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TRIBUNAL OF INQUIRY

(Into the Infection with HIV and Hepatitis C of Persons with Haemophilia and Related Matters)

PROCEEDINGS: Tuesday 3rd July 2001 - Day 151

Today Professor. Van Aken from the Dutch Blood Transfusion Service, gave evidence. He is a Professor of Medicine at a university in Holland, and is also the Medical Director of the Central Laboratory (CLB) in Amsterdam which is responsible for the production of blood products.

Background

The CLB does not receive any direct Government funding, but raises revenue from the sale of blood products to hospitals. In the 1980's the CLB had significant scientific and medical expertise to deal with the fractionation of blood products and employed about 800 full time staff. Dutch hospitals bought both CLB produced factor concentrates and imported American factor concentrates. The hospitals were free to choose which product they preferred. Both types of product required a licence in Holland in the 1980's.

Professor. Van Aken said that in 1985 the CLB started heat treating its factor concentrate products. They also managed to heat treat cryoprecipitate; which was difficult and which many other blood services and fractionation services throughout the world did not attempt to do. Heat treating cryoprecipitate is more difficult because of the variety of proteins it contains.

In Holland between 1981 and 1985, the amount of cryoprecipitate produced from regional blood banks increased. When heat treated products became available in 1985, the amount of cryoprecipitate being produced from regional blood banks fell. Professor. Van Aken said that dry cryoprecipitate was suitable for home treatment. He said that factor concentrates were easier to use at home, but until they were certified as being safe, dry cryoprecipitate was used for home treatment in Holland.

Haemophilia physicians had a large input into what products the CLB produced. It was at their insistence that CLB concentrated on the production of dry cryoprecipitate. The importation of factor concentrates from the United States was only encouraged to allow some very severe haemophilia A patients to use it for home treatment. The CLB first attempted to import factor concentrates from the Swiss Red Cross, because they knew that the plasma collected there would be from volunteered donations as opposed to paid donations. However, this wasn't possible and they eventually entered into an agreement with the pharmaceutical company Baxter for the supply of factor concentrates. Armour Pharmaceuticals , having argued that Competition Law entitled them to also sell their products in the Netherlands, obtained a licence as well. By 1981 the CLB was able to manufacture its own factor VIII concentrate to intermediate purity standards.

Dr. Van Aken said that the Gail Rock method of fractionation to make intermediate purity products was adopted by one fractionation unit in The Netherlands, which was situated in Gronigen. He said that at the CLB, they were very sceptical about the use of the Gail Rock method to make intermediate purity product. They could not see the improvement in yield which was claimed for this method, and they were concerned about the heparin which would remain in the final product.

In 1982, Dutch physicians preferred cryoprecipitate and Dutch concentrate to imported products.

The Emergence of AIDS

In September 1982 the head of the infectious diseases laboratory in the Netherlands wrote to physicians and other persons working in the health service, asking for information in regard to the increase in the number of persons with AIDS symptoms. In November 1982 the CLB first learned that AIDS might be transmitted by blood. The CLB devised a plan to deal with the threat of AIDS which was emerging. In December 1982 they decided to see if they could reduce the size of the donation pool which was used to make factor VIII concentrate. The haemophilia community was warned about the potential danger of factor concentrates made from large donor pools. The CLB also started talking to high risk groups to discourage them from donating blood. Dr. Van Aken described how they had initial difficulties with representatives of homosexual groups, because homosexuality was just being to be accepted in Holland and homosexual organisations felt that a blanket request to them not to donate blood would be a step back in their campaign for recognition and acceptance. However, after fierce discussion, representatives of the homosexual societies agreed to circulate information amongst homosexuals to discourage them from giving blood.

Members of the CLB tried to keep up-to-date with emerging knowledge about AIDS. In March 1983, a representative from the CLB attended an AIDS conference in New York. In April 1983, the CLB organised a symposium on AIDS. It was at this symposium that the results of a trial which had been carried out by the CLB on people with haemophilia were published. The results of the study showed that patients who had lower ratios of T4/T8 cells (and who were consequently considered to be at a greater risk of developing AIDS), were patients who had been treated with commercial, imported factor concentrates rather than cryoprecipitate and concentrates prepared in Holland. These results indicated that there was much higher risk of developing AIDS by using foreign factor concentrates. The chief public health officer for drugs in Holland recommended a complete banning of factor VIII concentrate imported from America. However, commercial factor concentrates imported from the US were not banned entirely, but the CLB had a policy of restricting their use.

Of the 1100 people with haemophilia in Holland, 170 were infected with AIDS between 1981 and 1985. Of these, half were infected by commercial products, the other half by domestic product. The majority infected by domestic product had used factor concentrates. Few were infected who had used cryoprecipitate only.

Heat Treated Products

In 1983, Baxter's product, Hemofil T (a heat treated product), was registered on the market in Holland. Some physicians began to use this immediately. It was believed to prevent the transmission of NANB Hepatitis. The CLB considered introducing heat treatment for its own product in 1983. Fears of inhibitors, however, outweighed the benefit of non-transmission of NANB Hepatitis, and the CLB subsequently decided at this stage not to heat treat products.

In 1984 the CLB became aware of evidence that retroviruses were sensitive to heat. In October 1984 it was believed that heat treatment would inactivate the virus which caused AIDS. The CLB started heat treating its factor VIII concentrate in October 1984. A month later they started to heat treat factor IX concentrate. In January 1985, they attempted to heat treat dry cryoprecipitate. This was a difficult task, but eventually they managed to do it. Clinical trials took place in April 1985on the heat treated factor VIII domestic product.

