BBC Scotland : Frontline Scotland

Risks:

1) We understand that as early as 1978 there was a known risk attached to large pool (i.e Factor VIII) blood products.

"Systematic screening of forty-seven haemophiliacs in Sheffield revealed abnormal liver function tests in thirty six (77%)...A wide spectrum of chronic liver disease was demonstrated, including chronic liver hepatitis and cirrhosis....The high incidence of chronic liver disease seems to be a recent development and probably related to factor concentrate replacement therapy."

(Percutaneous Liver Biopsy and Chronic Liver Disease in Haemophiliacs, **F, E Preston** et al, The Lancet September 16, 1978)

2) Concerns were raised in the Lancet in 1982.

"Hepatitis as a complication of treatment remains a substantial difficulty....The oncogenicity of the non-A, non-B group of viruses is unknown, but the possibility of risk cannot be ignored....Elimination of the risk of hepatitis in the treatment of haemophilia and related disease would represent a major step forward in the long-term management of these congenital bleeding disorders."

(Hepatitis and Haemophila Therapy in Australia, The Lancet, July 17 1982)

3) A BMJ article in 1983 suggested NHS Factor VIII was causing liver problems:

"Thirty patients who had not previously received treatment with factor VIII concentrate or who had been treated only infrequently with Factor VIII concentrate were studied after a transfusion of Factor VIII....All of the nine patients who had not previously received Factor VIII transfusion developed non-A non-B hepatitis. Four out of 10 patients followed up for a year had persisting abnormalities of liver function. The pattern of illness suggests that more than one serotype of non-A non-B hepatitis virus may be transmitted by factor VIII concentrate prepared by the National Health Service..."

(Non A Non B hepatitis after transfusion of Factor VIII in infrequently treated patients, British Medical Journal, 10th December 1983)

4) In 1983 the First UK Haemophiliac died of Aids (Fatal AIDS in a UK Haemophiliac, Lancet. November 1983)

5) Knowledge that the first heat treatment processes eliminated HIV but not NANB Hepatitis:

"Dr Foster said it was known in 1985 that, while heat treatment processes were effective against HIV, that they didn't inactivate NANB Hepatitis."

Early awareness of the need to eliminate NANB Hepatitis:

"Dr Foster said that the initial motivation prior to 1983 to undertake research on viral inactivation in factor concentrate products was a fear of the transmission of NANB Hepatitis. Dr Foster said that this was a very serious concern and there was also a belief that commercial products carried a higher risk of NANB transmission than products manufactured in Scotland. However, Dr Foster said they didn't have evidence in the late 1970's that the consequences of contracting NANB Hepatitis included the development of cirrhosis and possible chronic active Hepatitis"

(Lindsay Tribunal, Day 162, Evidence of Dr Peter Foster, Manager of SNBTS Protein Fractionation Centre.)

6) An Article in the Lancet in 1984 recommends the use of cryoprecipitate and DDAVP over Factor VIII because of the risks:

"In the UK unheated large-pool concentrates, even those prepared from voluntary donations, have transmitted non-A, non-B hepatitis , and we learn that a first-generation dry heated concentrate has also transmitted the disease...."

"Cryoprecipitate (or fresh frozen plasma for haemophilia B) prepared from a small number of donors is recommended for the treatment of children under 4 years of age and newly diagnosed patients....

"DDAVP is effective only in mildly affected patients with haemophilia A and von Willebrand's disease but is an attractive option in this group who are at high risk of infection from concentrates."

(Blood Transfusion, Haemophilia, and AIDS, The Lancet, Dec 22/29, 1984)

7) In 1985 A Lancet article suggests the safety of small donor pool products over even heat-treated large pool products when it comes to NANB hepatitis:

Letter reporting severe reactions in two patients given Armour heat-treated FVIII: "Both patients became ill with malaise, nausea, and jaundice. Patient 1 required admission to hospital. He had severe jaundice...which persisted for 16 weeks....NANB hepatitis was diagnosed. (This)...contrasts with the uneventful progress of the third patient, given 11 675 units of small donor pool, dry-heat treated, intermediate purity NHS FVIII concentrate...her hepatic indices have remained persistently normal."

(Non A Non B Hepatitis and Heat Treated Factor VIII Concentrates, **F. E Preston** et al, The Lancet, 27th July 1985)

8) Article in the Lancet in 1985 suggests Factor concentrates associated with chronic liver disease:

"In an 8-year study of 79 unselected patients with haemophilia who had received clotting factor concentrates, there was evidence of chronic progressive liver disease in at least 17 (21%). 8 patients had chronic active hepatitis and 9 had cirrhosis (5 with oesophageal varices). Histological evidence suggested that non-A non-B hepatitis was mainly responsible, although the influence of other viruses could not be excluded. Serial liver biopsies showed progression from chronic persistent hepatitis to chronic active hepatitis and cirrhosis within 6 years, suggesting that chronic persistent hepatitis in haemophiliacs is not as benign as hitherto supposed."

"Abnormal liver function tests have been reported in 20-100% of patients with haemophilia who have received blood products."

(Progressive Liver Disease in Haemophilia: An Understated Problem?, **F.E Preston**, The Lancet, 29th June 1985)

9) Article in the Lancet in 1985 refers to 100% rate of infection of NANB hepatitis following treatment with Factor VIII:

"Clotting factor concentrates manufactured from thousands of units of pooled plasma are likely to transmit viral infections to haemophiliacs. The risk of post-transfusion hepatitis B is reduced but not abolished by screening donors for hepatitis B surface antigen (HBsAg), and HBV vaccination may reduce this risk even further. However non-A, non-B (NANB) hepatitis, with an attack rate close to 100% in haemophiliacs not previously exposed to blood or blood derivatives..remains a formidable problem."

