the paper but on reviewing it about five families were studied, each with about 5 members. Thus, a total of about 25 patients, carriers and relatives. g. none. The families had attended our centre for carrier testing and when we had additional information resulting from the linkage analyses, they were recalled to convey the information, either that carriership was confirmed or excluded.

83(gg) Hutton R, Wickam, Reid, Tuddenham. Studies on the action of ethamcylate (Dicynene) on Haemostasis. *Thromb Haemost* 1986; 56:6-8. a. to understand the effect of the drug on haemostatic function. b. none. c. recruited healthy volunteers and helped analyse results. d. none e. The company making the drug may have supplied some funds for assays, but I do not recall details if they did. f. 12 normal volunteers received the drug. g. The study participants were employees of the centre and had good understanding of haemostasis and research undertaken there. h. This publication led to use of Dycynene in platelet function disorders.

83(hh) Takase T, Rotblat F, Goodall AH, Kernoff PBA, Middleton S, Chand S, Denson KW, Austen DEG, **Tuddenham EGD**. Production of factor VIII deficient plasma by immunodepletion using three monoclonal antibodies. *Br J Haematol* 1987; 66:497-502. A laboratory study to show how to make deficient plasma for use in one stage assay of

factor VIII. Widely used subsequently for assays that did not depend on obtaining plasma from untreated severely affected individuals as had previously been the practice.

83(ii) Tiarks C, Ghalili K, Humphreys RE, Goodall AH, **Tuddenham EGD,** Pechet L. Identification of six functional clotting factor VIII:C epitopes by analysis of cross-reactive public idiotypes in murine monoclonal VIII:C inhibitors. *Thromb Res* 1987; 45:527-537.

83(jj) Takase T, **Tuddenham EGD**, Chand S, Goodall AH. Monoclonal antibodies to human factor VII: a one-step immunoradiometric assay for VII:Ag.. *J Clin Pathol* 1988; 41:337-341. A laboratory study with no patient involvement.

83(kk) Takase T, Chand S, **Tuddenham EGD,** Goodall AH. Monoclonal antibodies to human factor VII: Production of immunodepleted plasma for VII:C assays. *J Clin Pathol* 1988; 41:342-345. A laboratory study establishing a method to make deficient plasma for use in one stage activity assays without recourse to the exceedingly rare individuals with severe factor VII deficiency.

84. The von Willebrand disease working party was mainly concerned with issues of diagnostic classification and recording in the National database. At the time assays were not well standardised or in many cases even available. My basic research interests in laboratory assay development and classification of this complex and variable disorder were the reason I took on chairmanship of the working party. We were less involved with treatment. I do not recall that we addressed an aspect of treatment by any means then available in the working party other than as noted in my answer to the next question.

85. The reason that a test involving infusion of a human blood product was 'no longer ethically justifiable' was the emerging awareness that all blood products carried a risk of transmitting viral hepatitis including NANB.

86. Starting from my time with Arthur Bloom in Cardiff I became interested in the long-standing problem of the nature of factor VIII. (For a published historical

account see '**Tuddenham E.G.D**. In search of the eighth factor: A personal reminiscence. *J Thromb Haemost.* 2003 ;1(3):403-409.). The entity was only defined as an activity lacking from haemophilia A plasma. Previous efforts to isolate and characterize the responsible entity had been frustrated by its fragility and loss on purification and (as transpired) the extremely low quantity present in blood, in which it has the lowest molar concentration of any factor of the haemostasis cascade. My work with Hoyer in Connecticut introduced me to the use of antibodies for purification and assay development. Returning in 1978 to take up Katharine Dormandy's post at the newly built haemophilia centre, gave me the opportunity to pursue this project with the resources of a centre devoted to haemophilia in both laboratory diagnosis and clinical service areas. Several fortunate circumstances led to rapid progress. The new polyelectrolyte process was being applied to isolation of porcine factor VIII by Speywood Ltd under David Heath's leadership. We began discussing with him a project to purify human factor VIII for a genetic engineering approach. Also, the new monoclonal antibody technology was being introduced in the immunology department at Royal Free Hospital by Alison Goodall, who was looking for interesting antigens against which to raise monoclonal antibodies. We supplied her with some factor IX we had purified by an affinity column - heparin Sepharose. The monoclonal antibodies to factor IX were of considerable use for developing assays and purifying the protein. This gave us the confidence to tackle factor VIII. We first derived monoclonal antibody against Von Willebrand factor. We then used this antibody to bind the factor VIII, partially pre-purified by polyelectrolyte ion exchange column, in which a much higher ratio of factor VIII to von Willebrand factor was present. By this means we leveraged a potent fraction to immunize mice for an attempt to isolate monoclonal antibody clones specific to human factor VIII. The first attempt was a success with a series of clones being isolated, each making a specific antibody neutralizing factor VIII. We could then use these antibodies in the final purification step to ultra-pure factor VIII. The final product was a tiny amount of protein, but just enough to visualise on a polyacrylamide gel stained for protein. It had multiple bands, but all reactive with a polyclonal human antibody to factor VIII. We knew we had to scale this up to industrial levels to have enough protein for conventional