NANB Hepatitis

The concern about the inactivation of NANB Hepatitis was much less than the concern about inactivating the AIDS virus. In 1990, when solvent detergent treated products were introduced, the heat treated products were not recalled from the market. Professor Van Aken said that it was thought that Hepatitis NANB was a fatal disorder at this stage.

Dr. Van Aken said that it was very feasible for a small country to achieve self sufficiency.

The Tribunal then adjourned to Wednesday 4th July.

PROCEEDINGS: Wednesday 4th July 2001 - Day 152

Prof. Gerard Van Aken continued his evidence today. He was first examined by Mr. Bradley on behalf of the I.H.S, who asked why the Dutch adopted a policy of self sufficiency. Prof. Van Aken said that self sufficiency was important for two reasons: it gave the country a certain independence and provided safer products. In 1979 the Dutch recognised the danger of contracting NANB Hepatitis from imported factor concentrates. Prof. Van Aken accepted that there was concern about NANB Hepatitis, there was concern that donors in the US were high risk, it was realised that there was a greater risk of infection by the use of imported factor concentrates, and therefore self sufficiency was seen as a solution to some of these difficulties. Prof. Van Aken said that the Government was aiming for self sufficiency, and in fact this was enshrined in Dutch Law. However, on the other hand, patients and treaters were interested in the use of factor concentrates which would improve lifestyle.

In 1982, Travenol licensed its heat treated product in Holland. In Holland they were aware in 1982 that retrovirus was more susceptible to heat. This was one of the reasons for introducing heat treated product. In 1984, the incidence and prevalence of HIV infectivity decreased significantly. This was because of the use of both cryoprecipitate and heat treated products.

Prof. Van Aken said that there were between 1100 and 1300 people in Holland with haemophilia. He said that if the incidence of HIV in the population had been lower, there would have been a lower rate of infection amongst people with haemophilia.

Prof. Van Aken was then cross-examined by Mr. Butler for Prof. Temperley. Prof. Van Aken said that in retrospect, it was amazing how quickly they managed to heat treat their own factor VIII and factor IX products. He said that today the process would probably take a year or two years, but they managed to achieve the development of heat treated products in a number of months.

In 1984/85, the Dutch authorities attempted to ban the importation of American factor VIII concentrate. People with haemophilia in Holland actively campaigned against such a ban. Prof. Van Aken said that the concern that people with haemophilia had was that quality of life would be affected if they weren't able to treat themselves at home. Mr. Butler asked Prof. Van Aken whether or not it was then appropriate for Dutch people with haemophilia to use cryoprecipitate at home. Prof. Van Aken said it was, but it was more difficult to administer than factor concentrate.

Frank Clarke for the BTSB then cross-examined Prof. Van Aken. He put it to Prof. Van Aken that the decisions that were taken in 1984 and 1985 about what treatment should be given to people with haemophilia, were based on incomplete knowledge. Some of the decisions turned out, with hindsight, to be right and some of them turned out to be wrong. But nobody can really blame the individuals who made the decision because they were doing so with incomplete knowledge. Prof. Van Aken agreed that it was easy with the information we have today to say in hindsight what products should have been used and what products shouldn't have been used. Prof. Van Aken also agreed with Mr. Clarke that, irrespective of which product was used, there was still a very high prevalence of Hepatitis C infection. Prof. Van Aken said that there was only one plasma product which was easy to make and that was cryoprecipitate. The manufacture of any factor VIII concentrates was more difficult. In order to manufacture factor concentrates from plasma, you required a protein chemist, a virologist, a biochemist and analytical personnel with specific training. Prof. Van Aken said he would never recommend that any small organisation manufacture factor concentrates. He said that IR£25 million was the cost of renewing the CLB plant in Holland.
The Tribunal then adjourned to Thursday, 5 July 2001,

PROCEEDINGS: Thursday 5th July 2001 - Day 153

Today, Seamus Dooley of the Virus Reference Laboratory, gave evidence. The function of the Virus Reference Laboratory is to provide a diagnostic virology service to clinicians all over the country who want to investigate viral infections in their patients.

Mr. Dooley described how the Virus Reference Laboratory (VRL) had been involved in testing samples of blood for HIV in the 1980s. He said that at that time, manual records were kept and he had a book containing records of tests which had been carried out.

Mr. Dooley gave evidence of the overall figure of persons with haemophilia who tested positive for HIV. There were, he said, 104 people with haemophilia who had tested positive for HIV. The VRL also recorded that there were 217 people with haemophilia who had tested positive for Hepatitis C. According to the VRL records, a total of 252 people with haemophilia were infected with one or other of either HIV or Hepatitis C, 69 people with haemophilia were infected with both viruses, 35 people with haemophilia were infected with HIV only and 148 were infected with Hepatitis C only.

Mr. Dooley went on to describe the workings of the VRL and the administrative work that was carried on when conducting tests. He produced a worksheet in evidence which showed tests carried out on a number of people with haemophilia between 1980 and 1985. This worksheet had incomplete data; not every person on the sheet had a test carried out in every year. Nevertheless, for each person on the sheet there was data of the last time a test was carried out which had a negative result, and the first time a test was carried out which had a positive result. This information was collated from a retrospective study which was carried out in 1986. The names of people whose test reults appeared in this worksheet had been disguised.

In a number of cases the VRL had recorded what are described as false negative results. These are tests which were carried out on samples of blood which showed negative for HIV, but which were subsequently tested again and showed positive. This discrepancy occurred because different tests were used to analyse the samples. In 1985, many different tests were being developed and the reliability of some was superior to others. One of the tests used in the VRL was devised by Abbott Laboratories. The VRL sent samples tested by Abbot laboratories over to Middlesex in England for confirmatory testing. Many of the false negatives occurred because of the inaccuracy of the Abbott test.

