MERSEY REGIONAL HAEMOPHILIA CENTRE

RESPONSE TO QUESTIONNAIRE: HIV LITIGATION MAIN STATEMENT OF CLAIM

Preamble:-

I have consulted with Dr Vanessa Martlew, Director of Mersey and North Wales Regional Transfusion Service and do not disagree with any of her responses to the questionnaire. I have not attempted to address those questions most properly addressed to her, but have enlarged on some of them where appropriate.

Having taken up post in May of 1987, I am unable to answer some of the questions, and suggest that you direct them to Dr B A McVerry. Read the answers along with the historical summary provided and the original questionnaire.

Paragraph 91.

Patients were supplied with home therapy factor VIII and IX from the Regional Centre, and reviewed at the centre when clinical problems arose.

In 1986 regular review clinics were organised which I improved and developed. A physio reviewed all patients from 1987. From December 1988 we also had a haemophilia nurse and social worker, and a joint orthopaedic service was established at about the same time. A comprehensive dental service based at the dental school has been in existance for some time. Patients are reviewed regularly in clinic by the multidisciplinary health-care team and on ward 7Y, should a clinical problem arise. Both the haemophilia nurse and the social worker make domicillary visits. This period has also witnessed the

appointment of a consultant haematologist and haemophilia nurse at Alder Hey Hospital.

Paragraph 91, 10(e):

Manchester Royal Infirmary Haemophilia Centre acted as our reference centre.

Directors since 1970 : T. Black — 1975

Frank Boulton	1975 — 1980
B A McVerry	1980 - 1986
M Mackie	1986 - 1987
C R M Hay	1987 - to date

(This has been communicated * Dr Hay)

The centre director is responsible for monitoring HIV/AIDS in our centre.

Paragraph 10(e)

Please find enclosed photocopies of papers published by myself or from this centre on hepatitis or HIV in Haemophilia.

Paragraph 91, 10(f) & 11(e)

Regular meetings of the haemophilia directors from Mersey and North West Region took place during the period in question. Patients from North Wales were joint-managed by Liverpool and local haematologists in Wrexham (Dr Watson), Bodelwyddlan (Dr Edwards) and Bangor (Dr Korn).

Paragraph 91(b)

The haemophilia director is the regional specialist in haemophilia care, and had sole responsibility for their management in

most cases. Exceptions were those living in North Wales, and those choosing to attend other hospitals.

Paragraph 92(b)

The requirement for clotting factor concentrates was reviewed and revised upwards on an annual basis towards the end of each financial year. Many documents exist which describe monthly deliveries and dispatches of factor VIII/IX but they are not systematically arranged and give limited information about batch numbers. I have enclosed these and would be grateful if they could be returned after photocopying. I also asked Mr Wright (Senior Chief MLSO) to find any delivery notes. A few of these are still in existance but they were generally thrown away after a year. It will be difficult to trace any individual's infection to specific batches of factor VIII.

Paragraph 92 (see Para. 31)

Figures for consumption of concentrate assessed by Oxford are usually, if not always, under-estimates because not all centres report back fully.

Occasional handouts of factor VIII arrived from SNBTS.

Paragraph 92(f)

I can't give dates and amounts.

Paragraph 92(g)

Donor Pool size 1,500 - 15,000 donations/pool (both BPL and commercial). Donation pool size increased production efficiency.

See paragraph 23 (aa)

Did NHS pools range from 200 - 760? - No they were larger. BPL pool sizes were generally a bit smaller than commercial ones. BPL are best qualified to explain why. This is largely irrelevant however, given that BPL and commercial concentrates are equally infectious for hepatitis. (Crask et al BMJ 1983 see enclosure). This occurs because 1% of the donor population are infectious for NANB hepatitis. Pools of more that 100-200 donations will <u>always</u> be contaminated, therefore. Although it was a widely held view, expressed frequently in the main statement of claim, that American factor VIII transmitted more hepatitis, there is no evidence that this was the case, and there is evidence to the contrary (enclosed). The Skid-Row blood banks closed in the sixties and seventies and although the Americans still pay donors, high risk patients are excluded. In contrast, UK transfusion centres were taking blood in prisons up until the early eighties, certainly in Trent and Mersey!! The unfavourable comparisons between the US and UK transfusion services in the main statement of claim is rather biased and unfair.

