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EXPERIENCE IN ENGLAND.

I would like to take this Inquiry back to the period of 1983 – 1985 when the impact of AIDS [now HIV/AIDS] on the community of people with haemophilia was emerging. Much of the part of my testimony that relates to my period as a haemophilia centre doctor consists of memories of the time [I have very few notes or files from that time – these were left for my successor]. These memories have been reinforced by a number of sources, including papers released by SNBTS to various inquiries and investigations since 1999. I have also referred to original papers in the medical press and to the extremely valuable books “The end of innocence – Britain in the time of AIDS” by Simon Garfield and Douglas Starr’s “Blood – an epic history of medicine and commerce.”

From 1982 until 1992 I was a consultant haematologist at a large teaching hospital in England. There were two other colleagues, both of whom had University appointments and so between us there were two whole time consultants to run a busy laboratory, general haematology, sickle cell disease, leukaemia care, bone marrow transplantation and haemophilia. After I had been there one year or so I assumed the responsibility for the haemophilia care at the hospital, supported by an additional colleague who contributed about one day per week in time, but more in intellectual input.

There were about 100 severe patients registered, and another 2-300 more mild patients. There was one out patient clinic a week for routine review, which was run by two consultants, myself and my colleague, supported by registrars or senior registrars if one of us was absent. So the out patient clinic was a consultant delivered service. There was also a small, initially one room, treatment area where patients could attend on an ad hoc basis, to collect treatment and for those not on home therapy to receive urgent care. During the working day, a nurse was on duty for the haemophilia unit, but at other times patients would be seen by the duty haematology doctor. The nurse would also call for medical support as needed. This day area also stored patient treatment records, the Factor concentrates and the hospital case notes. When I started, there was a well established system of product and batch dedication – that is, one person would receive only one product and would remain on the same batch as long as that batch was available. This system continued, as I recall, throughout my time there. Some younger men led chaotic lives, and attended irregularly but quite frequently on an ad hoc basis for emergency care. A small number of such patients provided a substantial amount of the out of hours work. This service was barely adequate for the delivery of the treatment regime then current, which was home therapy based, but did not include prophylactic treatment at that time. Prophylactic treatment means that the person administers Factor VIII injections regularly, whether or not they are having a bleed. In the early 1980’s, treatment was administered at home when the person thought a bleed was starting.

It was on this base level of service that the AIDS problem arrived, and proved to have infected between 60-70 of the patients at my hospital.

- The culture then prevailing in the doctor patient relationship, issues around the consent to testing and the provision of information about test results – based on my own experience.

Those people with haemophilia who attended the clinic regularly would have consultations about their joints, their treatment, liver test results. We would have physiotherapy support at the clinic, as I recall, although this was dependent on the physiotherapist allocated to the service at any one time. There was anxiety about the emergence of AIDS from soon after I started on the haemophilia service, in later 1983. Advice from the reference centres and the Haemophilia Society seemed to be to carry on with the treatment. **[check out editorial from Jones in BMJ, December 1983]**. The World Federation of Hemophilia endorsed this approach in the summer of 1983 [as I will discuss]. By this time most, although certainly not all, patients had already been exposed to HIV [Garfield, p.69, suggests this occurred between 1979-1981 for patients on imported concentrates]. Should we have known more and done more? In retrospect, it is easy to see that more might have been done, but from the overall medical activity at the time it is not so easy to say that. The MRC first convened a Working Party on AIDS only in October 1983, so the greatest medical minds in the UK didn't take the issue on until then. Twenty-five years ago, I think the prevailing culture in medicine was that evidence was needed before action. From reviewing the papers from that time, the view prevailed that there was insufficient evidence to take dramatic action, although a few voices were raised and they proved to be correct in hindsight – although by then it was probably too late for many, or even most, patients.

Testing of patients has been a very controversial area, and it is clear now that some formal consent should have been obtained. But that was not the medical policy in the 1980's – and not only in haemophilia care. As quoted in Garfield [p.55], about the Middlesex Hospital approach at the G-U Medicine clinic;

'We performed a large number of anti-HTLV-III tests without written consent. Blood was taken from patients with AIDS, What we told the patients at that stage was that "We don't know what this test means. It may well mean that you've been infected with the virus and you've recovered. You've got antibodies, and you may be immune."'