amino acid sequencing, then requiring multi-milligram amounts to get extensive peptide sequences. This was achieved using industrial size polyelectrolyte columns from Speywood. We also prevented proteolytic degradation during the process by adding Di-isopropyl Fluorophosphate to all the buffers and starting material. DFP is a nerve gas type agent requiring very careful handling. The final product consistently recorded a specific activity of 5000 units per mg, equating to a single unit (the amount in one ml of plasma) being 200 ng of protein. We formed a partnership with Speywood and Genentech to supply pure protein and monoclonal antibodies for the major attempt to clone the gene by first sequencing the protein, then predicting a gene sequence to make a DNA probe to identify and isolate a fragment of the gene from a library of human DNA fragments. With that in hand the gene was cloned in overlapping clones, a source of messenger RNA was found and a copy of the spliced mature messenger RNA cloned and finally used to express factor VIII in a cell line. My research group worked continuously making batches of pure factor VIII starting from 5 kg blocks of commercial cryoprecipitate from paid donors in California. The protein was sequenced in overlapping peptide fragments (38). The project was completed in 18 months with the demonstration of active factor VIII secreted by a cell line containing the factor VIII cDNA in an expression cassette (37).

37. Wood WI, Capon DJ, Simonsen CC, Eaton DL, Gitschier J, Keyt B, Seeburg PH, Smith DH, Hollingshead P, Wion KL, Delwort E, **Tuddenham EGD**, Vehar GA, Lawn RM. Expression of active human factor VIII from recombinant DNA clones. *Nature* 1984; 312:330-337.

38. Vehar GA, Keyt B, Eaton D, Rodriguez H, O'Brien DP,Rotblat F, Oppermann H, Keck R, Wood WI, Harkins RN, **Tuddenham EGD**, Lawn RM, Capon DJ. Structure of human factor VIII. *Nature* 1984; 312:337-342.

87. After completion of the sequencing, cloning and expression of factor VIII, I turned to other early clinical spin off projects using the DNA and monoclonal antibody tools we developed in the main project. These included finding the first mutations, finding informative DNA markers of carrier testing and antenatal diagnosis of haemophilia A. I did not work on the development of

the recombinant product which was taken forward by Genentech with Cutter laboratories and then by Bayer who bought the rights from Genentech to the development of the product named Kogenate. I had obtained a Royalty agreement for the Royal Free that at 10% could have earned the school an estimated $1 billion dollars during the life time of the patent. Unfortunately after I left the Royal Free to join the MRC the agreement was renegotiate with a fatal flaw in the wording around patents which meant that Sanofi – who had bought Speywood and its rights could avoid paying any such sum to the medical school. They made a token payment of £4.5 million pounds. This bitter experience guided me to patent our work on developing gene therapy using the factor VIII gene.

The recombinant products were first trialled in 1989 and came into general use in the early 1990s.

88. No - in view of the technical difficulties of scale up, purification and formulation on a large scale for an extremely large protein. Overcoming these challenges in the new field of recombinant protein production required innovation and massive investment in people and equipment to achieve the goal of supplying a highly defined safe effective product.

89. Because there was no company in the UK capable of taking on a such a project at the time we started in 1982. We did consider the British company Cell Tech, that had recently been set up with government funding, but their experience and track record were very limited compared to the US genetic engineering pioneers.

90. I gather that there was a slow process of rolling out synthetic factor to all adult recipients during the early part of decade 2000-2010. By the time I returned to clinical practice this had been completed at Royal Free. This means that apart from patients on trial, few adults in the UK were receiving recombinant factor concentrates until 2005. It could be argued that since the plasma derived products were virus safe that was clinically acceptable. Also, the relative price would have favoured plasma derived factor concentrates. Notwithstanding it is also the case some infectious agents are not inactivated by the procedures

that are effective for Hepatitis viruses and for HIV. The agent of most concern is the prion that can trigger a cascade process causing spongiform encephalopathy. Hence pressure built up for recombinant factor to be widely available, not just for children but for adults with haemophilia as well. Perhaps I am biased by my involvement with recombinant factor, but I consider that all factors used in haemophilia care, should be synthetic, where possible, for safety reasons.

91. My work on gene therapy for haemophilia began while at Northwick Park in the early 1990s, when we explored the possibility of preventing immune response to Adeno-Associated Virus (AVV) capsid in mice, thus enabling repeated administration of gene therapy vectors using AAV. One of my PhD students from that time was Amit Nathwani, who later spent two years at St Jude Childrens' Research Hospital in Memphis under Arthur Nienhuis. While there he helped design and create a vector containing the factor IX gene. This was successfully tested in mice and non-human primates. Returning to University College London Haematology department in 2000 he continued this work, which was supported by the Katharine Dormandy Trust. Highly encouraged by the progress of Amit's research I applied for and was appointed Director of the Katharine Dormandy Haemophilia Centre in 2006, returning after 20 years with the MRC, for the purpose expressed at my appointment interview of starting trials of gene therapy. Thus it was that in 2010 the first patient with severe haemophilia B was treated in our trial of a new AAV vector containing an optimised factor IX sequence in a capsid with high tropism for liver, such that it could be infused into a peripheral vein. 10 years later this patient continues to have a clinically significant level of factor IX in the moderate range. By carefully increasing the dose we reached a dose level where all but one of the subjects now has a sustained factor IX level in the mild range with no prophylaxis and no bleeding episodes for up to 8 years. Publication of this work in in the New England Journal of Medicine in the Christmas Issue of 2011, with a follow up in the same journal in 2014 led to a surge of interest with 10 current gene therapy trials ongoing, using various vectors in haemophilia B and A. Further research in Amit Nathwani's group led to development of an AAV vector which for the first-time produced levels

of factor VIII in the normal to high supraphysiological range in mice and monkeys. This was achieved by modifying the factor VIII DNA sequence through codon choice and optimising the linker between light and heavy chains. A successful trial based on this work is in phase 3 run by Biomarin Inc and has dosed 130 patients with severe haemophilia A. At least four other trials in haemophilia A are ongoing, including one we are running in the Katharine Dormandy Centre. During the corona virus pandemic all these studies are on hold to new recruitment because part of the protocol is a period of moderate immune modulation to enable tolerization to the transgene and long-term stability of expression. If a patient were to be infected it might necessitate cessation of immune modulation with loss of effect of the gene therapy. So far, no patient on any of the trials has experienced this complication, thanks to observation of shielding procedures. As soon as control of the pandemic has been achieved and it is safe to do so, recruitment will resume.