Mr. McGovern, Counsel for Prof. Temperley, then cross examined Mr. Dooley. Mr. McGovern pointed out that it appeared that the results presented by Mr. Dooley were made up of information gathered from the retrospective study and the medical records of those people who had given consent to an examination of their records. In one instance there was a record of counselling having been given to a particular person, but no record of a positive result on the chart. Mr. Dooley agreed that the fact that counselling had been given to this person indicated that there must have been a positive result. Mr. McGovern wondered why, if there was a positive result, it had not been recorded on this chart. Mr. Durcan intervened at this point and explained that, since some people had not given consent to an examination of their medical records, not all the positive results could be included on the chart. The fact that the chart was made up both of information from the retrospective study and an examination of medical records where that had been permitted, meant that there may be some gaps in the data.

Mr. Dooley was then examined by Ms. Power for the Southern Health Board and Dr. Cotter. Ms. Power asked Mr. Dooley about the date which appears on the bottom of a report form which accompanies the

test result. She asked him whether this date was the date upon which the report was made, or the date on which the results of the test were dispatched. Mr. Dooley said it was the date on which the report was signed and that would normally, he said, have been the dispatch date. Ms. Power asked whether it was possible that there would be some considerable delay between the date of the report being generated and the date of dispatch. However, the Chairperson intervened saying that the evidence had been given that the date which appeared on the report was either the date that the report was made or the day after.

Ms. Power then asked Mr. Dooley about a patient with the pseudonym of Andrew. Ms. Power was anxious to discover whether or not there had been a subsequent test carried out after 1985 which produced a negative result. The Chairperson intervened and said that this question could not be asked. She said a question of this nature, or requests for information of this nature, had already been made, and that the answer had been given that there had been no extra test which was not recorded by the VRL. Ms. Power insisted that her clients said that there had been a test in 1986, and that this test completed a pattern of a negative, a positive, a positive and a negative test. The Chairperson ruled that evidence of a negative test in 1986 was inadmissible. However, Mr. Durcan, in re-examining the witness, indicated to the Chairperson that if this information was available concerning a negative test in 1986, and if Mr. Dooley could find that information, the Tribunal would be supplied with that evidence.

Dr. Alan Shattock was then examined by Mr. Durcan. Dr. Alan Shattock was an assistant in the Department of Medical Microbiology in UCD. He is currently a senior lecturer at University College Dublin. Mr. Shattock said that he was friendly with Dr. Tedder, a virologist who had been working on an experimental test to identify HIV/HTLV-III. He said that he had visited Middlesex Hospital in 1984 where Dr. Tedder told him about the test he was working on. He said that at his request, Dr. Tedder had agreed to carry out tests on samples supplied by Dr. Shattock from patients in Ireland. Dr. Shattock was asked about a list of patients and samples which he had received from Prof. Temperley. He said this list related to specimens which had been received from Prof. Temperley and had been passed on to Middlesex for testing. When the test results came back, some of the specimens on the list were marked as "borderline". The test results, in relation to these specimens, weren't conclusive. There was a small note on the list which pointed out that any test result which is underlined was considered to be a borderline result. Also on the list was marked "please repeat" beside some of the results. Prof. Tedder had advised that in the case of borderline cases it was necessary to repeat the test. In order to repeat the test it was necessary to gather a fresh specimen. Dr. Shattock said when the results came back from Prof. Tedder, he sent the list and the results off to Prof. Temperley. He said it was his understanding that there was no discussion or request for re-testing of any of the specimens. However, Dr Shattock said that he expected that in relation to those specimens which required re-testing, that he would receive fresh samples from Prof. Temperley. Dr. Shattock said that at this time he was also attempting to evaluate a commercial test which had been put on the market by Abbott. In order to evaluate the test he picked at random some specimens which had been returned from Middlesex with both negative and positive results. The specimens which he selected were those which carried a "repeat test" request beside them. In a number of cases tests which had been returned as negative but "borderline" from Middlesex had a positive result when tested with the commercial kit.

Dr. Shattock was then asked whether he reported the results of his test with the commercial testing kit to Prof. Temperley. He said he had no copies of anything in writing, but he believed that he had reported them by telephone to Prof. Temperley's office; he said it was the most likely thing that happened. Mr. Durcan for the Tribunal asked was this his belief or did he actually remember it. Dr. Shattock said he didn't remember doing it, but he was absolutely certain that it would have telephoned Prof. Temperley's office with the information.

Mr. Durcan suggested that this was important information that a treater should have had at his disposal to discuss with his patient, and that it was strange that it had not been communicated in writing. He also

pointed out to Dr. Shattock that at the time, Prof. Temperley wasn't in the country, that he was away on sabbatical. Dr. Shattock said that he would have telephoned Prof. Temperley's office and spoken to his secretary.

Mr. Durcan then asked Dr. Shattock why, when he discovered that a number of the borderline cases were coming up with positive results on the commercial tests, but had been given negative/borderline results from Middlesex, he did not then go and test all of the other negative/borderline results from Middlesex. Dr. Shattock said he could not think of a reason why. Mr. Durcan said that there were six borderline cases which had been returned as negative but which were borderline. He said by chance two of those had been tested by Dr. Shattock and had proved to be positive. Mr. Durcan asked him whether it would not have been prudent to go back and look at the other four negative/borderline tests. Dr. Shattock agreed that it would have been prudent.

When examined by Mr. McCullough for the I.H.S., Dr. Shattock agreed that the incidence of Hepatitis B in patients could be used as a surrogate marker for the presence of other viruses. Studies carried out by Dr. Shattock showed that in the 1980's there was a sharp increase in the level of infection of people with haemophilia with Hepatitis B, and that this increase was thought to be related to the use of imported American factor concentrates. Mr. McCullough asked whether those people in the study carried out by Dr. Shattock who showed increased levels of infection with Hepatitis B subsequently turned out to be infected with HIV. Dr. Shattock said he didn't know, but he said that it was possible to determine this information from his records.