This concurs with my recollection of my own practice. The regional virology laboratory offered a test sometime in early 1985. I have had sight of papers suggesting that we collected blood for such a test as early as January 1985. I do not think that we tested stored samples [as suggested by Garfield for another haemophilia centre, p.63] but I cannot be certain. My recollection is that specific blood samples were taken but specific consent not always obtained and consent certainly not recorded. I believe that the reason for taking the samples was discussed. Results took weeks to come back, and were stamped 'for research purposes only' as I recall. I imagine this was because the test was not yet approved for diagnostic use. I don't know why the tests took so long, perhaps because the kits were in short supply and the samples were batched up. The quote above explains the uncertainty over what the tests meant, and I have seen a note of a meeting in which an eminent virologist stated the possible meanings of such a result at that time – in the same terms. My colleague and I took a decision that results would only be given in person, and in the clinic. Results were not mailed out, nor were they to be given out in the treatment area which would have meant inexperienced staff giving out the result. This was to ensure that we could explain and discuss the results with the patient, and provide support. I

wouldn't say at that time it was counselling, but we wished to support the person at the time of giving out the news – as I would do for any communication of complex information or bad news to any patient. What we did not do, was recall people as soon as the results were available. In retrospect, we should have done this. This decision did lead to some months passing before a person might come back to clinic. Some time later, we did have to give some results out in the day ward area, because a small proportion of people repeatedly failed to come to clinic, and perhaps because the significance of a positive result was more clear. The emergence of AIDS was a turning point in the expectation that people expect to be asked, and consent obtained, before important, life changing investigations are performed. Prior to AIDS, implied consent was the doctrine. A person came to you with a problem and this gave consent to do all necessary tests to investigate it. The argument over whether it was permissible to test for HIV without first obtaining specific consent continued until 1988 [correspondence to BMJ; BMA Annual Conference, July 1988; advice to doctors from the General Medical Council, August, 1988].

- The resources available in that haemophilia treatment centre [not a Reference Centre] to cope with the emerging problem of HIV/AIDS.

At the time of the emergence of AIDS as a risk, my haemophilia unit had less than a half time consultant cover, the support of doctors in training, and one nurse. Quite early on, my colleague and I sought additional resources for counselling, medical staff and other infrastructure. After a few years, a counsellor was appointed, and larger accommodation obtained. A secretary was made available to reduce pressure on the nurse and to improve record keeping. A second nurse may have been appointed. Central government funding was made available for counselling towards the end of 1985 [Garfield, p. 64] but this was given only to reference centres [I do not recall the definition but my centre was not a reference centre, possibly because not all required services for haemophilia were on the one]. This meant that patients had to travel some hours to receive specialist counselling and this had to be arranged in advance – there was a wait – and what records I have suggest this did not happen until 1987. By this time we had a counsellor locally. Support for additional resources was not universal within the 'bidding' process – comments such as that all the patients would be dead in two years – a common perception in the early days – were not uncommon. Central government funding for AIDS was either not spent or was spent on other projects. This was a feature in my region [Garfield, p.197]. This continued into the 1990's, and it was not until then, maybe 1992, that a full time haemophilia consultant was appointed to the adult service in my city. The slow arrival of additional support was not helpful to either the medical care of people with haemophilia and HIV/AIDS, nor to their emotional or other support.

- The awareness of hepatitis as a problem associated with treatment with Factor VIII concentrates.

My recollection is that the discussion of abnormal liver tests in the haemophilia patients was a regular occurrence throughout the period of my time working as a haemophilia doctor. My colleague, Dr Foster, has identified the warnings on Factor VIII bottles, packaging and patient information sheets. Many patients developed abnormal liver tests or became jaundiced after their first exposure to concentrated Factor VIII in the 1970's. Although there was regular discussion and monitoring of blood tests it is true to say that the importance of this was not over-emphasised. Words such as 'transaminitis' were used, and the then non-A, non-B hepatitis [almost