92. My research, undertaken with Medical Research Council support of the Haemostasis Research Group which I directed during 20 years from 1986 to 2006, led to over 100 publications in peer reviewed Journals. The research ranged from structural biochemistry studies such as solving the crystal 'Structure of Tissue factor' (Harlos et al Crystal structure of the extracellular region of human tissue factor. *Nature* 1994; 370:662-666.) to the first demonstration of diagnostic PCR amplification of a Y chromosome marker from single human blastomere cells (Handyside et al Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1989: i:347-349.) The human material used in these studies was either provided by colleagues (for example the human blastomeres from Robert Winston's group at Hammersmith Hospital) or from patients under the care of other physicians at the Royal Free Haemophilia Centre, where I continued to consult and advise, especially on matters of genetic diagnosis or from and other haematologists who sent me interesting cases to study from around the world. For one large study on the rare recessive bleeding disorder combined factor V and factor VIII deficiency I travelled for a month in Iran collecting family samples with support of the Iranian Haemophilia Society. This work led on

through genetic homozygosity mapping to the identification of two genes necessary for the export of factors V and VIII. Disabling mutations in either of the genes (which code for endoplasmic reticulum cargo transporters) causes combined factor deficiency. Informed consent was obtained from all family members.

I will select a few representative studies: -

O'Brien DP, **Tuddenham EGD**. Purification and characterization of factor VIII 1689 Cys: a non-functional cofactor occurring in a patient with severe haemophilia A. *Blood* 1989; 73:2117-2122.

The first purification and biochemical characterisation of a mutant non-functional factor VIII variant from a patient with severe Haemophilia A. We showed that loss of function was due to the fact that the amino acid altered from Arginine to Cysteine at this position meant that thrombin cleavage of the bond was prevented and hence factor VIII with this mutation cannot be activated and released from von Willbrand factor to take part in forming the tenase complex of factor IXa and factor X, which is the mechanism of Factor VIII activity. The subject was registered at Royal Free Hospital and upon explaining why we were interested in his factor VIII willingly provided several samples for our studies.

We studied several other mutant factor VIII proteins to resolve their molecular pathology at a mechanistic level.

O'Brien DP Gale KM, Anderson JS, McVey JH, Miller GJ, Meade TW, **Tuddenham EGD**. Purification and characterisation of factor VII 304-Gln:- A variant molecule with reduced activity isolated from a clinically unaffected male. *Blood* 1991; 78:132-140. This was the first mutation analysed from a patient with extremely low factor VII activity. Unusually he had no bleeding and we showed this was because the reagent used to perform the activity assay was tissue factor from rabbit brain, whereas using human tissue factor the level was nearly normal. (O'Brien DP, Kemball-Cook G, Hutchinson AM, Martin DMA, Johnson DJD, Byfield PGD, Takamiya O, **Tuddenham EGD**, McVey JH. Surface plasmon resonance studies of the interaction between

factor VII and tissue factor. Demonstration of defective tissue factor binding in a variant FVII molecule (FVII-R79Q). *Biochemistry* 1994; 33(47):14162-14169.) The subject had been found in a population survey of clotting factor levels intended to discover predictive markers for thrombotic disease in the Glasgow heart study series. We analysed many cases with factor VII deficiency and bleeding after this and eventually developed a gene therapy for treating this rare severe bleeding disorder. This is planned to enter clinical trial in future years. We set up a data base for factor VII mutations as part of this project at http://f7-db.eahad.org/structure.html.php

Continuing work on factor VII we solved the crystal structure as shown here https://www.rcsb.org/structure/1CVW

Tuddenham EGD, Cooper DN, Gitschier J. *et al.* Haemophilia A: database of nucleotide substitutions, deletions, insertions and rearrangements of the factor VIII gene. *Nucl Acids Res* 1991; 19(18):4821-4833. This was the first full database of factor VIII gene mutations published in print. Subsequent versions of the database were online. The most recent update is at http://f8-db.eahad.org/ . It contains over 10,000 individual patient records representing over 3000 unique mutations. It is the largest such single gene mutation collection online and is heavily used for diagnostic purposes. The patient level information is strictly anonymised. A similar database for factor IX mutations was also taken over from the original database set up by Brownlee and colleagues and is available on the European Association for Haemophilia and Allied disorders website at http://f9-db.eahad.org/ and is frequently used in genetic diagnosis.