Dr. Shattock was then examined by Mr. McGovern for Prof. Temperley, who asked him about the discovery of positive results for samples which Middlesex had marked as negative/borderline. He said he was not sure why he had not communicated this information in writing to Prof. Temperley. He accepted that the information was important. He said that he was conscious that written reports had to be signed by the director of the laboratory. He said that the director of the VRL would have had to sign the report before it was sent to Prof. Temperley. Mr. McGovern asked him was there any difficulty in doing this, and Dr. Shattock replied that he could not remember. He agreed that he had written to Dr. Cotter in the Southern Health Board with test results in a similar context, and that this communication had not been signed by the director of VRL. When asked by Mr. Govern what the difference was between the report sent to Prof. Temperley and the report sent to Dr. Cotter, Dr. Shattock said he just could not remember what had happened.

The Tribunal then adjourned to Monday, 9th July at 10.30am.

PROCEEDINGS: Monday 9th July 2001 - Day 154

Today, Prof. Richard Tedder gave evidence. He is Professor of Virology at the Royal Free and University College Hospital Medical School in London. He qualified as a medical doctor in 1973 and has worked in the Department of Virology in Middlesex Hospital since 1975.

Development of HIV test

From 1980 onwards, Prof. Tedder said that he spent a lot of time developing tests to identify viruses. In 1984 he was given access to antigens derived from tissue cultured from the HTLV-III virus. Access to these antigens allowed him to develop a test for the HTLV-III virus. Prof. Tedder described in detail the method used to develop the test which required highly complex, sophisticated research.

False Negatives

Once the test had been developed, Prof. Tedder invited doctors from around Britain to submit samples from patients with haemophilia for testing. The majority of the samples tested were either clearly negative or positive. However, a number of samples fell just below the cut-off point for a positive test. These results are sometimes referred to as false negatives. In relation to these samples, Prof. Tedder described how he returned the results to the doctors with a note stating that while the sample was negative it was advisable to re-test.

Compulsory Testing

In February or March 1985, Prof. Tedder started to collaborate with Wellcome Diagnostics in order to produce a commercial version of the test he had developed. In April 1985, Abbott Pharmaceutical Company produced its own commercial test. At this time he said that there was a discussion in England as to whether or not blood banks should introduce compulsory HIV testing of donors. They did not want to introduce compulsory testing until there was free testing available in the genitourinary medical clinics in the UK. There was a fear that free compulsory testing in the blood transfusion service would attract donors purely for the purpose of discovering their HIV status. Therefore, a deliberate decision was taken to delay the introduction of testing in blood banks while alternative test sites were set up.

When tests were carried out on people with haemophilia, it was discovered that approximately 30% of those who had received factor VIII concentrates were HIV positive. Only 18 patients among 166 who received British factor VIII exclusively became seropositive. 15 of these people came from a group of 33 Scottish haemophiliacs given a uniquely infectious batch of British concentrate. Leaving aside these 15, therefore, three out of 166 patients who used standard British factor VIII concentrate became infected. This equates to approximately 2% of the entire population of people with haemophilia.

NANB Hepatitis and Heat Treatment

In relation to NANB Hepatitis, it was a near certainty that anybody using factor concentrates would become infected. It is relatively common in the donor population, and would therefore be transmitted even from voluntary donors.

In relation to the use of cryoprecipitate, Prof. Tedder was asked if it was likely that, following continuous use of cryoprecipitate, a patient would develop Hepatitis C. Prof. Tedder said he couldn't answer this directly but that it would depend on the amount of cryoprecipitate that was used, the length of time over

which it was used, and the number of infected donors in the donor pool. Heat treated factor VIII concentrates manufactured in the UK would not transmit HCV, non heat treated factor VIII UK concentrates would transmit it but not as easily as commercial factor VIII concentrates imported from the USA which were non-heat treated.

In relation to factor VIII concentrates that were heat treated at 60 degrees for 32 hours, Prof. Tedder said that this would not completely destroy virus, and the effectiveness of this heat treatment could only be measured depending on the amount of virus that was put in the sample treated. Super heat treatment at 80 degrees for 72 hours was shown to be entirely effective in inactivating all known virus.

Prof. Tedder also discussed the solvent detergent method of viral inactivation. He explained how it was effective, but that it was not introduced until mid to late 1980s.

Donor Pool Size

Cross examined by Mr. Bradley for the I.H.S, Prof. Tedder agreed that there was an increased risk in using blood products manufactured from large pool rather than small pool donor groups. So the optimum pool was a pool of 10-15 users which was used to manufacture cryoprecipitate. Between 2000 and 3000 donors were used to manufacture factor concentrate, but factor concentrate manufactured in the United States used much larger pools. Asked whether the introduction of heat treated products by commercial companies in the early 1980s was a reaction to the knowledge that Non-A, Non-B Hepatitis could be inactivated by heat treatment, Prof. Tedder replied that he could not comment on what the motivation of commercial companies was. Prof. Tedder said from the date it was discovered that AIDS was caused by a retrovirus, it might be reasonable to presume, for a virologist, that heat treatment or solvent detergent treatment would destroy the retrovirus in blood products. Prof. Tedder said that there was also a risk, however, with heat treatment that it could cause inhibitors in factor VIII deficient patients. When asked if the difficulty with inhibitors could have been realised very early on in the use of heat treated products, Prof. Tedder said that he could not comment. Prof. Tedder rejected the suggestion that Hepatitis B core antibody testing could be used as a marker for HIV. He said that anti-HBc was not, in his opinion, a marker for high risk lifestyles in England and Scotland.