all cases of which proved to be caused by the Hepatitis C virus] was not thought to be serious until a publication by a group from Sheffield carried out liver biopsies on their patients. This was published in 1985 [Hay et al.]. Shortly before this, a paper from Manchester had given a much more reassuring assessment [Stevens et al., 1983]. Few people with haemophilia received liver biopsies prior to the Sheffield study because of the need for considerable Factor VIII injections and the perceived risk of the procedure in patients with bleeding disorders. I do not recall there being any treatment, either, other than alcohol avoidance, until liver transplants were offered later in the 1980's. What was clear to me then and now, is that all of my colleagues preferred to use UK-derived Factor VIII because it was believed that these were safer from hepatitis – indeed, safer generally. There was never enough UK product and I recall meetings to discuss the allocation of what was available attended by haematologists treating haemophilia in the region. I recall being unhappy about the allocation to my hospital on at least one occasion. The bottom line was, that there wasn't enough to go round. I remember discussions about the situation in Scotland, that there was a much better supply of Scottish plasma derived Factor VIII available there.

- Some information about the treatment strategy at that time, and the advisory process for patients.

As I have stated, there was a preference for UK derived products, but there wasn't enough of it. I cannot recall on what basis a person would receive UK or imported product, but patients were treated by a batch dedication system, to minimise exposure to products and to batches of product. The idea of trying to reduce donor exposure was prevalent. When the first anxiety about AIDS arose there was discussion about what to do. I don't recall specific discussions at my centre, but I do recall communications from the late Professor Bloom, writing on behalf of the Haemophilia Society, I think, advising that the risk of bleeding was paramount and that patients should continue to use concentrates – and for most adult patients that meant imported products. I do not recall when this letter was sent out. However, Douglas Starr [p.276] states that a World Federation of Hemophilia meeting in June 1983 agreed a resolution that 'there is insufficient evidence to recommend, at this time, any changes in the treatment of haemophilia, therefore present treatment should continue with whatever blood products are available.' Starr makes clear that the Dutch were against this and that Bruce Evatt, a US expert on hemophilia, expressed a more cautious view. The precautionary principle as understood now, and used in the introduction of precautions against vCJD [although not as far as I am aware for BSE in beef], was not in evidence. Risk assessments were made, but seemed to come out in favour of the risk of bleeding being the most important, on the balance of probabilities and uncertainty about what was happening with AIDS. In retrospect, this balance does not seem wise, since the regular use of Factor VIII as home therapy was a quality of life, rather than life saving, approach. Most home therapy was for incipient joint or soft tissue bleeds. However, it was endorsed by most of the haemophilia treating community of which I was aware, and supported by the society. Members of the Society attended the meetings of the UK Haemophilia Centre Directors [later, Doctors] Organisation. I was present at one such meeting and members of the Society were active participants, not mere observers. I remember this because it was a new experience for me to see patient representatives [who were patients themselves] involved in the meeting.

At some point, heat treated products started to become available, and a decision was taken that only heat treated products should be used. From reading Starr's book, this appears to have been in December 1984. This was certainly when in Scotland heat treated product was first issued, and unheated Scottish products recalled and heated in the bottle. The impact in my service was quite severe, as I recall, because although we stopped using non-heated product, very little heated product was available, if any, for some time. Home treatment had to be suspended, and only emergency treatment was given. My recollection is that these changes were communicated to patients by us, and also via the Haemophilia Society to its members [but perhaps not all people with haemophilia were members]. Unheated products were actively recalled back to the hospital, so all patients had to be contacted and advised. At my hospital, I do not recall a 'mixed economy' of unheated UK product being used alongside heated US products in my centre, but I could be wrong at this distance in time. I recall unheated products, then virtually no products, then heated becoming available. For most of the adults at my hospital, heat treatment came too late.

- The extreme difficulty experienced by people with haemophilia, their families and the medical, nursing and other staff working in haemophilia centres in an atmosphere of an emerging, stigmatising and complex disease.