"13 Haemophilia A patients who had not been treated previously with blood or blood products were given a dry-heated factor VIII concentrate....Hepatitis developed in 11 patients (84%) and was invariably of type non-A, non-B."
(Transmission of Non-A, Non-B Hepatitis by Heat Treated Factor VIII Concentrate, The Lancet, 6th July 1985)

10) We have spoken to a lab technician who worked in the laboratories of Glasgow Royal Infirmary who admits there was a kind of 'denial' that the Scottish population might also be carriers of HTLV III/HIV, that one Haemophilia Director in the West of Scotland decided to warn his patients about the risks, and that Aberdeen was late in bringing in screening for HTLV III:
Study carried out by Glasgow Royal Infirmary Department of Medicine laboratories, (done in 1982/3 and published in the British Medical Journal in 1983; vol 287, pages 1091-1093) found the same immunological abnormalities in haemophiliacs as were found in people dying of this new disease (Aids) in the US and Haiti. But authors mis-interpreted data, suggesting the abnormalities might be being caused by factor VIII itself.
When the virus was identified, serum samples were sent for identification. 16% were antibody positive (published in the Lancet, 1984; vol ii, pages 1444-1446) and they knew Aids was in the haemophiliac population:
"I suppose, in retrospect, we had been showing the kind of denial - that HIV is not something that we in Scotland needed to be concerned about - that most communities around the world have shown since.
Dr (now Professor) Forbes, then Head of the West of Scotland Haemophilia Unit, and head of the research team, understood the implications of these results immediately, and told all the haemophiliacs that, by using factor VIII, they were at risk, not only of being infected, but of passing the infection on to their sexual partners. He also counselled them about safe-sex (ie condom use). The antibody test was still at the early stages of being developed, and there was still some uncertainty about the reliability of individual results. In time, as individual results were confirmed, those who were antibody positive were told.
In July 1985 I went to work for the Blood Transfusion Service in Aberdeen, and was very surprised to found that blood was not being routinely screened for HIV (then still called HTLV-III). They did not appear to be treating the issue of possible blood contamination and HTLV-III infection with the urgency that I felt was required.

11) Testimony from a leading academic at the Lindsay Tribunal suggests it was known during the 1980's that NANB Hepatitis was a serious virus, and was transmitted by Factor concentrates:
Testimony of Eric Preston From the Lindsay Tribunal:
Prof. Preston reiterated his belief that in the late 1970s and early 1980s, it was known that NANB Hepatitis could progress. He accepted that there may have been two views, but it had always been his view that NANB was progressive. Prof. Preston said that his views about the progressive nature of NANB Hepatitis would have been known to treaters of people with haemophilia and would have been discussed.
...Prof. Preston said it was clear from studies by Fletcher and others, that there was a 95%-100% chance of transmission of NANB Hepatitis using other factor concentrates

12) This known risk was acknowledged by the Lindsay Tribunal in Ireland:
"It was understood that the risk of infection from concentrates made from large pools of plasma was higher than the risk of infection from products made from single donations or small

pools of plasma. It was probably generally thought that concentrates fractionated from donations from paid donors carried a higher risk of infection than concentrates fractionated from voluntary donors"

"The evidence from Dr. Prince and Professor Preston was, however, clear that in the period up to June 1982 the consensus or general view of NANB hepatitis remained that it was relatively mild or benign. Professor Preston stated in evidence that the general consensus at the end of the 1970s coming into the early 1980s was that while NANB was persistent and chronic, it was not considered to be dangerous or very serious and that most individuals would have been of the view that it was relatively mild, although worrying because it was there."

Screening/minimising the risk:

13) Tests should have been in place to screen out blood donations containing risks such as syphilis:

"Tests for infectious agents:
....each donation of whole blood shall, if required by national authorities, be subjected to a serological test for syphilis. If so tested, only units giving negative results shall be used for transfusion or component preparation"
(29th Report of WHO Expert Committee on Biological Standardization, 1978, p36)

14) The Council of Europe introduced protocols in 1983 which should have been implemented to reduce the risk of transmitting diseases through blood products:

"Recalling the basic principles to minimize the hazard of transmissible infectious diseases by blood or blood products drawn up in the context of the work of the Committee of Experts on Blood Transfusion and Immunohaematology:

1. to expose the recipient to a minimum number of donations of blood when the transfusion is of cellular and coagulation factor products....

...to avoid wherever possible the use of coagulation factor products prepared from large plasma pools"
(Council of Europe, Committee of Ministers, Recommendation No R (83) 8, 23 June 1983)

15) In 1984 other countries in Europe began introducing precautions to prevent the risks of transmission of AIDS and other Immunological Disorders:

"A questionnaire...was sent to directors of 201 European countries....Of 135 respondents 40 admitted to a recent change of clinical practice presumably due to the development of AIDS in treated haemophiliacs. Among these 40 the changes were as follows: stopped using US material, 7; reduced US material, 23; increased use of cryoprecipitate, 26; increased use of FFP, 8; stopped prophylaxis, 4; stopped elective surgery, 5; advised curtailment of activities, 11; and increased use of heat-treated concentrate, 4. A high proportion of haemophilia physicians in some countries (e.g Netherlands and Sweden) had changed their practice but overall about two-thirds had made no changes."
(Acquired Immunodeficiency Syndrome and Other Possible Immunological Disorders in European Haemophiliacs, The Lancet, 30th June 1984)