The Tribunal then adjourned to Tuesday 10th July 2001 at 10.30am.

PROCEEDINGS: Tuesday 10th July 2001 - Day 155

Today, Dr. Terence Snape gave evidence. Dr. Snape is a fractionator of blood products and has worked at BPL (British Plasma Laboratory). Dr. Snape gave evidence about the history of the production of factor VIII concentrate in the UK. He said they began producing factor VIII concentrate in 1968. In comparison to today's product, it was a very unsophisticated product. It was usually administered in hospital rather than at home. It was not suitable for home treatment.

Manufacture of Factor Concentrates in the UK

In 1974, the process for fractionating factor VIII concentrate changed. The Johnson method was applied; Alan Johnson was an American who had developed a more effective method of fractionation. The Johnson method used cryoprecipitation as the fractionation method. Basically, plasma was frozen and then thawed in order to refine the factor VIII out of the plasma. Having extracted the factor VIII concentrate from the thawed plasma, the product was then lyophilised. It was freeze dried into a powderous state. Unlike its predecessor, this product was suitable for home use. At this time, the BPL were managing to produce factor VIII concentrate from pool sizes of 160 litres; the commercial factor concentrates manufacture in the US were using pools of up to a 1000 litres of blood. In the early 1980s pool size increased to 5000 donors in the UK.

Transmission of Virus in Blood Product

In the early 1970s, fractionators became aware of the possibility of the transmission of viruses in blood products. Testing for Hepatitis B was introduced in the mid 1970s and that reduced the risk of transmission of Hepatitis B by using blood products. It was accepted in or around 1982 that the use of cryoprecipitate was more likely to prevent the transmission of Non-A, Non-B Hepatitis. This was because the size of the donation pools used to manufacture cryoprecipitate were considerably smaller than those used for the manufacture of factor concentrate. However, repeated and regular treatment with cryoprecipitate diminished its benefit from a safety perspective. Dr. Snape said that in relation to the manufacture of factor concentrates, they tried to keep the pool sizes as small as possible. However, there were considerable significant constraints in doing so. It wasn't a cost effective way to work. Nor was it easy to scale down the processes of manufacturing. He said it also became very difficult to achieve regular and appropriate quality assurance if you were trying to make small pool products. At this time in the early 1980s concern focused on the risk of NANB Hepatitis; the risks of AIDS was not yet apparent.

Heat Treatment

Dr. Snape described how in the early 1980s they were developing methods of heat treating factor concentrates. They were attempting to heat treat them with a view to inactivating NANB Hepatitis. However, there was no great urgency about this work. They also encountered difficulties with actually testing heat treated products. They wanted to test for the safety and efficacy of heat treated products. In the United States, scientists had access to colonies of chimpanzees for testing. There was no such test bed available in the UK. There was also concern about the danger of thrombogenicity and inhibitors from heat treated product.

Dr. Snape said that fractionators became aware in the UK in 1982 that there was a possibility that the condition known as AIDS could be transmitted by blood. He said that he was also aware in 1983 that Travenol had developed a heat treated factor VIII concentrate product. The claim made by the

manufacturers of this product was that it was heat treated to the extent that it was reducing the transmission of heat labile virus.

Dr. Snape said that at this time there were two fears in relation to the use of heat treated products: in relation to heat treated factor VIII there was a fear of the development of inhibitors; in relation to the heat treated factor IX there was a fear of thrombogenicity.

Super Heat Treatment

In October 1984, a batch of plasma collected from an infected donor resulted in the transmission of AIDS to a large number of people with haemophilia in Scotland. The fact that these patients had only received products manufactured from a Scottish fractionation plant and from Scottish donated plasma, highlighted the danger of continued infection with HIV from the use of nationally produced product. From this time on, the focus of fractionators was to produce heat treated factor concentrate. Information from the American CDC had indicated that heat treatment could inactivate the virus which caused AIDS. The BPL concentrated its resources on developing a heat treatment programme, and eventually came up with the heat treatment process of 80 degrees for 72 hours (otherwise known as super heat treatment).

From September 1985, all issues of factor VIII concentrate would be super heat treated by the BPL. The super heat treated factor VIII concentrate was referred to as 8Y.

No Product Re-call

There was no recall of unheat treated product by the BPL. They continued to use it and starting supplying the super heat treated 8Y as soon as it became available. There was no withdrawal of the product because withdrawal would have deprived haemophilia treaters and people with haemophilia of valuable therapeutic material. They never had sufficient stock of 8Y to replace the non-heat treated factor concentrate that was on the market. Rather than a withdrawal of product there was a gradual replacement of non-heat treated product with 8Y. If there had been a withdrawal of non-heat treated product, the only alternative would have been to use either commercial concentrate or cryoprecipitate. It would not have been possible, Dr. Snape said, to produce sufficient amounts of freeze dried cryoprecipitate to replace the non-heat treated factor VIII stocks. The only real option would have then been to use imported factor concentrates, which was not desirable.

Factor IX

In relation to heat treated factor IX, it took some further time before the heat treated product was available. There was a fear of thrombogenicity and the product had to be tested on animals in a laboratory before it was deemed to be safe. Super heat treated factor IX was made available for clinical trials in July 1985; 9A (as it was called) became widely available in October 1985 in the UK. It was recommended that the NHS change to 9A as soon as possible. In 1985 there was a considerable amount of commercial concentrate used. Dr. Snape couldn't say definitely whether or not the commercial concentrate used in 1985 was heat treated.