Shovlin CL, Hughes JMB, **Tuddenham EGD**, Temperley I, Perembelon YFN, Scott J, Seidman CE, Seidman JG. A gene for hereditary haemorrhagic telangiectasia maps to chromosome 9q3. *Nat Genet* 1994; 205-209. The uncommon bleeding disorder hereditary haemorrhagic telangiectasia fascinates haematologist because the disorder primarily affects small blood vessels, which proliferate into fragile tangles of tiny blood vessels from which serious chronic bleeding results. It is dominant and of moderate effect on reproductive fitness such that large families with affected individuals in many

generations can be traced. I found a particularly large family segregating this condition, from Irish ancestry. We collected enough samples from 4 generations to perform a single family linkage study locating the gene defect to a particular site on chromosome 9. Subsequently the gene which was mutated in the disorder was shown to be Endoglin, which is a critical component of the pathways regulating blood vessel growth. The study was approved by the Hammersmith Hospital ethics committee. Family members were willing participants.

Schwaab R, Brackmann HH, Seehafer J, Kirchgesser M, Olek K, **Tuddenham EGD,** Oldenburg J. Haemophilia A: Mutation type determines risk of inhibitor formation. *Thromb Haemost* 1995; 74(6):1402-1406. This study based on our own and published cases proved that there is a genetic basis for the development of inhibitors in haemophilia A. Severe gene lesions such as multi exon deletions are most prone to be associated with development of neutralising antibodies to factor VIII after treatment.

Pemberton S, Lindley P, Zaitsev V, Card G, **Tuddenham EGD**, Kemball-Cook G. A Molecular Model for the triplicated A domains of human factor VIII based on the crystal structure of human caeruloplasmin. *Blood* 1997; 89(7):2413-2421. This study used the crystal structure coordinates of ceruloplasmin to model the A domains of factor VIII. Factor VIII and factor V A domains clearly share strong sequence homology and structure, having evolved from a common ancestral small blue copper type protein at least 450 million years ago (Davidson C. J., Hirt R. P., Lal K., Snell P., Elgar G., **Tuddenham E. G. D.**, McVey J.H. Molecular evolution of the vertebrate blood coagulation network. *Thromb.Haemost.* 2003 89(3):420-8.).

A former PhD student Dr Jonathon Pattinson contacted me for help in understanding the mechanism of warfarin resistance, which he had come across in a patient who failed to respond at all to oral warfarin given as prophylaxis for thrombosis. I pondered this problem noting that warfarin resistance also occurred in mice and rats. Not long after Johannes Oldenburg contacted me to ask if we had any patients with a rare hereditary form of vitamin K dependent clotting factor deficiency as they wanted to isolate the

gene by linkage analysis, similarly to the studies I had done in Combined factor V and VIII deficiency. On reflection I realized that the two conditions, warfarin resistance and multiple vitamin K factor deficiency were likely to be allelic, that is mutations in the same gene. By combining all the information on the different conditions in humans and animals it was possible to narrow down the likely site of the gene on the human chromosome map. Then the task was to use information from the human genome project to study each of the genes in the region for mutations in patients with warfarin resistance and those with hereditary multiple coagulation factor deficiency. This led to the gene called Vitamin K epoxide reductase type I in which mutations were found in the patient whose sample I was sent by Dr Pattinson and in the families with the hereditary condition. (Rost S., Fregin A., Ivaskevicius V., Conzelmann E., Hortnagel K., Pelz H. J., Lappegard K., Seifried E., Scharrer I., **Tuddenham E. G.,** Muller C. R., Strom T. M., Oldenburg J. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature* 2004. 427, 537-541). Soon it was found that variants of this gene are responsible for variations in response to warfarin therapy, which mandate that when it is given clinically as a thromboprophylaxis agent, the response is regularly monitored.

By using extension of the method of PCR on single cells that we first demonstrated in 1987 (Handyside AH, Pattinson JK, Penketh RJA, Delhaty JDA, Winston RML, **Tuddenham EGD**. Biopsy of human preimplantation embryos and sexing by DNA amplification. *Lancet* 1989: i:347-349.) and by now able to identify the mutation causing most types of haemophilia, we realized that it could be feasible to undertake mutation specific analysis of a blastomere, not just for sex but for presence or absence of a disease defining mutation in a particular embryo prior to implantation after standard in vitro fertilization. We successfully demonstrated this for the first time in the case of two haemophilia A carriers (Michaelides K, **Tuddenham EG**, Turner C, Lavender B, Lavery SA. Live birth following the first mutation specific pre-implantation genetic diagnosis for haemophilia A. Thromb Haemost. 2006 Feb;95(2):373-9.).

93. The first ethical principle of research involving humans is the one we inherit from Hippocrates "First do no harm". The second principle is that consent to take part in research must be a voluntary choice of the participant after a full explanation of the risks. These and other principles are well described in the Helsinki declaration of 1964. It took several decades for a full implementation of these principles to be instituted through a formal network of ethics committees and establishment of local research departments tasked with monitoring the clinical research undertaken in host institutions. At the beginning of my career in medical research no formal procedures had been established to demonstrate informed consent, or ethical approval by officially constituted local or national committees. This is documented by examination of clinical research publications in which no mention is made of ethical approval until the late 1980s. Looking back over my career I recall that we discussed with patients what we were doing and why their donation of samples might help them and others. On the occasions before 1987 when I took part in interventional studies with new drugs, we did not go through detailed and formally documented procedures to obtain ethical approval and informed consent. Since I returned to clinical research in 2006 I have complied with all regulations that now control clinical research.

94. No, although consent was not documented on paper as far as I can recall.

95. In the genetic linkage studies on kindred segregating haemophilia we used samples taken for earlier methods of carrier detection, such as factor VIII to von Willebrand factor ratio, and assumed consent as they had been supplied by consultands and their families, who wished to have their carrier status established. Nowadays consent to use a blood or tissue sample in subsequent analysis is taken and recorded at the time of sampling. Clearly this is a practice that has changed and improved over time.