Para 92(i)

The proportion varied but about 40-50% of factor VIII and all factor IX was domestically manufactured.

Production increased but did not keep pace with increased demand. Lack of investment is the principal reason for the failure.

Para 92(j)

Domestic factor VIII was unavailable for 3 months and at the end

of 1983 and beginning of 1984 because of production difficulties at Elstree. There was a further reduction with the first unsuccessful attempt at heat treatment at the end of 1984 and beginning of 1985, and production fell for 2 years because of the yield was reduced by heat treatment from Summer 1985.

Paragraph 92(k)

What consideration was given to the use of heat treated concentrate:-

See the enclosed introductory chapter of my MD. Liver disease was not considered to be a serious problem until 1985 - well into the HIV era. See enclosed papers. Although Behring started experimenting with pasteurised factor VIII in 1980, there was no general awareness of this, it was not licenced or available in the UK and the trial showing that it was effective was not published until 1988. Although various companies (but not BPL) experimented with heat treated factor VIII, results were not reported until 1985, 86 and 87 and the trials published at this time showed that the heat treatment regimes used at this time were did not inactivating hepatitis viruses. The products were not generally adopted. There was no reason to expect that the heat treatment regimes used would inactivate HIV any more effectively. It was not until late 1984 when HIV had been identified that it transpired that HIV was more sensitive to heat treatment than hepatitis viruses. Even then some heated products transmitted HIV (see enclosed letter from Armour). It was only at that time that a consensus emerged that heat treatment should be generally adopted. Centres in Sheffield, Leicester and the Royal Free and St Thomas's in London used only commercial heat

treated factor VIII and IX from November 1984. Other centres continued to use domestic unheated concentrate until Autumn 1985 when 8Y became available.

Heat treatment might have been developed earlier, but heat destroys factor VIII. Pasteurisation destroys 50% of the factor VIII and would have caused a factor VIII shortage. There was little evidence of death from liver disease or HIV by the mid 80's and so there seemed little reason to jeopardise supply, by the introduction of heat treatment until it became evident that heat treatment killed HIV. It should be born in mind at all times that the average life expectancy of severe haemophiliacs in the pre-treatment era was 15 years. No one wanted to go back to this. Balanced against this, HIV appeared the lesser risk and various agencies recommended that treatment with concentrate should continue. It was not until HIV testing became available in 1985 that it was realised that a high proportion of patients were infected. At this time the risk of developing AIDS was still considered small. It appeared a well balanced risk, given the information available at the time.

See paragraph 65

Early heat treatment did not remove the risk of hepatitis and was not completely effective in removing the risk of HIV (see enclosures from Armour detailing HIV transmission by their heated product).

Paragraph 39

Albumin has been heat treated since the 70's and is

virologically completely safe. However, see comments above.

Paragraph 43

Yes, consideration was given from about 1982. The problem did not really emerge in the UK until 1983 but in 1983 and 1984, based on the known risk from no treatment (life threatening bleeding) as opposed to the largly unknown but apparently small risk of AIDS, it was considered by the Haemophilia Directors Organisation and the World Federation of Haemophilia that treatment with concentrate should continue, as a balanced risk.

Paragraph 41

Clotting concentrate is a generic term for a number of blood products including factor VIII or IX. Yes limited amounts of pasteurised factor VIII for trial purposes only were available in Germany in 1980. This product, has as far as I know, never had a UK product licence (please check the details). It was not generally available.

Heat treated concentrate was not available in the U.S. until 1984 (and then didn't work). Only limited amounts were available, initially on a trial basis, and like any other pharmaceutical, clinical trial preceded general adoption. It became available in larger quantities only in late 1984 when the trials (published in 1987) appeared promising. It is unlikely that sufficient quantities would have been available to supply the whole UK until late 1985.

Paragraph 92(l)

Yes I was involved as S.R. in Sheffield in Clinical trials of heat treated factor VIII in 1983/84/85. See enclosures. This product did not transmit HIV to our patients although it did to others (retrospective testing) and transmited NANB hepatitis to all patients.

Para 92(m)

Heat treated factor VIII was not fully tested, not licenced, and not generally available. The perceived risk from unheated material appeared small, and until 1985 few deaths could be attributed to its use. The risk of both hepatitis and HIV were considered small, until 1984/85.