Licensing

The BPL was part of the National Health Service, and as such enjoyed Crown immunity under English Law. It was therefore not subject to the formal licensing regime which was in place in the UK. Even though EEC Law required that products used within the European Community be granted product authorisations, the BPL never successfully or fully completed an application to the UK licensing authority

for product authorisation for their product. Dr. Snape said that the absence of these licensing restrictions allowed the development of heat treated products to proceed more quickly.

Super Heat Treatment effective against NANB Hepatitis

By September 1986, UK treaters were confident that their heat treated products did not transmit HIV. There were no reported cases of seroconversions in patients using heat treated UK product. It was also believed that the heat treatment applied to the products was extremely robust in terms of dealing with NANB Hepatitis. There was no recorded transmission of NANB Hepatitis in 1986 from the use of heat treated BPL product.

By 1988, BPL products accounted for 50% of the national requirement. Dr. Snape said that BPL could have manufactured as much product as required for the UK. However, it was up to individual treaters to decide which product they wanted to use. Some treating doctors preferred to use imported factor concentrate.

Supply of Product to Ireland

Dr. Snape said it would have been feasible for BPL to carry out custom fractionation of Irish plasma for the BTSB after 1988 when a new facility for fractionation was opened. Prior to that, BPL was constrained by demand for product in the UK. Dr. Snape also said that, had he been requested to supply small amounts of product for treating physicians in Ireland of factor VIII , this would not have been possible in or around 1986. However in relation to factor IX there was no reason why small quantities could not have been supplied to physicians in Ireland from BPL.

Other Countries Which Super Heat Treated Products

Dr. Snape was then cross examined by Mr. Bradley for the I.H.S. Dr. Snape agreed that the super heat treatment methodology was used in other jurisdictions such as South Africa and Australia. He said that different jurisdictions used the super heat treatment method with varying degrees of success.

The Tribunal then adjourned to Wednesday, 11 July, 2001.

PROCEEDINGS: Wednesday 11th July 2001 - Day 156

Today, Dr. Peter Jones, Consultant Paediatrician in Newcastle upon Tyne, gave evidence. There was a delay in beginning Dr. Jones' evidence and the Tribunal sat at 2.00pm. The reason for the delay was that there had been a dispute between lawyers for the I.H.S. and lawyers for the Tribunal as to whether or not Dr. Jones could give evidence in relation to certain documents that had come into his possession. Those documents were internal documents from Armour Pharmaceuticals, which dealt with Armour's state of knowledge about the safety of its heat treated product in 1985. An agreement had been reached between the I.H.S. lawyers and lawyers for the Tribunal that Dr. Jones would commence giving evidence at 2.00pm, and that the question of whether or not he could give evidence in relation to the documents would be reserved for a decision by the Chairperson at a later date.

Dr. Jones said that for a large part of his career he had been Director of the Newcastle Haemophilia Centre.

History of Treatment in Newcastle

Dr. Jones described the history of the treatment of people with haemophilia in Newcastle. He said it was not until the mid 1960s that cryoprecipitate became available as a treatment option. He said that it was in the early 1970s that factor VIII and factor IX concentrates became available. There was a risk that Hepatitis B could be transmitted through these products. Although this risk was recognised, the risk of exsanguination in people with haemophilia was greater. The risk of Hepatitis compared to the risk of bleeding in haemophilia was considered to be relatively small. The importation of commercial factor concentrates allowed haemophilia treaters to teach people with haemophilia how to treat themselves at home.

Dr. Jones described the facilities in the Haemophilia Centre in Newcastle. He said prior to 1980 the Haemophilia Treatment Centre consisted of a consulting room, a small waiting room, a coagulation laboratory, a treatment room, and rooms for haemophilia nursing sister and a social worker. After 1980 they expanded. This expansion was undertaken with the assistance of the Haemophilia Society. They had a larger treatment room which was able to cope with people without haemophilia who needed transfusions; they had a consulting room which allowed doctors to examine patients in privacy. There was a social work room, a laboratory in a building next door, an area for storing blood products on site and a room for a nursing sister.

Dealing with the AIDS crisis

Dr. Jones then described the crisis which occurred with the emergence of AIDS in the early to mid 1980s. He said that the facilities that they had in place were not sufficient to deal with the crisis. At the beginning of the HIV epidemic, 143 people with severe haemophilia A or B attended the treatment centre in Newcastle. He said a specific procedure was drawn up on how to deal with breaking the news to a person with haemophilia that they had become infected with HIV. The first thing was that no patient would ever be told a result of a test over the telephone. Secondly, a senior doctor would always give the result in the privacy of a consulting room. Thirdly, the nursing sister or her deputy was always present when a diagnosis was given. He said that once diagnosis was given, it was common for the nurses to talk or hold hands with the patients and comfort them for as long as the patient wanted. Sexuality and mortality were always discussed with the patient by a senior social worker or consultant, or the nursing staff. Dr. Jones said he also felt it was important to destroy the myth about HIV and to give accurate information about the nature of the infection. Finally, Dr. Jones said they encouraged people who had

been giving a positive diagnosis to talk to other people with haemophilia in a similar situation, so that they could share their difficulties and help each other come to terms with the problem.

Dr. Jones said of 140 people with haemophilia who were tested, 99 were found to be HIV positive. Of that 99, 76 were people with haemophilia A. These results became available in January 1985. Dr. Jones said the task of testing and delivering diagnoses for so many patients was extremely demanding. It put great strains on the resources they had, but Dr. Jones said that they just got on with the work that had to be done. Dr. Jones said that there were very few patients with haemophilia A who received exclusively either commercial or NHS factor concentrates. Dr. Jones said if all patients had been treated with NHS factor concentrate, the likelihood of them becoming positive would have been much less. Dr. Jones said that in January 1985 they moved to using heat treated commercial factor concentrate.