Donor Selection:

16) We understand that in 1978 the WHO had advised that donor selection was of utmost importance, and all measures should have been taken to prevent blood collection from risky sources:
"Countries with a low incidence of hepatitis should not use whole blood or blood products obtained from source material collected from an area in which there is a high incidence of hepatitis."
"National health authorities shall develop policies designed to prevent the transmission of other infectious diseases based on the prevalence of these diseases in the donor population and the susceptibility of recipients to the same diseases."
(29th Report of WHO Expert Committee on Biological Standardization, 1978, p36)

17) The Scottish Executive has confirmed that there was no data confirming whether prisoners were, or were not, a high risk population during the 1980's:
"Enquiries of the Scottish Centre for Infection and Environmental Health (SCIEH) indicate that neither SCIEH nor the Scottish Prison Service hold any date relating to hepatitis infections in prisoners for the period in question" (i.e 1980's. Parliamentary reply from Andy Kerr, Health Minister to letter from Fergus Ewing, MSP, 4th Feb 2005)

18) In 1983 the Council of Europe also advised about the importance of selecting donors from non-risk groups:
Recommendations "To achieve national self sufficiency in the population of coagulation factor products from voluntary non- renumerated donors.
To avoid the importation of blood plasma and coagulation factor products from countries with risk population and from paid donors."
(Preventing the possible transmission of aids from affected blood donors to patients receiving blood or blood products, Council of Europe recommendations, 1983 <1st minute expressing concern – 1982>)

19) In 1984 it was known that Americans were a high risk population for Aids:
"In USA there are over 6,000 cases of AIDS including 52 haemophiliacs"
(Aids Advisory Document, Haemophilia Centre Directors Organisation, Dec 1984)

20) In the same month an article in The Lancet again referred to the importance of donor selection:
"The aim of plasma fractionators should thus be to prepare factor concentrates from non-infected donors and to ensure sterility before use."
(Blood Transfusion, Haemophilia, and AIDS, The Lancet, Dec 22/29, 1984)

Facilities:

21) In 1978 the World Health Organisation highlighted the importance of proper facilities for blood processing:
"The premises shall be of suitable size, construction, and location to facilitate their proper operation, cleaning, and maintenance in accordance with accepted rules of hygiene....and in addition provide adequate space, lighting and ventilation for the following activities where applicable:...Processing and distribution of whole blood and blood components in a manner that prevents contamination, loss of potency, and errors."

(29th Report of WHO Expert Committee on Biological Standardization, 1978, p36)

Informing patients:

22) In 1983 the Council of Europe directed member states to inform haemophiliacs of the health hazards of haemotherapy:
"To take all necessary steps and measures with respect to the Acquired Immune Deficiency Syndrome and in particular:....to inform attending physicians and selected recipients, such as haemophiliacs, of the potential health hazards of haemotherapy and the possibilities of minimising these risks."
(Council of Europe Committee of Ministers, Recommendation no R(83)8, 23 June 1983)

23) In Dec 1984 an article in The Lancet refers to counselling patients with HTLV III and highlights the importance of this as the virus may be transmissible to close contacts:
"Ethical questions are raised by HTLV antibody testing of blood donors and haemophiliacs. An unenviable task will be the counselling of people with positive results – a task made all the more necessary by the detection of virus in semen and saliva..."
(Blood Transfusion, Haemophilia, and AIDS, The Lancet, Dec 22/29, 1984)

24) In the same month the Haemophilia Centre Directors Organisation AIDS Advisory Document instructed clinicians to inform HTLV III infected patients, counsel them and advise them about transmission:
"Ab positive people should be informed, reassured and counselled regarding transmission to spouses etc., including the possible use of barrier contraception. This seems to be the most practical method available."
(Aids Advisory Document, Haemophilia Centre Directors Organisation, Dec 1984)

Infection of Scottish haemophiliacs with a batch of Factor VIII contaminated with HTLV III/Aids:

25) In Dec 1984 the Haemophilia Centre Directors Organisation were aware Aids had been transmitted by a batch of SNBTS Factor VIII:
"It seems probable that HTLV III has been incorporated into at least one BPL and one Scottish batch of Factor VIII. Recipients are being followed up..."
(Aids Advisory Document, Haemophilia Centre Directors Organisation, Dec 1984)

26) Reference to a previous study carried out on these haemophiliacs in 1983:
"We have now confirmed, by testing stored serum samples, that at the time of our previous study (Spring 1983) all the patients who received solely SNBTS blood products did not have anti HTLV III."
(Human T-Lymphotropic Virus Type III/HTLV III Infection in Seronegative Haemophiliacs After Transfusion of Factor VIII, C. **A Ludlam** et al, The Lancet, August 3 1985.)

27) An a contemporaneous article in The Lancet in 1985, authors note that for such a study they had obtained written informed consent:
Authors of a study on patients note: "21 patients...gave their written informed consent."
(Transmission of Non-A Non-B Hepatitis by Heat Treated Factor VIII Concentrate, The Lancet, 6th July 1985)

28) Article in The Lancet refers to a study of these haemophiliacs:
"In 1983 we measured immune function in a group of haemophiliacs in Edinburgh. In 1984, 18 of these patients became infected with HIV-1 from contaminated factor VIII. We have followed-up these patients since their seroconversion."