Para 92(n)

I started to use HT factor VIII in November 1984 in Sheffield. Unheated factor VIII was used in Liverpool until Summer/Autumn 1985.

Para 92(o)

All patients were treated with whichever material was available. No cohorts were treated with any specific product. Many centres treated children with cryo and reserved domestic concentrate for children to defer the onset of hepatitis.

NHS factor VIII was free of charge but always in limited supply. The commercial sector had to make up the shortfall. Our budget was increased without demur by district on an annual basis. Local financial factors have never constrained supply, although they may have indirectly favoured commercial supply. It was often

considered cheaper to buy commercial VIII instead of investing in increased plasma procurement to increase the pro-rata supply of BPL products.

Paragraph 92(r)

Yes, I used imported heat treated VIII from November 1984 but in Liverpool it was not used till Summer 1985.

Supplies were available from Alpha Therapeutic.
Documents?

Paragraph 92(w)

I became aware of the risk of hepatitis in haemophilia in 1976 as a houseman on a unit with a particular interest in this area. The clinical importance of haemophilic liver disease was disputed until the publication of my landmark papers on the subject in 1985 and 1987. Also see photocopy of chapter 1 of my MD which answers the question more fully.

See paragraph 23

(Craske et al 1983 and others). All unheated concentrates transmitted NANB hepatitis to all patients on their first exposure. 15% develop cirrhosis. (Hay et al 1985). The size of the risk was only appreciated at this time. (Hay et al 1985, Aledort et al 1985). The risk was <u>not</u> greater for patients treated with American products. I enclose documents from the Haemophilia Directors Organisation.

Paragraph 92(x)

From 1970 how much commercial factor VIII did we use? About

60%. Mainly Armour and Cutter and Travenol.

Patients were treated with what was available and were not reserved particular products or batches (as was the practice in some centres). There was no pattern of use, and this did not change. All factor VIII used prior to mid 1985 was untreated and after that all was heat treated.

In my opinion, insufficient use of cryo was made in this centre. Children and mild haemophilics should have been treated preferentially with cryo and possibly domestic concentrate.

Advice on treatment of adults and children was the same in this centre. In many centres children are treated with cryo for as long as possible to delay the onset of NANB hepatitis. I can find no documentation of advice from my predecessor regarding the use of blood products. I do know that DDAVP was used less here than in other centres.

Paragraph 92(y)

I became aware of HIV/AIDS in late 1981, early 1982.

The implications were not obvious at the time. The agent responsible, and mode of transmission were not known and it was not until 1982 that reports of possible blood transmission emerged. The natural history was uncertain and it was assumed that like other viruses, such as hepatitis B and Influenza, that it would cause death in only a very small minority (approx. 1%) of patients infected. Early in the epidemic (1981-1983) when the natural history of HIV had not yet unfolded and the agent had not yet been identified, estimates of its pathogenicity were often made by comparison with other viral infections. This was the only thing to do at the time, but mortality

estimates made on this basis at that time now seem hopelessly optimistic. By the time the agent was identified and a test became available almost all the infected patients were already infected, (most were infected 1982-1984).

What were our actions in the light of this?

In most centres the patients were counselled in 1983 and told to:

1. Use safe sex
2. To continue treatment

This occured in Liverpool but was probably not complete. The first suggestion of blood spread was in MMWR 31, 305, July 1982. In December 1982, 4 cases of AIDS in haemophilia were described but no common batches of factor VIII identified (MMWR 31, 644).

The first case of transfusion associated AIDS in California was reported in (MMWR 31 652) December 1982. The link between blood products and AIDS was suggested in early 1983, but there was no consensus about what to do about it since withdrawal of treatment carried a haemorrhagic risk and heat treatment had not yet been shown to be effective against even hepatitis viruses.

June 1983, General recommendation on treatment policy (continue treating as before) sent out by UK Haemophilia Centre Directors Organisation to all haemophilia directors.

There were continued doubts about the link with blood products until 1984 (BMJ 288 1782 editorial accepts AIDS transmission by blood). The implications were uncertain until late 1984, and even then the natural history was not known, it was not known how many were infected, and the agent had only just been identified. (April 1984 Lancet 1, 753). Sexual transmission was established, and most

centres were therefore advising all haemophiliacs to practice safe sex from mid 1983.

Paragraph 92(z)

Most Directors kept themselves informed with the Lancet, BMJ, New England Journal of Medicine and MMWR.