96. Yes, we provided patient data to the UKHCDO national database. As I did not do any of the detailed data collection and transmission, which my colleagues at the centre carried out I do not know if it was anonymised in the earlier period of my career from 1978 to 1986. I can remember looking at national data with Rosemary Spooner in the days when it was all on paper, and there were no

names, just numbers for the patients. So there must have been some degree of anonymisation. Later the full implementation of the data protection act was applied, and consent recorded for transmission of anonymised data. I think this happened during the period after 2006 as security and consent for data transmission were brough into line with new legislation. The data was provided from the start of the national database in Oxford to have numbers of patients treated and amounts and types of treatment to use in negotiations with the Department of Health. The UK has the best national set of data of bleeding disorders of any country and these are invaluable in guiding and justifying development of the service.

97. At the time I left the haemophilia centre in 1986 we had just started to see clinical events that in retrospect must have been due to AIDS/HIV. One adult patient died from Chicken pox pneumonia. Another developed rapidly progressive dementia and died. Soon after I left the full range of complication of AIDS began to emerge in our patients.

97(a) As I had left before the full range of problems emerged I cannot reply in detail to this question.

97(b) Please refer to my colleagues for answer to this question. I presume that in 1996 all patients with low CD4 counts were given the first highly active anti-retroviral drugs alone or in combination as they became available.

97(c) Management of HIV/AIDS became a speciality of the infectious disease unit which was provided in a purpose-built unit – the Ian Charleson Day Centre (ICDC). By the time I returned to the centre in 2016 all HIV care was managed from the ICDC by amongst others Dr Sanjay Baghani.

98. This was and is all managed through the ICDC. When necessary we consult with the medical staff of that centre and they with us. The centre is located a few yards from the haemophilia centre on the ground floor of the hospital.

99. I defer to my colleague Dr Thynn Thynn Yee to answer this in detail as she manages the patients with chronic hepatitis in conjunction with the liver department.

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102. I refer you to my former colleague Professor Christine Lee (retired) and to Dr Sanjay Bagani of the ICDC to answer this question. I expect the patients of the centre with HIV would have been entered in the trial of HIV therapy.

103. After I returned to the centre in 2006 of course all the children with haemophilia who were infected before 1986 had become adults if they survived. I have met some of them and reminisced about old times, because they came on adventure holidays with me in North Wales or the Pyrenees.

104. I refer you to my colleague Nicola Dunn who is our family therapist and psychosocial worker, having succeeded Mrs Riva Milla (deceased).

105. I refer you to my former colleague Professor Christine Lee (retired) and to Dr Sanjay Bagani of the ICDC to answer this question.

Records

106. All the patients who were infected with HIV up to 1986 had either died before active therapy became available in 1996 or are now stable and well on various combinations of drugs supervised by the ICDC. One patient died from late recurrence of Hepatitis C after liver transplant. I do not know what was recorded on his death certificate. Another patient died of liver disease related to double HIV Hepatitis C infection at home. I do not know what was recorded on his certificate either. Cause of death is reported to the UKHCDO national database, so it must be a matter of record.

107. All records were kept in the centre in room that was a subsection of the hospital records department. This was for rapid reference when patients attended in an emergency. The system was instituted when I first came to the centre in 1978 and still in use when I returned. All paper records have now been scanned for digital preservation and the paper records destroyed.

108. No. With one exception (see below) we only keep the hospital records- now digitally. For the purposes of clinical trials, trial documentation was compiled and stored in accordance with data safety management rules. I believe that all trial data must be kept for a set period time. The exception is the genetic counselling and pedigree data. There is an extensive set of pedigrees dating back to my time at the centre from 1978 which exists as paper files. We have kept them because they are an invaluable resource when people who suspect they may be affected, for example more distant relatives of an index case, request carrier testing. We can then rapidly ascertain likelihood of carriership from family pedigree. To some extent this is now superseded by direct genetic testing for a mutation.

109. No.

110. No.

Section 5: Treloar's

111. Although when I first became director of the haemophilia centre in 1978 we looked after many children with haemophilia and some of them attended Treloar's, I cannot remember referring any new cases to go there.

111(a) None that I can recall.

111(b) Not applicable.

111(c) None for those already attending.

111(d) When they came to the centre during holidays, we must have treated them in the usual way. But on reflection I am not sure if we had any young boys still attending Treloar's from 1978 to 1986.

112. None that I was aware of or recall.

113. No. It is hard to think why they would be.

Section 6: Self-sufficiency

114.

114(a) In 1978 when I first became acting director, I remember being told that there was a plan for UK to become self sufficient in blood products including factor VIII concentrates. We were then or soon thereafter self sufficient in factor IX concentrate – or so I believe as I do not remember using any commercial factor IX in our patients.

114(b) All blood products needed for therapy to be manufactured from UK donor plasma at the UK fractionation centres in Elstree, Oxford or Edinburgh.

114(c) I remember being told later that self sufficiency had been abandoned, but not by whom or when.

114(d) I think we all had the same idea and aspiration as defined above.

114(e) I talked with then director of Elstree (Richard Lane) about ways to improve purification using monoclonal antibodies. This was followed up and a monoclonal antibody concentrate prepared, but not in large quantities. One of the commercial manufacturers produced a monoclonal plasma derived factor VIII. I suggest that Richard Lane could give a more detailed account of how the proposal to reach self-sufficiency in factor VIII concentrate production ended.