(Determinants of HIV disease progression: six-year longitudinal study in the Edinburgh haemophilia/HIV cohort, Christopher **A. Ludlam** et al, The Lancet, 9th November 1991)

28a) Article refers to frequency of study of these haemophiliacs:
"In Edinburgh we have had the opportunity to study a unique group of haemophiliacs who became infected in the Spring of 1984 by transfusion of a single batch of factor VIII concentrate....This cohort of haemophiliacs has become one of the most extensively studied groups of HIV infected individuals in the world...A great deal has been learnt from the careful study of these unfortunate individuals."
(The Edinburgh Haemophiliac Cohort, MRC News, Sept 1990, No 48)

Extracts of Minutes of meetings of Regional Transfusion Directors, SNBTS, Haemophilia Centre Directors and others:

29) Regional Transfusion Directors' Meeting, 15th October 1980: Self sufficiency:
"Because of exploitation of plamapheresis donors in developing countries and the risks of transmitting hepatitis international opinion was recommending national self-sufficiency in blood products."

30) Haemophilia Directors Working Party Report 1980-81
Study of NANB Hepatitis, transmitted by Factor VIII, and awareness that risk increases with commercial products:
"Table 1 shows the preliminary results of hepatitis reports where there was enough information to categorise these incidents and being related to Factor VIII or IX therapy...A total of 283 episodes of hepatitis were reported....Of the total of 283, 197?(unclear) were non-B hepatitis and therefore probably non-A non-B...The question of the significance of chronic hepatitis observed by several groups of workers in liver biopsies of patients with chronically elevated transaminases is still unanswered...there is strong evidence that different types of non-A, non-B hepatitis are related to different products (see later.) Most patients in this group are still entirely symptomless. The natural history of there (sic) disease in non –haemophiliacs is still not known...There have been no further deaths directly or indirectly attributed to liver disease in the past year.
...Incidence of hepatitis due to commercial versus NHS associated hepatitis:
Table (2) compares the figures for B and non-B hepatitis in patients receiving only one product in any year for the years 1977-9 and was presented in last years report. It shows that there is a 4-20 times higher incidence of overt non-A, non –B hepatitis associated with U.S Commercial concentrate compared with NHS...
...70-80% of cases of non-A non-B hepatitis were associated with the first dose of concentrate that the patient received....Most of the patients treated with any batch of concentrate will be immune to non-A non-B hepatitis, since batches of concentrate of any brand are contaminated with one (or more) serotypes of these agents."

31) Directors of SNBTS and Haemophilia Directors meeting, 30 January 1981
Recognition Scotland should be self-sufficient:
"The Chairman introduced paper 81/2, a Council of Europe Recommendation concerning blood products for the treatment of haemophiliacs....(it) urged member states to become self-sufficient in these products."

32) SNBTS Directors Meeting, June 1981: Minutes refer to transmission of NANB Hepatitis by transfusion. Proposals for studies of NANB Hepatitis to MRC.. "Dr McClelland offered to circulate to the Directors the test of a leading article in the New England Journal of Medicine of 23 April 1981..."

33) Medicines Inspectorate Report, 1st October 1981, Protein Fractionation Centre, Edinburgh. Following inspections on 11th/15th June by D Haythornthwaite and on 30th September-1st October by K J Ayling and D Haythornthwaite.
"The present buildings and facilities continue to fail to reach minimum standards of GMP, and a licence would not be recommended for an industrial equivalent unless agreed upgradings were instituted as a matter of urgency."

34) SNBTS minutes 16th March 1982: Testing for hepatitis:
"Dr Cash recalled that the SNBTS had proposed to the NBTS Directors that a UK Working Party should be established on the subject of microbial contamination of blood products. It had been noted at the previoius meeting that the proposal would be considered at the NBTS Directors' meeting in February. In the event the item had been deferred from lack of time and Dr Wagstaff had written on 25 February to all the Directors asking for their views on a proposal to studay post-transfusion hepatitis. Dr Cash agreed to draw Dr Wagstaff's attention to the fact that the SNBTS proposal had not been confined to hepatitis. Dr Cash reported that the MRC's Blood Transfusion Research Committee had decided recently to disband their Hepatitis Working Group, because a number of groups in the UK were studying hepatitis."

35) Medicine Inspectors report, visit to Aberdeen and North East Scotland Transfusion Service, 24th March 1982 (Mr K J Ayling, Mr D Haythornthwaite)
Contaminated blood transfused in error:
"Storage Facilities
This Centres suffers from a chronic shortage of storage space, hence one of the needs for a new facility.
Access to this is via the Grouping Laboratory. It is hopelessly overcrowded. Erroneous issue from this store has resulted in hepatitis positive blood being transfused on one occasion, yet it is still not possible to physically segregate between quarantined and cleared stock and there is a danger of HBsAg positive blood being issued."

36) Medicines Inspectors Report following visit to East of Scotland Blood Transfusion Centre, Dundee, 25th March 1982. (Mr K J Ayling, Mr D Haythornthwaite)
Not licenced:
"Licenses held by the Centre expired on 30 June 1981 and have not been renewed."
Blood from prisoners:
"Brief discussions were also held on sources of donated blood. At the time of this visit the Inspectorate had not visited donor sessions with 'Mobile Teams'. However it would seem most unlikely that we could continue to endorse the continued collection of blood from such places as Prisons and Borstals.

This recommendation is based on the following:

(a) Prison Medical Officers are often not involved in assessing the suitability of donors.
(b) The increased risk of infection associated with prison populations and the increased risk of transmitting disease through such donations.
(c) The unreliable answers to the pre-donation questionnaire that can occur in such environments as well as the motive of some of the donors."

Dangerous storage:
"Corridors were being used to store material as diverse as:
Product eg stable plasma protein solution.
Materials potentially contaminated with hepatitis
Fresh frozen plasma on a temporary basis awaiting collection by the PFC van.