It is difficult to describe the degree of uncertainty and lack of knowledge that prevailed in the mid-1980's. Even after the impact of the HIV epidemic was clear, and we knew that positive tests meant the virus was present, the evolution of HIV disease was new, and protean. Respiratory medicine was not strong then – TB was seen as beaten and the management of the immune compromised was in its infancy – so I had to learn how to do bronchio-pulmonary lavage to diagnose PCP myself. I am grateful to over-pressed colleagues at nearby hospitals for helping with this. Some patients developed unusual complications of HIV disease – CNS infections, lymphoma, general wasting. By this time, 1987, we had more counselling support and my colleague was tireless in this area. But it didn't overcome the uncertainty. There was quite a lot of anger. This problem affected a community of patients with an inherited disease and some families had many members affected. A man might have nephews affected, and one family had three brothers all HIV positive. In the early period, soon after testing was available, we had all the cliched events. Patients having food left outside their rooms [as described in Garfield], over-zealous gowning up. A few instances occurred where consultants would not see patients who needed specialist advice – fortunately, I cannot remember precise examples. Other examples I do remember, of great humanity. One urological surgeon, confronted with an HIV positive haemophiliac needing bladder surgery, calmly said that he needed the operation, and we would have to find a way of doing it safely. The operation was performed successfully.

EXPERIENCE IN SCOTLAND.

The experience I have gained within SNBTS over the past decade would enable me to contribute, from personal involvement, discussion with colleagues and inspection of original documents, to the following issues:

- Self sufficiency in plasma products in Scotland.

From my reading of the relevant papers, and discussion with colleagues, I believe it is likely that Scotland was the first country in the world to have become self sufficient in home-grown, unpaid donor Factor VIII concentrates. This occurred some time in 1983. There was certainly sufficient Scottish derived Factor VIII available for the treatment of bleeding episodes using the regimes of treatment then current.

Furthermore, Scotland also was first to provide sufficient HIV safe heat treated Factor VIII for all its patients, in December 1984, within weeks of the awareness that heat treatment of freeze dried concentrate would work. This was clearly a major feat that avoided the exposure of many patients to HIV.

Thirdly, Scotland was the first country in the world to have sufficient Hepatitis C safe heat treated Factor VIII for all patients in 1987, and was the second country to have such a heat treated product. The English product 8Y was released earlier, in 1985, but was in short supply and was never, in my time as a haemophilia doctor, available for all patients. In my view, therefore, it is a misrepresentation to imply that Scotland did not introduce Hepatitis C safe product quickly enough when this was achieved many years before, for example, Australia, France and the United States.

SCOTTISH SELF SUFFICIENCY IN FACTOR VIII.

Factor VIII is a complex molecule, the structure of which was poorly understood in the 1980's. For some decades fresh plasma or blood transfusions were the only treatment for haemophilia, and this left a legacy of crippling joint disease in the surviving patients. Most of the older men with haemophilia under my care had such disabilities. The use of cryoprecipitate – which is made from plasma in a cold room – improved greatly the treatment of serious bleeds, but it is a cumbersome and large volume treatment, at least in adults. It is not portable as large amounts of cryo must be kept in a freezer. Concentrates replaced cryoprecipitate [cryo] as the treatment of choice because they had more Factor VIII – the active ingredient – in them and they were portable, relatively quick to make up and could be stored in a domestic refrigerator. So the new concentrates were easier to dissolve and were portable.

Making the new concentrates was a highly sophisticated process, and was undertaken by a range of companies – largely those already in the albumin business – or by blood services. In the UK, three NHS laboratories were working on this. The SNBTS facility in Edinburgh (The Protein Fractionation Centre - PFC), one in Oxford (The Plasma Fractionation Laboratory - PFL) and at Elstree (The Blood Products Laboratory - BPL). The product from the English NHS was, I recall, known as 'Lister.' I think this reflected its earlier origins at the Lister Institute in London, but was probably by now an anachronism.

At this time, Factor VIII was unstable and tended to co-purify with Fibrinogen and Fibronectin, which are particularly difficult proteins to deal with because of their poor solubility and adherent nature. That is, they all tend to stick together and turn to glue.

Despite SNBTS collaborating with the leading US expert at the time, the product was found to be extremely difficult to manufacture, because of the instability of Factor VIII activity and the poor processing characteristics of the other proteins present. Consequently processing was always problematic, Factor VIII yields were low, capacity was very limited and there was insufficient Factor VIII available to meet patient needs. These are important issues to recall when considering the technical difficulties of heat treating these protein soups that want to turn to a gel.