Paragraph 92(aa)

The link with blood products was first suggested in January 1983 (Ragni et al Lancet; 213). This link was disputed, and was not fully accepted until after the agent responsible was demonstrated in April 1984 (BMJ editorial finally accepted this in June 1984, BMJ 288, 1782).

Paragraph 62

July 1982 first cases of AIDS in haemophilia. November 1983, first case in UK.

Paragraph 63

The link between blood and AIDS was not formally established until mid 1984, and could only be suspected (and was therefore constantly disputed) until the infective agent, HIV, was identified in April/May 1984.

I did not publish this area until 1989.

Paragraph 92(ad)

What steps were taken in the light of this knowledge.

Safe sex counselling took place from mid 1983. Regular meetings

with patients and regular counselling about the state of knowledge (or uncertainty) took place from early 1983. Heat treated factor VIII was used only from December 1984 in Sheffield but from mid 1985 in Liverpool.

Paragraph 61(ac)

Yes, this article (Ragni et al, Lancet January 1983i, 213) describes persistent generalised lymphadenopathy in haemophiliacs but is unclear whether this would progress to AIDS. It suggests that AIDS may be caused by an agent transmissable in blood products.

Paragraph 61(ad)

Yes, this article (Editorial, Lancet, i, 745) reviews the NEJM editorial in January which reviews a further paper (White et al Annuals Internal Medicine of 3, 403) proposing a switch to cryo but does not present any strong argument for change. The suggestion was considered extreme at the time because AIDS was uncommon in Haemophilia and the link with blood products had not been proven.

Paragraph 92(ab)

See above

Paragraph (ac)

No steps were taken in most centres. Children were generally treated with cryo as long as possible to defer NANB hepatitis. I would refer back to the advice of the Haemophilia Centre Directors in June 1983.

When published evidence of the heat lability of HIV appeared

(Levy et al, Lancet, ii, 722) in September 1984 several centres (not Liverpool, but Sheffield, Leicester, Royal Free and St Thomas's) stopped using unheated material altogether from October 1984.

DDAVP was used as the treatment of choice in mild haemophilia whenever possible after the publication of its use, (Mannucci et al, Lancet 1977) to minimise hepatitis transmission. There was no need for any further change in its use in HIV era. Tachyphylaxis, and its lack of efficacy in severe and moderate haemophilia limit its use. Cryo was also used in this group of patients but is not ideal for surgery in severe haemophilia, where several day's treatment may be needed. It was also always in relatively short supply, and the treatment necessarily hospital based. Home treatment schemes would have had to be abandoned had cryo been used for all treatment. Haemophilia B can only be treated with plasma, and factor IX concentrate.

As far as I know, the hospital medical committee and the pathology committee did not issue advice on this issue.

Paragraph 92(ag)

I don't know what the policy was.

I started to use heat treated factor VIII on a trial basis in 1984 and went over to heat treated in November 1984. This did not happen in Liverpool until Autumn 1985 when UK heat treated VIIIc became available.

Although heat treated commercial material was available on a named patient basis in February 1985 there were insufficient quantities available for the entire UK, and <u>most</u> centres continued to use unheated NHS material until 8Y became widely available.

Paragraph 71(p)

Advice from Department of Health in November on imported VIIIc? I haven't heard it.

Paragraph 71(l)

13th May 1983. The Haemophilia Directors advised the use of DDAVP where possible. Most centres were already doing this. They also advised the use of British Products and cryo for children to defer the onset NANB hepatitis and minimisd any other risk from blood products. There was still some uncertainty about the blood borne transmission of AIDS but this advice was not controversial since it made some sense in terms of hepatitis spread, and was being practiced in most places already.

I was not in post at the time, and do know whether any action was taken in the light of this advice.

Paragraph 46

DDAVP was available in 1977. It is used for minor surgery in mild haemophilia A. It increases factor VIII levels 2-4 fold. It has the advantage of avoiding blood product use, but is ineffective in severe and moderately severe haemophilia. Tachyphylaxis and water retention are a problem. They limit its use to minor surgery in mild haemophilia. It is ineffective in haemophilia B.

In those centres enthusiastic about it, its use has not changed in recent years. It is my impression that it should have been used more in this centre in the early 1980s. Its use was widespread from 1977.