<u>37) Medicines Inspectors Report following a visit to Edinbugh and SE Scotland BTS, 10-11 March 1982 and 10-12 May 1982.</u> Inspectors Mr D R S Warburton and Mr D Haythornthwaite.

A highly critical report:
"This proved to be a difficult Centre to inspect. This was caused partly by the considerable changes in progress. There is no doubt that the existing facilities for the processing and handling of blood are grossly deficient and would have been quite unacceptable. It therefore seems unreasonable to 'dwell' unnecessarily on facilities which will only be used for 3-4 months....A further inspection of Edinburgh will therefore be necessary within 6 months."
No licence: "The manufacturing licence for this Centre expired on 30 June 1981 and no application has been made for renewal"
Criticism of use of prisons and borstals: "The location of bleeding and type of donor. For example, whether Prisons and Borstals were really appropriate or necessary as a source material."
Other criticisms about manufacturing methods:
"The surprising practice of retaining blood routinely at ambient temperature for up to 18 hours. Two new refrigerated vans have recently been purchased so presumably this practice can cease immediately. Certainly protocols should be established for this process."
"Edinburgh is a Centre which appears to do a number of activities 'differently' from elsewhere. The full significance and range of 'differences' was not gone into due to lack of time. It is not suggested that a difference 'per se' is important but they might rank as 'query-able'. (Examples include: storage of washed red cells for 5 days (elsewhere 12 hours); the time lag before blood is cooled; differences in centrifuge practice; repeat checks in Grouping which rely on the use of the same reagents and the same equipment; pigtail packs; lack of agitation and close temperature control of platelets."
"Entry for staff and materials is via the back door where one is confronted with an appalling mess of rubbish which is totally inadequately controlled and removed. Whilst it may be very difficult to control the cockroach and rodent infestation in old buildings of this type, the unacceptable health hazard posed by the additional material in this area must be given continuing priority attention by the hospital authorities."
"Hepatitis and Microbiology:...the autoclave located here used for inactivating contaminated items still runs on a pressure guage (20 lbs for 45 minutes) and has not been checked or regularly maintained."
"Brief discussions were held over the matter of QC tests. Much reliance would seem to need to be placed on 'accrediting' the donor as per WHO guidelines."
"Existing facilities are quite inadequate and must rank amongst the worst seen anywhere."

38) Directors of SNBTS and Haemophilia Directors - 21st January 1983 – not self sufficient in blood products:

"Concern was once again expressed about the amount of commercially produced Factor VIII which was still being purchased ....It was noted that while purchases of commercial FVIII had declined in Glasgow....purchases in Edinburgh had increased. Dr Ludlam explained that the reasons for the use of commercial material in Edinburgh were partially clinical, and partially a policy of conserving a cushion of NHS VIII against an anticipated shortage when production at the PFC would be suspended to carry out alterations required by the Medicines Inspectorate..." *(presumably in response to the inspection report noted above.)*

"The Chairman stressed that the SNBTS had been set up to have the capability to cope with all Scottish requirements, other than those few therapeutic agents the production of which might not be justified on a very small scale, and that in terms of national policy the purchase of commercial products should be avoided so far as possible."

Commercial concerns:

"Heat Treated FVIII Concentrate Associated with the foregoing development the PFC was also going ahead with the development of a heat-treated product with reduced risk of transmitting hepatitis. However concern was expressed about the commercial firms who were anxious to capture the market for their own heat-treated product, and by offering supplies of their material for clinical trials might pre-empt the available suitable patients before the PFC product was ready for similar trials. Mr Watt explained the problems which had to be overcome in preserving acceptable yields and providing a product which was not too expensive, consideration that were of less importance with the commercial product. Directors were made aware of fierce competition facing the PFC from commercial concerns ans were asked to bear in mind the stated policy for the Scottish Health Service to be self-supporting in blood producs. The PFC would have limited amounts of heat-treated Factor VIII available for trials in the near future, and haemophilia directors agreed to support the PFC as much as possible in the development and clinical trials of the NHS product."

AIDS

"Acquired Immune Deficiency Syndrome (AIDS)

Dr Cash drew members attention to recent articles in the United States, and also in the Observer and the Lancet, about this problem. A MMWR extract (CDC, Atlanta) had been circulated with his paper. Dr Ludlam informed members that in the UK a letter and questionnaire had been sent out to haemophilia directors."

39) SNBTS Directors meeting – 29th March 1983

Prisons and Borstals

"Dr Cash reported that the Medicines Inspector had commented adversely on the practice of collecting blood in prisons and borstal institutions, and he invited Directors to comment on the practices in each region and to give their view on the Medicines Inspector's criticism.

It was reported by all Directors present that sessions were held in penal institutions in all regions, although Dr Brookes and Dr Urbaniak intended to review the situation in their regions.

It was not possibly for the Directors to agree on future policy, but it was agreed that Dr Brookes, as the Scottish representative, should ask the Working party on the Selection and Care of Blood Donors to consider this issue. In the meantime, Dr Cash agreed to inform the Medicines Inspectorate of these SNBTS discussions and conclusions."

40) SNBTS Directors meeting – September 1983

Concern noted about collection in Prisons and Borstals:

"On the matter of collection in prisons and borstals it was noted that the Medicines Inspector has expressed concern at this practice. Owing to different circumstances in the Transfusion Regions the Directors had been unable to reach a consensus. The Chairman of the Working Party thought that the practice was diminishing in all regions in England and Wales. Dr Brookes felt strongly that donations should not be collected from prisoners because of the uncertainty about replies to questions concerning health.