In order to increase its output of Factor VIII, the SNBTS undertook a programme of research aimed at resolving the scientific and technical problems, which were limiting output, and also sought to obtain more plasma for fractionation by changing the way in which blood donations were being used clinically. That is, it is not enough to have a method for making Factor VIII, the unpaid, volunteer source plasma had to be obtained, too. The drive to make enough Factor VIII for all patients in Scotland required more donors, more plasma removal from the donations, and the factory. The research bore fruit and these advances enabled Scotland to have available, from its own blood donor population, sufficient Factor VIII for the treatment of all people in Scotland with haemophilia A according to the then current UK clinical practice (i.e. to be self-sufficient in Factor VIII concentrate derived from unpaid blood donors). I believe that this degree of self-sufficiency was achieved in Scotland in 1983. As we have heard, many other parts of the world continued to rely on imports of US derived, paid donor plasma for some considerable time.

- The development of heat treatment as a virus safety measure, in which SNBTS was a world leader.

SNBTS worked throughout the 1970's to try to remove the risk of hepatitis from coagulation factor products, collaborating on research into methods for removing viruses from Factor VIII and Factor IX concentrates. Some products had been exposed to heat treatment, but there was evidence in the medical and scientific literature that heating could cause damage to the Factor VIII molecule, and that even then it might not prevent hepatitis transmission. If heat treatment were to go wrong then patients might react to the Factor VIII by producing antibodies to it – because the heating had made the protein foreign – and that these antibodies would stop future Factor VIII infusions from working. These antibodies are known as inhibitors of Factor VIII, and after virus infections are probably the most serious complication. So it was, and is, vital that any Factor VIII product does not produce inhibitors. SNBTS had been carrying out work on heat treatment and it was known that the current product [NY] could withstand dry heat treatment for up to 24 hours at 60°C or for up to 2 hours at 68°C before becoming insoluble – turning to egg white.

HIV safe Factor VIII concentrates.

The stakes were raised substantially once HIV was discovered in 1984, and a test became available for HIV antibodies soon afterwards. This development also enabled laboratory experiments to be done on whether heat treatment would be effective against HIV. Preliminary results on the efficacy of dry heat treatment of Factor VIII were first reported on 2nd November 1984 at a meeting in the Netherlands at which SNBTS scientists were present. The data presented demonstrated that a substantial degree of inactivation of HIV was obtained after 'dry' heating Factor VIII at 68°C for

1 hour; we already knew from our own studies that the SNBTS NY product could tolerate heating at 68°C for 2 hours. The availability of the test also showed that a number of Scottish haemophiliacs, who had only ever been treated with SNBTS products, were HTLV-III [HIV] positive, indicating that contamination of the Scottish blood supply with HIV was already taking place. It was decided to take all of the SNBTS Factor VIII already manufactured and in stock and 'dry' heat treat it at 68°C for 2 hours. This provided an immediate supply of product which was HIV-safe. By heat treating the existing stocks of product, representing almost 12 months supply, we were able to ensure that all Factor VIII issued by SNBTS from December 1984 onwards would be HIV-safe. Product that had been issued was recalled and heated. In this way sufficient heat-treated, HIV-safe Factor VIII was available to treat all patients in Scotland from the end of 1984. Further developments were made to the process and this work was completed in time for 24 hour heat treatment of FVIII to be introduced in January 1985. If this had not been done, it is known now that four batches of Factor VIII produced at that time would have transmitted HIV, but did not do so because of the heat treatment.

Hepatitis C safe Factor VIII concentrates.

It was known that 68°C was not warm enough to eliminate the risk of transfusion associated hepatitis, and so efforts to achieve this continued. During 1984, PFL colleagues in Oxford discovered that one of their experimental preparations was able to withstand 'dry' heat treatment at 80°C for 72 hours. This was a unique achievement, which was expected to provide a greater margin of safety against the risk of HIV transmission. At this time there was no information to indicate if 80°C 'dry' heat treatment would have any effect on hepatitis viruses. It was thought generally that the more fierce the heat the better the safety would be, provided that the Factor VIII remained in good condition and inhibitors were not produced. Scientists at SNBTS in Edinburgh identified that it was the nature of the freeze drying process rather than the purity of the product which was critical to achieving 'dry' heat treatment at more severe conditions. SNBTS / PFC set to work to develop a process for making a new product, and this change in strategy was endorsed by SNBTS Management in February 1986.