115. I was not involved in making estimates of future use of factor VIII containing blood products.

115(a) Centre directors submitted their own annual usage to the Oxford data collection which was compiled by Rosemary Spooner under the direction of Charles Rizza.

115(b) None.

115(c) I do not know how UKHCDO made the case for future need but they must have used some predictive model

115(d) I do not know but it would surely have been based on numbers of patients and current usage plus added growth to take account of new born patients and their growth.

115(e) I think Dr Rizza and later Dr Hay did this in consultation with the Department of Health annually.

115(f) I do not know.

115(g) I do not know except that as more and more prophylaxis was introduced demand would have gone up markedly.

116. The answer to this question is the same as the answer to the previous one.

116(a) In 1978 when I first became acting director, I remember being told that there was a plan for UK to become self-sufficient in blood products including factor VIII concentrates. We were then or soon thereafter self-sufficient in factor IX concentrate – or so I believe as I do not remember using any commercial factor IX in our patients.

116(b) All blood products needed for therapy to be manufactured from UK donor plasma at the UK fractionation centres in Elstree, Oxford or Edinburgh.

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monoclonal plasma derived factor VIII. I suggest that Richard Lane could give a more detailed account of how the proposal to reach self-sufficiency in factor VIII concentrate production ended.

117. Not to my knowledge.

118. Self-sufficiency was never achieved. Perhaps enough was made for low level on demand therapy to be available, but with not enough for prophylaxis or major surgery. That is the situation now in low income countries or as it was in the UK before the advent of cryoprecipitate and concentrates in the 1950s. There is a high rate of morbidity and mortality in haemophilic patients at such low levels of factor availability. The self-sufficiency project was quietly dropped by civil servants after David Owen was shuffled to another cabinet positions (Lord Owen. Pers. Comm.).

119. No. The data was there to see that we used much more factor VIII concentrate than was being produced by the UK fractionation centres.

120. 120(a) HBV infection rates from blood products were low by 1978, thanks to testing for Australia antigen in donors. The availability of a vaccine prepared from the blood of patients in the New York gay community, which I received along with other medical staff and I think some of our patients was also lowering incidence of infection. I do not have the detailed information on the timing and effect of these developments to deduce the benefit that self-sufficiency would have had on hepatitis B, but I think it might not have been as large as for the other infectious agents during the critical period between 1976 and 1986.

120(b) Hepatitis C is prevalent in the normal population of blood donors without other risk factors such as the volunteer donors who supply the plasma used to make factor VIII and IX concentrates in the UK. Therefore, self-sufficiency would not have affected the rate of infection of our haemophilic patients by treatment with UK sourced concentrates versus imported concentrates. All concentrates were infectious for hepatitis C until viral inactivation was achieved by heating in 1986.

120(c) For HIV the conclusion must be different as HIV infection is much lower in UK volunteer donors in the critical period before specific testing and viral inactivation became available. We know this from the observation that HIV transmission was much lower in patients treated with UK concentrates of factor IX and factor VIII. The number of infections avoided could be calculated from the different incidence rates of infection. I suspect it would have been at least a three-fold reduction for haemophilia A patients. It would be interesting to do a more detailed calculation and someone may have done that. One could take the proportion of haemophilia B patients who were infected with UK factor IX concentrate and project that to the numbers of haemophilia A patients with a factor to allow for the numbers of donors that went into the factor IX concentrates versus the number that went into the factor VIII batches. Or project from the proportion of infected batches of UK factor VIII concentrates to the number that would have been made and used had we achieved self-sufficiency by a given date. There can be no doubt that the numbers infected would have been considerably lower.

121. Yes, I believe they did as I do not recall using any imported factor IX concentrates to treat our patients at the Royal Free during the years I was there.

122. No.

123. It was to gather and maintain verifiable statistics on numbers of patients and the treatments they received for medical monitoring of the status of treatment of haemophilia in the UK. This kind of epidemiology is essential for planning purposes, negotiations with government and both maintaining and improving services which depend crucially on government support. The World Federation of Haemophilia deems accurate gathering of statistics as the very first step in developing services for haemophilia in developing countries. The series of publications deriving from this work continues as the most impressive time series of changes in haemophilia care with its ever improving health outcomes in this country. This is what we use to justify the expenditure on

haemophilia care in this country to tax payers who support us in this endeavour.

Section 7: Blood services and BPL and PFL

124. My knowledge of these questions is rather limited as the formal relations were handled by my colleague Dr Peter Kernoff (deceased).

124(a) The blood transfusion service would have provided platelets through the blood bank of the Royal Free Hospital, which was under direction of another haematologist, not a member of the Haemophilia Centre staff. Fresh frozen plasma would also have come through the hospital blood bank where it was stored. I do not recall how the cryoprecipitate was sourced or where it was made and stored. We must have had some stored in the centre because I recall late one night getting 10 bags and thawing them to give to a severe Von Willebrand Disease patient who had a dangerous post-partum haemorrhage. She responded well and survived.

124(b) Blood Products Laboratory in Elstree provided us with the concentrates that they made, Factor VIII Y foremost. I think they were also making a prothrombin complex concentrate for treatment of factor IX, factor X, prothrombin and factor VII deficiency. As well as for reversal of warfarin overdose and other acquired causes of deficiency of those factors. The procuring of their concentrates was arranged by Dr Kernoff as far as I remember.

124(c) I think we did get supplies of factor IX concentrate from the Oxford Plasma Fractionation Centre. I did not personally have any dealing with them.