It was reported that the practice had been raised at the Medicines Inspectors' Action Group who had referred it to the DHSS Administrative Division who confirmed that some Transfusion Centres in England still collected from prisons and borstals and that cessation of this practice would place them in difficulty. The NBTS Directors were due to discuss the matter and the DHSS would wish to consult the Home Office who had been anxious previously to encourage donation in prisons.

It was acknowledged that prisons and prisoners differed greatly from one place to another and some Directors felt that a blanket decision to cease visiting prisons would be a mistake. Dr Mitchell in particular felt that it would be unfortunate if such a recommendation was to be included in the 'Red Book'.

Dr Brookes undertook to circularise the English/Welsh Transfusion Directors and report back to the meeting."

41) SNBTS meeting 8th December 1983 – Continued use of commercial products by a children's hospital:

"During a full discussion, in which it was acknowledged that the Glasgow Western Infirmary/Royal Hospital for Sick Children appeared to be the last remaining hospital to use substantial quantities of commercial FVIII in the West of Scotland. It was agreed that Dr Mitchell should write to the consultants concerned to enquire why they needed commercial products. In addition Dr Cash would include the matter in a document which he was preparing concerning planning for self-sufficiency in clinically safe products."

And prisons and borstals:

"Reporting her consultation with the English/Welsh Transfusion Directors concerning collections in prisons and borstals Dr Brookes explained that only one of the 12 which she had consulted was attending prisons. It was noted that the only Scottish region to continue holding sessions in prisons was the West."

AIDS:

"Hepatitis Working Party:

Dr McClelland reported on a recent meeting of the above which had received a report of two cases of Aids in haemophiliacs in UK. There had been discussion of the fact that the main suppliers to BPL of plasma for hepatitis BIgG was a group of declared homosexuals who donated at the Edgware Centre. Dr McClelland and a colleague hoped to produce for the Working Party a paper on use patterns in Scotland and it was noted that Dr McClelland and Dr Mitchell were due to report to the Scottish Directors on the use of hepatitis B IgG in Scotland."

42) Directors of the SNBTS and haemophilia Directors meeting on 2nd Feb 1984 - suggests there was no reason to buy in commercial FVIII?:

"Trends over the last 5 years indicated that the SNBTS production of FVIII concentrates may be exceeding clinical demand in that current stocks at RTCs appear to be increasing."

Children should be treated with cryo:

"Members discussed the suggestion that the production of cryoprecipitate could now be reduced. Dr Ludlam said that in the treatment of children cryoprecipitate was preferred at present because of the new danger of AIDS. Dr Hann concurred."

Call for heat treated Factor VIII:

"Dr Cash asked for views about the phasing in of heat treated Factor VIII for routine clinical use and how this could be achieved and quantified."

Self-sufficiency:

"Dr Bell emphasised the aimof the SNBTS was for Scotland to be self sufficient and although the Department would not intervene in what was prescribed. It was not sensible to purchase when NHS material was available."

AIDS

"Members discussed the reports from abroad which suggested that recipients of blood could also be at risk. The effectiveness of the leaflet was discussed and it was felt that modification to the questions too was necessary and the leaflet given to all prospective donors in the absence of a test to screen out donors."

Hepatitis:

"Reporting of Hepatitis: It was agreed that reporting of incidence was good. Dr Ludlam was collecting data on patients who go completely yellow. It was agreed to leave meantime."

43) SNBTS Directors meeting – 11th December 1984

An infected batch of Factor VIII (which was infected with Aids) – decision taken to use the red cells and plasma because of shortages:

"Factor VIII batch no: 023110090

Dr Cash recalled the decision taken at the Co-ordinating Group meeting on 20 November to quarantine the plasma from subsequent donations by donors who had contributed to the suspect pool and to discard the red cells, platelets etc. It had transpired that discarding cells would cause considerable shortage in some Regions, particularly over Christmas and the New Year and it had therefore been relaxed: the final decision on the matter would lie with individual Directors.

All the plasma had been identified and notified to the Transfusion Centres who would continue to keep the donor samples. Dr Mitchell explained that a donor had been identified in his region who was presumed to be a homosexual and had given one donation which was weakly positive for VD. He hoped to have the actual donation tested for HTLV-III by Dr Tedder of the Middlesex Hospital: there was no possibility of testing the 4,000 other donations in the suspect pool.

After discussion it was agreed that the Directors should continue to hold the plasma of donors who had contributed to the pool, releasing the red cells and platelets for clinical use, until the result of Dr Tedder's test of the donor sample mentioned earlier. Dr Mitchell and Dr McClelland would notifyu the result of the test to other Directors."

44) SNBTS Directors Meeting, 20 June 1985 HTLV-III antibody testing:

"it was agreed that:-

.....The first contact (counselling) of all confirmed antibody positive donors would be the BTS medical staff.....That BTS medical staff would ensure the establishment of appropriate counselling and medical follow-up of A/B donors.

The BTS would take steps to track the recipients of A/B positive blood products produced at RTC's by informing the consultant responsible for the care of the patient. All subsequent actions would be determined by the clinician."

45) SNBTS Directors meeting minutes 2nd October 1985 refers to contaminated batch of Factor VIII:
"CDSC prospective study of staff: Accidental contamination with HTLV-III: Dr Brian McClelland had received the protocol for this joint PHLS/CDSC study from the Lothian Health Board AIDS group. After discussion Dr Cach undertook to consider with Dr Emslie of the CDSC whether such a study was appropriate at the present time."