Armour Heat Treatment

Dr. Jones was then asked, was he aware of an article which appeared in the Lancet in1985, written by John Petricianni, Bruce Evatt and Steve McDougal. Dr. Jones said he was. The authors were from the Centers for Disease Control in the US. They had published their findings in relation to the efficacy of certain heat treating methods. The article suggested that heat treating at 60 degrees for 10 hours would cause a minimal reduction of 20 logs of virus in a sample of factor concentrate. Dr. Jones said he was not reassured by this article and he still had fears that the heat treatment which was being applied to some commercial factor concentrates was not sufficient to eliminate all virus. Dr. Jones' concerns were subsequently proved right when, in the first six months of 1985, a patient seroconverted having used heat treated products. Dr. Jones said that he came by this information in the form of an anecdote from a London hospital. He said it was sufficient to raise his fears further in relation to the efficacy of heat treatment. He said he also came by information that patients in the Netherlands had seroconverted having used heat treated product.

In February 1986 Dr. Jones organised a conference on AIDS in Newcastle. It was at that conference that he indicated publicly his concerns in relation to products which had been heat treated for 30 hours at 60 degrees centigrade. On 18th February 1986, Dr. Jones wrote to the Medical Assessor of the Committee of Safety of Medicines in London; he provided information relating to reported seroconversions with patients using factor VIII concentrate which had been heat treated at 60 degrees for 30 hours. He pointed out that he was concerned about the inefficacy of this heat treatment protocol. He suggested that products produced by Armour Pharmaceuticals should be withheld in the UK until their safety could be endorsed. On 25th February, Dr. Jones wrote to Armour raising concerns about certain products which had been heat treated. He didn't identify the Armour product in particular as being responsible for seroconversions, but he did report the fact that he was concerned about the efficacy of some heat treatment methods.

The Tribunal then adjourned until Thursday 12th July at 10.30am when Dr Jones would continue with his evidence.

PROCEEDINGS: Thursday 12th July 2001 - Day 157

Today, Dr. Peter Jones continued giving his evidence. Dr. Jones is a Consultant Paediatrician who worked with people with haemophilia in Newcastle. Dr. Jones continued giving evidence about fears he had in 1985/86 that some methods of heat treatment were inefficacious in inactivating virus in factor concentrates. In particular, he gave evidence about how he had written to Armour Pharmaceuticals questioning them about the safety of their product which was treated for 30 hours at 60 degrees centigrade. The response he got from Armour was to confirm their belief that the product was safe. Dr. Jones said that at the height of the AIDS crisis he was only prescribing cryoprecipitate for children who had not been treated before with factor concentrate.

Armour Withdraw Product

In July 1986 Armour withdrew their heat treated product from the market. They claimed they were doing this because of reports that it may have been linked with seroconversions in a number of patients. Their explanation of this was that the product had been made from pooled donors which included some unscreened donors. They made no reference to the fact that the product's heat treatment regime was not effective. In October 1986, Armour unilaterally withdrew all of their non-tested but heat treated product from the market.

Prior to this in September 1986, Dr. Jones had published an article suggesting that there may be a link between seroconversions and the heat treated product.

Dr. Jones was then examined by Ms. Murphy on behalf of St. James' Hospital. Dr. Jones said that the population of Newcastle was approximately 3.1 million, similar to the population of the Republic if Ireland.

Treatment of Children

Mr Bradley on behalf of the Irish Haemophilia Society, cross-examined Dr. Jones. Dr. Jones said that in 1983, having become aware of the possible danger of AIDS, children who had not been treated with factor concentrates before, were being treated exclusively with cryoprecipitate. He said the use of cryoprecipitate was also linked to the concern about the transmission of Hepatitis through factor concentrate. Dr. Jones described again the extensive nature of the care offered in the Newcastle Haemophilia Centre. Patients were given all information in relation to what treatment options were available, and were consulted in relation to their choice of treatment. He also described the system that was put in place for carrying out tests for HIV in 1985. He said they recognised at that time how important it was to keep a close surveillance on all patients with haemophilia.

In relation to the use of cryoprecipitate with children, Dr. Jones said that it was less convenient but worthwhile to use. In relation to the threat of Hepatitis, Dr. Jones said that prior to the threat of AIDS, patients were constantly tested. He said their liver functions were tested, their antigen and antibodies were tested, and they were told the results.

Choice of Product

In relation to the choice of product available, Dr. Jones said that there wasn't enough BPL (British Plasma Laboratory) home made factor concentrate available. They were forced to use some imported factor concentrate. He said that they knew even in 1983 that imported factor concentrates were less desirable because of the risks associated with paid donors. Dr. Jones again described his fears in relation to the

Armour product in 1985 and 1986, how he had written to Armour expressing his fears and how Armour had subsequently withdrawn their product from the market. He described how Armour had explained that any infectivity associated with the product was caused by unscreened donors, whereas Dr. Jones had been concerned about the safety of the product because of the inefficacy of the heat treatment applied to it. Dr. Jones had gone so far as to notify the national authorities about the danger that, he felt, was associated with this product.

Did Armour Know The Heat Treatment Used Was Not Effective?

Mr. Bradley asked Dr. Jones several questions which concerned what Dr. Jones thought Armour's state of knowledge to be when they were distributing their heat treated product in 1985 and 1986. Counsel for the Tribunal, Mr. Finlay, and the Chairperson both intervened to restrict the line of questioning to matters which were within Dr. Jones' own state of knowledge in 1985 and 1986. Mr. Bradley said that detailed facts had come into Dr. Jones' knowledge since that time. However, the Tribunal would not allow Dr. Jones to give evidence of facts which had come into his knowledge since 1985.