Acceptable safe animal factor VIII has been available in small

quantities from 1980. It is used for treatment of inhibitor patients. The only published evidence of its use for regular home therapy is by me, published this year. The incidence of antibodies and side effects is such that NO-ONE would consider its general use. 7½ % of patients get reactions and a significant proportion develop antibodies and become refractory to it.

Paragraph 92(ag)

Although porcine factor VIII is more widely used than in the past, it is used exclusively for the treatment of a selected sub-group of patients with factor VIII inhibitors.

Is the increase in its use linked to the use of factor VIII concentrate? I don't understand the question, but the increased use of porcine VIII is linked with increasing purity and fewer side effects.

When confronted with a haemophiliac faced with elective surgery, I would exclude a factor VIII inhibitor, consider whether the patient had been treated with concentrate before, had been vaccinated for hepatitis B (available from 1983) and consider the severity of the haemophilia and the nature of the procedure. If the patient had not been treated with concentrate before and had mild haemophilia, I would avoid the use of concentrate if possible. If it was a major procedure, eg cholecystectomy, I would use concentrate for all those with > 30% factor VIII, because tachyphylaxis could be a problem with DDAVP.

I would not advise a mildly affected haemophiliac against surgery, and such patients were not generally advised against surgery during the mid 1980's unless the surgery was very minor and could be

deferred, eg. vasectomy or varicose vein surgery. From the legal point of view each of these cases must be assessed individually since there are so many variables to consider. Mild haemophilia is ≥ 15-20% VIIIc.

During the period 1983-1985, I would have warned the patients of the risk of AIDS as it appeared at that time. The risk would have been presented as small, since there was no evidence to the contrary.

Paragraph 92(am)

Severe haemophilia is characterised by spontaneous joint and muscle bleeding which is not affected by any change in life style. Most centres suggested that patients be moderate in their use of factor VIII. It seems unlikely that this influenced the prevalence of HIV infection.

Paragraph 92(an)

The use of prophylactic factor VIII varied from centre to centre and decreased after 1982/83. I used it for severe frequent joint bleeds and in inhibitor patients. This was not much practiced in Liverpool. It is a very widespread approach in the continent, the USA and in Newcastle and now that it is safe, I am using it more. The object of the exercise is to preserve joint function.

Paragraph 92(as)

Although we were using heat treated material in limited quantities as trial material, it was not clear that there would be sufficient quantities available for even few centres until the end of 1985. It was made clear by the company during 1984-85 (Alpha) that

there were insufficient supplies for the whole UK.

I don't know what advice was given in Liverpool. In Sheffield there was no delay in starting to use heated factor VIII in November 1983. My previous comments cover this.

Paragraph 92(bh)

Both in Liverpool and in Sheffield, samples were sent to Dr R Tedder, Middlesex Hospital for HIV testing in early 1985. This was very incomplete in Liverpool and Dr McVerry has left no record of his results even though he published them. Many Liverpool patients were not tested until late 1985 early 1986.

Paragraph 92(bl)

Some of the patients were informed of their HIV status by post. Parents of children were informed by Alder Hey in a similar way. Not all patients were informed with results until later in 1986.

Paragraph 92(bj)

Patients intimates were not generally tested. Most refused, and still refuse to be tested for various reasons.

Paragraph 92(bk)

Patients intimates were informed if they accompanied their husbands to hospital.

Paragraph 92(bm)

I was not in post and can not tell you (neither can the notes) what pre-test counselling patients had. The counselling, and in most

cases, the first test result is not documented.

Most patients were not adequately counselled until Dr Mackie took over the centre in 1986. See overleaf.

Most untested individuals were summoned by Dr Mackie in 1986 and most seen with their spouses. He counselled them and generally documented the counselling. This took place in his room or in OPD.

Paragraph 92(bo)

I don't know what was done to provide counselling for HIV negatives. I suspect nothing was done.

Paragraph 92(bp)

Positive patients were sometimes counselled after their result was found to be positive, but many were counselled for the first time when Dr Mackie took over in 1986.

Paragraph 92(bq)

Few intimates were and have been tested (despite efforts to persuade them). There were undoubted delays in counselling some of these and arranging retesting during which one or perhaps two, seronegative on the first occasion seroconverted.

Paragraph 92(bt)

Parents and guardians were the responsibility of Dr John Martin, Alder Hey.