And continued reliance on commercial blood products *(this meeting was chaired by Dr Cash)*
"In the case of Glasgow it was noted that Albumin consumption there was the highest in Scotland. The BTS were unable to meet demand there because of low fractionation capacity, not shortages of plasma. A plan to increase the process capacity had been approved and would be implemented giving 20,000 – 30,000 additional bottles per annum of SPPS....
It was noted that one purchaser of commercial SPPS was the Royal Hospital for Sick Children in Glasgow who were purchasing paediatric packs which would soon be available from the PFC." *Although article in the British Medical Journal, 12 September 1987, written by John Cash, National Medical Director of the SNBTS says that in 1985 Scotland was not buying commercial blood products.*

46) SNBTS minutes December 1985
Heat treatment:
"AIDS:
viral contamination of products: Dr Cash reported an expectation that Professor Montagnier and others from the Pasteur Institute in Paris would publish shortly a paper expressing the opinion that 68C dry heat for 24 hours might not eliminate the HTLVIII virus in Factor VIII. Dr Perry explained that staff at the PFC were preparing experiments to determine the facts, not only in respect of Factor VIII but also for immunoglobulins: access to live virus was necessary for these experiments. The PFC's long term plan was to heat blood products at 80C for 72 hours.
The PFC had a 9-month supply of factor VIII in stock, some of this having been processed in January 1985 and the total of plasma and product was 16 months supply. The first FVIII from plasma tested for HTLV-III antibody would be issued in February 1986 but it might prove possible to re-heat FVIII which has already been heat-treated for 24 hours and Dr Perry would know in a week or two if anything more could be done before fully tested product was issued. The Directors discussed the possibility of checking all FFP back to the donors who had contributed it. This would require considerable effort and might not be worthwhile, given that no HTLV-III antibody positive donors had yet been identified."
And collecting blood from US forces:
"The US Armed Forces were testing new recruits (for HIV): The position of serving men or women was unknown. Meanwhile it was noted that the Transfusion Centres continued to visit US bases to collect blood and it was agreed no change should be made meantime."

47) SNBTS minutes of 25th March 1986 - delay in introduction of tests for NANB Hepatitis? Minutes note that transfusion services in the US were about to begin ALT and 'anti-core' testing of blood donations to reduce the incidence of NANB hepatitis. "Dr Forrester said it was highly unlikely that the UK Departments of health would fund testing based on data from the USA, but it was recalled that the HBs-Ag and Aids antinbody testing had both been introduced without prior UK research. Certain clinicians and haematologists in

this country had felt that the Transfusion Services had been slow to commence Aids antibody testing and others had similar views in relation to Non-A non-B hepatitis surrogate tests."

Not following up possibly infected patients?:

"It was underlined that the BTS were concentrating on following-up patients who had received known contaminated (HTLV-III) donations. Apart from the need to inform clinicians treating hypogammaglobulinaemic patients the Service would not follow up patients receiving suspect (HTLV-III) product from fractionated plasma."

And continuing to take blood from US military bases:

"Dr Mitchell and Dr Brookes has held sessions recently at US Military bases and had reported no problems. It was understood that the US authorities were about to arrange for all serving men and women as well as new recruits to be tested for the AIDS antibody."

And awareness of need to test for NANB Hepatitis and suggestion that uptake of Aids antibody testing had been 'slow':

"It was noted that transfusion Services in the US might soon be undertaking ALT and anti-core testing of blood donations to reduce the incidence of non-A non-B hepatitis. Dr Forrester said it was highly unlikely that the UK Departments of Health would fund testing based on data from the USA, but it was recalled that HBs-Ag and AIDS antibody testing had both been introduced withouth prior UK research. Certain clinicians and haemotologists in this country had felt that the Transfusions Services had been slow to commence AIDS antibody testing and others had similar views in relations to non-A non-B hepatitis surrogate tests."

48) SNBTS minutes of 25th June 1986

"Factor VIII - material currently issued was derived from unscreened plasma but it was anticipated that the position would change fairly soon."

Talk about a recognition that they were 'coming under pressure' *to introduce tests for* NANB:

"There was increasing evidence that the USA and several European countries were introducing anti-HBc and/or ALT testing of blood donors in an effort to minimise the risks of NANB transmission through blood and blood products. Dr Cash believed that the SNBTS would soon come under pressure from clinicians to introduce testing."

49) SNBTS minutes of meeting on 3rd March 1987

Awareness of requirements for effective heat treatment:

"Dr Perry tabled a summary of preliminary results of virus inactivation in factors VIII and IX...he confirmed that the data represented more than a single experiment.
Heating for 72 hours at 80C gave satisfactory results using model vaccinia and SLF viruses.
It was noted that a company in the USA had patented the concept of dry heating coagulation factor in 1982 and had reinforced this in 1984 by a continuing patent. It was understood that companies manufacturing Factor VIII had not challenged the patent and were presumably paying royalties. It was believed BPL were being pursued for royalties. Dr Perry undertook to find out exactly what was happening at BPL and report back."

Testing for NANB Hepatitis had *still not* been introduced, and would not be introduced for another year:

"The directors...agreed the following: To recommend to the SHHD that surrogate testing for NANB should be implemented with effect from 1 April 1988..."

50) Inspectors report, 1988, of the Protein Fractionation Centre, Edinburgh.