125. Apart from the time when Richard Lane supplied us with some Polyelectrolyte purified factor VIII I had no direct dealings with BPL or PFL while I worked at the centre.

126. No. It seems like an obvious step to take in retrospect, but at the time it seemed like a step back to go from more purified, characterised and stable product to a very crude concentrate. If there were discussions on doing this I did not take part in them.

127. None that I can recall. Peter Kernoff must have had such discussions, but if so he did not relay them to me.

128. None that I can recall.

129. Very thorough and detailed with the batch number of every bottle of concentrate or bag of cryoprecipitate recorded along with dosage and response in the patient treatment folder. This information was compiled to be sent to the Database at Oxford for the Annual returns. Later this was computerised by a team set up by Dr Kernoff under a Mr Michael Trott (? I am not sure of his name).

Section 8: UKHCDO

130. I was a de facto member of the organisation as director of a reference centre. As the minutes show I attended most meetings of the committees, which were mostly held in the seminar room of the Royal Free Hospital Haemophilia Centre. I contributed to discussions and for a time chaired the working party on Von Willebrand Disease.

131. The UKHCDO had a written constitution under which it operated. This is a matter of record. My comments in answer to the questions below are made from my memory of the practical working of the organisation.

131(a) To bring together the doctors responsible for care of patients with bleeding disorders, to monitor the performance of the centres where such treatment was given, to develop and oversee application of guidelines for best practice in care of haemophilia and allied disorders, to note and respond to challenges in care of haemophilia such as supply of therapeutic products and generally to promote the advancement of knowledge and practice in managing the multiple

medical and social problems that bleeding disorders give rise to in the life of sufferers. In the nature of such a body it could not define in advance all the problems that might arise but be flexible in responding to them.

131(b) These are defined in the constitution of the organisation. In practice when an issue was deemed to require a working part to address particular problems in haemophilia care or the organisation of service, then a working party was set up tasked with addressing the issue under consideration. Such a working party had a chair and members invited to join, mostly from within the UKHCDO but others could be and were co-opted, where there skill and knowledge was needed for the particular issues under consideration. Each working party so constituted and tasked, was expected to produce a report and recommendations within a defined time. Working parties were to complete their work and disband in a maximum of three years (I think. It may have been two. A matter of record that can be checked).

131(c) I am only aware of such a relationship in terms of the annual general meeting where the companies had stands and may have contributed to costs by unrestricted educational grants. I never had any direct dealings with companies as I was never chairman or treasurer of the UKHCDO.

131(d) Decisions on critical matters may have been decided by vote but I cannot now recall votes being taken. The minutes of the meetings will show if so. Generally after discussion consensus was reached and usually the chairman or another designated member would take the action.

131(e) Practice guidelines could be disseminated to members as well as being published.

131(f) 131.f.1 No involvement.

131.f.2 No involvement.

131.f.3 No involvement.

131.f.4 I made proposals for innovative alternatives to blood products in a paper I presented at the World Federation of Haemophilia meeting in Stockholm in 1983. By then I had purified factor VIII to homogeneity and we well on the way to completing its sequence and that of its gene, so I knew synthetic factor VIII was feasible. I suggested that the way forward was much higher purity obtained with novel ion exchange columns and by monoclonal antibodies to remove viruses. I dismissed heating and ultraviolet light to inactivate viruses. In this I was proved wrong as the viruses of most importance, Hepatitis C and HIV, by happy chance are both lipid enveloped and the envelope can be disrupted with heat at a temperature which does not denature the proteins of interest. Of my other proposals, both genetically engineered factor VIII and factor IX have come to pass, although not in time to prevent the catastrophe of infection by blood transmitted viruses. The UKHCDO, while sympathetic to such proposals did not specifically promote higher purity factor concentrates except in so far as they would be more convenient to store and administer and have known potency.

131.f.5 The minutes of the meetings contain many discussions about hepatitis NANB risk and HIV risk. By closely monitoring patients treated for the first time with concentrates Dr Kernoff established that all concentrates transmitted hepatitis C.

131.f.6 I am not aware of any guidelines issued by the UKHCDO on sharing of information about risks with patients and/or their families.

131.f.7 I do not think that UKHCDO had any policies on consent from patients on the storing of patient's blood for treatment or research.

131.f.8 I am not aware that UKHCDO took an interest in the development of heat treatment until such methods were developed by industry.

131.f.9 If the members had any views on this, I did not learn of them.

131.f.10 vCJD exposure became a major issue once cases of blood donors who subsequently developed vCJD were found and reported. UKHCDO maintained that no patient should suffer adverse treatment if deemed at risk through having been infused with a product in which starting material had plasma in it which came from a vCJD positive donor.

131.f.11 UKHCDO was aware of progress in drugs for both Hepatitis C and HIV being made in the 1990s. It encouraged their trial and use and monitored outcomes of haemophilic patients so treated through the NHD.

Section 9: Pharmaceutical companies/medical research/clinical trials

132.

132(a) Between 1982 and 1986 I worked closely with Speywood Ltd on the project for purifying factor VIII and collaborating with Genetech Inc on the cloning and synthesis. I was in frequent communication with the CEO of Speywood, David Heath and his chief scientist Sarah Middleton during the period from 1982 to 1984 as we scaled up the purification to provide regular shipments of pure factor VIII and monoclonal antibodies to the teams at Genetech. Speywood paid the salaries of my team at Royal Free Hospital. Unfortunately, my liaison with David Heath ended when the company was taken over and he

moved on to found another company. I say unfortunately because it was later, after I left that the renegotiation of the agreement with the Medical School took place by which they lost the Royalties on recombinant factor VIII which I had arranged for them. Had David still been CEO this would not have happened.