The new 80°C product was known as Z8. Sufficient stock of the HIV safe product was available and so attention shifted to a new product. Further fine-tuning of the process was required at full production scale, as some of the initial batches of Z8 were unable to tolerate heating at 80°C and were instead heated at 75°C for 72 hours. I am advised that both these proved to be HCV safe. Full-scale production of Z8 was begun at PFC during the Autumn of 1986. However, before the product could be issued routinely it was necessary to undertake a clinical evaluation to ensure that the product was effective and well tolerated – especially that it did not produce inhibitors. The clinical evaluation of tolerability and effectiveness of 80°C heated Z8 was undertaken in March-April 1987, with satisfactory results enabling the product to be available for routine clinical use from April 1987. Additional data on the safety of the BPL 8Y were published in 1988 and these were consistent with the interim results reported in 1986. Further clinical studies have since confirmed both BPL 8Y and Scottish Z8 have been free from the risk of hepatitis transmission.

- The development of new Factor VIII products and the ethics of their production.

As might be seen from the above, the development of new Factor VIII products by SNBTS was a major enterprise, driven by the desire to produce sufficient safe products for patients. I would like to try to clarify some misconceptions about how these new products were developed that are apparent in other evidence submitted to the Inquiry. SNBTS has never provided any products for clinical use to which viruses have been added deliberately. In order to test whether new products are safe to use, or to check whether the steps – heating in this case – to reduce the virus risk have been effective, it is necessary to add virus to samples and then see if the heating step kills them. These steps are undertaken in a strictly controlled way, separate from material meant for patients. In addition, the actual virus that is the concern in humans is not normally used for the tests. This is a measure to further protect staff working on the safety testing. In this way, non-human versions of the relevant virus are used e.g. BDV instead of HCV. It is a matter of regret that it should even be thought that such unethical testing as giving deliberately contaminated treatments for patient use could have occurred. Such experiments were never done by SNBTS. Some of the details of the use of chimpanzees for testing of hepatitis C safety will be addressed by a colleague, but it is not my view that these tests would have been helpful. SNBTS did not carry out the clinical trials of its own products. However, from reading the papers available to me, it appears that such clinical trials were consistent with the then guidance of the WHO and the other professional bodies for testing new coagulation factor products. These specified a particular number of patients who had previously not been treated with coagulation factors. Until the mid-1990's these continued to require exposure of such untreated patients by EU requirement.

- Look-back studies on hepatitis C positive blood donors as performed in Scotland.

In Scotland, SNBTS performed a feasibility study on HCV lookback from the Edinburgh site and this was eventually published in *Transfusion Medicine* (1994; 4; 269-272), around the time that interferon therapy had been shown to be around 20-50% effective (50% responded but only about 50% of these were durable, by my recollection). This prompted the national UK HCV look-back and data for the UK was collated by the Health Protection Agency.

Multi-transfused recipients were HCV screened from 1991 onwards such that most haemophiliacs, renal dialysis patients and leukaemia patients were screened prior to the UK-wide HCV look-back in 1995. This look back was associated with a letter from the Chief Medical Officer.

Donors who donated only prior September 1991 were not traced, since there was no way of knowing which ones would have been Hepatitis C positive. To do this would have required the testing of the whole SNBTS archive sample library dating back to 1985 – well over 1,000,000 samples. Also, the rest of the UK did not have such a comprehensive archive of samples, and so any more detailed look-back could only have been done in one part of the UK. We know of no other country that performed this type of look-back procedure.

Soldan and Barbara published a paper on the impact that transfusion associated HCV has had on the overall HCV picture. They calculated that in the UK up to 5-7% of HCV in the community might have been acquired by blood transfusion. This equates to some 7,550 – 15,000 people UK wide, and perhaps 1,500 people in Scotland.

SNBTS has a formal process for investigating cases of putative, or alleged, transfusion transmitted Hepatitis C. Investigations of 46 potential transfusion transmitted infections ten were confirmed due to blood transfusion. *Every one* of the HCV cases were from before testing began in 1991. It was possible to exclude transfusion as the risk in those transfused after 1985 because of the donation sample archive, but not prior to that. .

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LESSONS LEARNED

Need for consent.

Precautionary principle.