Following one-day visit by K J Ayling and M L Kavanagh on 6th April 1988.
Products unlicensed:
"the site does not have a manufacturing licence.....Factor VIII concentrate and Factor II, IX and X concentrate were licensed but their PLs have expired. Albumin solutions have never been licensed. It is planned to submit PL applications for the clotting factor concentrates and albumin products within the next 12 months."
Heat treatment still not to 80C:
"The Pickstone ovens are used for the heat treatment i.e viral inactivation, of blood factors in their final containers. At present, Factor VIII is treated at 75C for 72 hours and Factor IX at 80C for 72 hours."
"Viral inactivation of Factor VIII at 80C is being investigated.....Virucidal efficacy trials of the process using spiked samples are being conduced by QC."
Inspectors indicate the facilities would not get a licence:
"the possibility of a future application for a Manufacturer's Licence was discussed and the inspectors indicated that such an application could not be supported on the basis of the present situation."

51) SNBTS and Haemophilia Centre Directors Meeting (5th May 1988) Delay in introduction of 80C heat treatment?
"The yield of the new Z8 product had not come up to initial expectation, partly because of losses inevitably incurred during heat treatment for virus inactivation. Thus greater production, especially in the face of the surge in demand, entailed greater throughput than before, and strained the design features built into PFC. Production of more than 9 million units of Factor VIII per year for Scottish use might be hard to achieve.
The new Z8 product now being developed is expected to give a yield of 250-300 units from each litre of plasma....it should be available for trial by the end of 1988...
...Laboratory studies of HIV inactivation will now proceed wholly within PFC, and not require University involvement any longer. It is hoped that progress will now be speedier, since DHSS will not recommend licences for Factor VIII and IX until the data is available...
There was general disappointment that the 58% increase in yield of Z8 and the adequate supplies held out to last year's meeting had not materialised. Technical difficulties have led to inconsistent yield....
The initial testing of a new product for haemophiliacs requires to be done in a number of untreated patients, as many as 60 being required. This number is hard to find in England and impossible in Scotland....
The new Z8 Scottish product is comparable to the English 8Y product. To mimic the 8Y product in Scotland would entail substantial changes in equipment, and acceptance of a lower yield."
NANB screening – an 'unacceptable delay':
"Non-A Non-B Hepatitis Screening: The Chairman said that a research project was being mounted in England and that a decision whether to introduce screening would probably wait upon its outcome. Dr McClelland and Professor Cash considered the delay unjustifiable. Haemophilia Directors had not identified any case of non-A non-B hepatitis transmitted by heat-treated PFC products for haemophiliacs."

52) Regional Transfusion Directors Comments and Report on the Medicines Inspectorate Report on North of Scotland Blood Transfusion Centre, 11/12 November 1988
Facilities were first criticised 6 years ago but are still in use:

"The proposed plans for the new Centre were discussed with Dr Kavanagh and his report quite clearly indicates that a new Transfusion Centre is the only possible way to remedy the very seriously inadequate facilities available for blood processing and plasmapheresis. All steps that can reasonably be taken for criticisms that are considered valid have been taken. The accommodation is fundamentally unaltered from his previous report in 1982 which was substantially to the effect that the building was totally unsuitable for modern blood processing."

53) SNBTS and Haemophilia Centre Directors meeting (21 July 1989)

Still using Z8 – but heated to what temperature?:

"The new S8 product was discussed. The haemophilia Directors expressed their hope that this product, which has the same purity as commercial product, would be in production shortly, as the present Z8 product had a low purity. There was an international movement towards high and very high purity products even though evidence of their value was lacking and Haemophilia directors were coming under pressure to use high purity product. It was pointed out that purity does not equate with safety and that efforts to purify the product resulted in a lower yield."

HIV:

"it was noted that Scotland had the lowest prevalence of HIV infection in Haemophiliacs in the World." *Although it is our understanding that Belgium and Finland had lower infection rates, as a result of greater precautions introduced at the start of the 1980's.*

54) SNBTS and Haemophilia Centre Directors meeting (11 May 1990) Problems with Z8:

"The general unsatisfactory standard of the Z8 product was discussed. Problems had been experienced during the year with the solubility when reconstituting and in addition Z8 did not contain sufficient von Willebrands factor for treating these patients. In defence it was countered that Z8 was a relatively safe product and, because of the manufacturing processes involved, higher purity products may be less safe. The SNBTS are committed to a high purity product but are interested in safety first and convenience second. Co-operation with the French to produce a high purity product was under consideration. Due to the quality problem Northern Ireland had not been taking up the full allocation."

Suggestion that England's product was safer:

"Dismay was expressed that during a radio interview on the withdrawal of a batch of factor VIII because of possible contamination with Hepatitis B, Dr Lane, Bio Products Laboratory, Elstree had given the impression that the English product was safer than the Scottish product which could alarm users of the Scottish product."

55) SNBTS and Haemophilia Directors Meeting (15th May 1992)

"Haemophilia Directors were delighted with the progress made towards the introduction of high potency Factor VIII and were grateful for the Departments assistance in setting up appropriate indemnity arrangements to cover the clinical trail period.

The product licence for Z8 (intermediate purity FVIII) would be terminated in December 1992.

The data collected during the PUP (Previously Untreated Patient) trial of Z8, when taken in conjunction with similar studies in England and Wales, indicated that terminal heat treatment of product at 80 degrees/72 hours was most efficacious....

High potency FVIII would be available under CTX cover for patients not entered into the clinical trials."

Notes usage of Factor VIII had increased yearly over previous 10-15 years
"Notwithstanding a slight decrease in usage during 1987 (thought to be associated with concerns relating to the emerging HIV problems), the usage patterns over the last 10-15 years indicated a 10% compound increase in uptake per annum."