132(b) With my experience of losing the Royalties on factor VIII I made sure we patented the gene therapy vectors for transferring the factor VIII gene. These then formed the basis for the collaboration between UCL-B, us and Biomarin which led to an agreement to license our patented IP for the gene therapy vector under confidential financial terms. The drug as developed by Biomarin is in Phase 3 with 130 subjects with severe Haemophilia A enrolled and infused with vector. Application for market authorisation will take place in November 2021 when all subjects have reached 3 years post treatment.

133. Yes, but only in the period 2006 to the present. I had no paid consultancies with pharmaceutical companies engaged in the production of blood products in the period 1978 to 2005. From my return to clinical practice at the haemophilia centre in 2006 until I retired from the Directorship in 2011, I was quite often invited to attend clinical advisory boards of companies introducing new products for which I was paid. I also was paid for lectures on subjects relating to their products at international meetings. All such payments were declared as income to HMRC and appear in detail on my tax returns. I only have records dating back to 2010. Payments I received from Pharmaceutical companies who manufactured and sold blood products for treating haemophilia are itemised below according to tax years: -

2010 to 2011	No payments.
2011 to 2012	Novonordisk paid me honoraria for lectures, including organising and running a course at Royal Free Hospital in the total amount of £3,123.00.

2012 to 2013	Novonordisk paid me Eu 1,000 for consultancy concerning management of elective orthopaedic surgery in patient with inhibitors of factor VIII. A consensus guideline was developed in consultation with other experts.
2013 to 2014	Pfizer paid me £1,500.00 for a lecture.
2014 to 2015	No payments.
2015 to 2016	Bayer paid me £1,200.00 for a lecture.
2016 to 2017	Bayer paid me £405.50 for a lecture.
2017 to 2018	No payments.
2018 to 2019	No payments.
2019 to 2020	No payments.

134. See answer to Q 133. I cannot differentiate between these two questions as they overlap in my experience. I have never had a permanent position on the board of any pharmaceutical company. All my financial dealings with pharmaceutical companies manufacturing blood products are detailed in answer to Q 133 by means of tax return records.

135. No.

136. No,

137. No

138. During the period 2006 to 2011 the rules concerning pharmaceutical company hospitality changed to restrict their expenditure on hospitality at conferences or elsewhere. This did not apply to payments for advisory lecturing work. I was not required to provide details of my income from advisory and teaching work to anyone other than HMRC.

139. Yes. From 2006 until 2011 I was in receipt of research grant funding for work carried out in my laboratories at Royal Free Hospital by Simon Waddington and his staff funded by NovoNordisk. The research concerned gene therapy delivered in utero to mice. He also was involved with the work on gene therapy with factor VIII and factor VII vectors.

140. Yes, but all preclinical data as described in papers referred to above, so not strictly medical- assuming that means clinical trial data. Since 2018 when we started trial of a new haemophilia B vector for Freeline Ltd, they have had full oversight of the trial results, which although sponsored by UCl is funded by Freeline Ltd.

141. Yes funding is always fully disclosed to UCL. In the first period of my work on factor VIII the funding from Speywood was approved by Royal Free Hospital Medical School, my employer.

Section 10: Involvement with the financial support schemes

142. On on two occasions I have applied for compensation awards for patients who have been infected with hepatitis C from the Skipton fund. On both occasions the applications were approved. Otherwise no involvement.

143.

143(a) I believe that the patients with haemophilia were kept well informed by Riva Miller and her assistant.

143(b) Not that I was aware of. In the case of the two patients for whom I applied to the Skipton fund, one had slipped through the net. She was a patient with platelet function defect who became infected after receiving multiple platelet infusions. She had cleared the virus but

after a period of liver dysfunction that met the criteria for the application. I noticed this on review and made the application. In the other case, a carrier with moderately severe haemophilia, an earlier application had been denied but, at her request we revisited the application with new information and the application was approved.

143(c) The information required on the application forms.

143(d) I did not personally act as a gateway. If the patient met the criteria we made the application. Indeed even if the criteria were not strictly met as in the second case I still made the application but with all the additional information supplied to me by the patient about the effect of the infection on mental health and well-being.

143(e) No.

143(f) Yes, but with the exception that a senior administrator of the Skipton fund was found to have embezzled money from the fund by inventing cases. I was told that a criminal trial led to a prison sentence.

Section 11: Other issues

144. No such complaints to the bodies listed.

145. I have addressed above all the issues of which I have knowledge from my direct involvement at the time that are relevant to the inquiry. Although I seem to be the last man standing from that era who is still working in haemophilia and can take the long view, it is hard to see how my colleagues who were taking the decisions about blood supplies could have realised in time the severity of the risks and have taken the extremely drastic actions necessary, in the absence of self-sufficiency, to reduce the infection rate. That would have meant stopping all imports and relying on limited local supplies and non-interventional traditional methods for controlling joint bleeds, that is rest, elevation, ice. Reserving the small stocks of UK and animal sourced factor concentrates for the most serious bleeding episodes. With that approach there is a high morbidity and mortality. Not as high as with HIV before effective

therapy but clinically difficult to justify unless one knew the case fatality and survival rate for HIV, which we did not and could not know until much later.

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed GRO-C

Dated: 9th October 2020

Table of exhibits:

Date	Notes/ Description	Exhibit number