Mr. Bradley then concluded his cross-examination. The Chairperson then stated that Mr. Bradley's questioning had gone outside the parameters of the statement that was originally issued by Dr. Jones to the Tribunal, and in those circumstances she was affording other parties another opportunity to consider cross-examining Dr. Jones. The Tribunal adjourned for a few minutes to allow parties to consider their position. After a brief adjournment the Tribunal resumed, and no party indicated that there were any further questions they wished to ask, with the exception of Mr. Finlay, Counsel for the Tribunal. Mr. Finlay asked Dr. Jones about his treatment of children with haemophilia at that time.

The Tribunal then adjourned to Friday 12th July at 10.30am.

PROCEEDINGS: Friday 13th July 2001 - Day 158

Today, Dr. Brian Colvin, Consultant Haematologist at Bart's Hospital in London, gave evidence. He worked at the Haemophilia Treatment Centre at the Royal London Hospital, which took care of approximately 600 patients.

History of Treatment

In 1985, he treated approximately 40 people with haemophilia who were HIV positive, and 80 people with haemophilia who were HCV positive. Dr. Colvin described how freeze dried factor concentrates dramatically altered the lifestyle and quality of life of people with haemophilia. He said, however, that the dangers of the transmission of Non-A, Non-B Hepatitis from factor concentrates was an issue. He said that it was recognised that there was a much lower risk of transmission of NANB Hepatitis from cryoprecipitate. Nevertheless, cryoprecipitate was not completely safe since it was still derived from blood donations and the instance of NANB Hepatitis was high in the population.

NANB Hepatitis

Dr. Colvin said that he had seen the effects of NANB Hepatitis on people with haemophilia. Many people infected with Hepatitis C, in his experience, had not suffered chronic disease symptoms for a long period of time; but that was not to say that Hepatitis C did not cause serious liver disease. He said there were a number of other factors which would determine whether or not NANB Hepatitis could be extremely serious. Scientific knowledge by 1985 was clear in relation to the dangers of transmission of NANB Hepatitis.

AIDS

In relation to the onset of AIDS, he said that in 1983 it became clear that there was a real threat of transmission of the virus by reason of blood products. He said in the early 1980s he was trying to treat all young children with cryoprecipitate. However, some children with severe haemophilia A had to be treated with factor VIII concentrate made from plasma from large pools of donors. As a result of this treatment, he had approximately six children with haemophilia who subsequently developed HIV. He said originally the policy of treating children with cryoprecipitate was driven in order to avoid Hepatitis infection. However, while treatment with cryoprecipitate at home was not impossible, it was certainly much more difficult than treatment with factor concentrate.

Viral Inactivation

In 1984, around October 1st, reports of viral inactivation of the HTLV-III virus became known. While heat treated product came onto the market, Dr. Colvin said that he was concerned to ensure the efficacy of the heat treatment of the products before administering them to his patients. Between October 1984 and June 1985, Dr. Colvin said that his policy was to either use non heat treated National Health product or to use heat treated commercial American product. As soon as National Health heat treated product came on the market this was given first to children. Adults continued to use a mixture of heat treated American product and National Health product. From 1985, the amount of products produced by BPL in the UK increased.

By 1986 virtually all transmissions of HIV and HCV in blood product had stopped. There was a policy from 1985 onwards to treat all mild patients or previously untreated patients, with heat treated National Health product (known as 8Y).

Dealing with the HIV crisis

Dr. Colvin described how when a test became available in 1985 for HIV, he discovered that approximately 40 of his patients had become infected. He said the responsibility for telling these patients of the positive test result lay on him. He said he tried to involve the nursing staff as much as possible, but principally it was his responsibility. He said they recruited a social worker from the Infectious Diseases Unit to assist them.

Dr. Colvin said that in June 1986, he attended a conference in Milan of the World Federation of Hemophilia. It was at that point that he became aware that the Armour heat treated Factorate product was linked with seroconversions.

Dr. Colvin was then examined by Mr. McCullough for the I.H.S. Dr. Colvin said that in 1983 the policy of treating children with cryoprecipitate came largely from the fear of infection with NANB Hepatitis. Although it wasn't clear exactly what the dangers of NANB Hepatitis were, they were aware, he said, that it could lead to liver disease. He said knowledge derived from treatment over the last 20-30 years had shown that the danger of Hepatitis C for non-HIV positive, non-drinking patients was so far shown to be relatively small. He said, however, in the future those people may become ill.

Mr. McCullough was prevented from asking Dr. Colvin to comment on the situation in Ireland; the Chairperson intervened stating that Dr. Colvin could only give evidence about his own experience in England.

In relation to the use of factor IX concentrates, Dr. Colvin said that there was some concern about the risk of thrombogenicity. However, the figures for the use of factor IX concentrate between 1984 and 1985 show that there was an increase in use of heat treated commercial factor concentrates and a decrease in the use of British non-heat treated product. Dr. Colvin said that the fear of thrombogenicity related only to patients who were undergoing orthopaedic surgery. There was a danger when large amounts of factor IX concentrate would be transfused after surgery, that thrombogenicity might develop. However, in normal day to day use as a treatment for haemophilia B, the risk of thrombogenicity wasn't that great.

Mr. McCullough asked Dr. Colvin whether he had consulted with his patients as to what method of treatment would be used. Dr. Colvin said he had not. He said that the situation was moving extremely rapidly. Difficult decisions had to be made, and there was very inadequate information generally amongst the treating population. He said that as a general practice in medicine over the last 30 years, it had become much more common for physicians to consult with their patients and provide them with information in relation to treatment choices. However, this process was still evolving in the early 1980s. At that time in the early 1980s there was no close involvement of patients in treating decisions.

The Tribunal adjourned to Monday 16th July 2001.