

## **The Penrose Inquiry**

Report by Professor Brian Colvin on the subject:

The use of blood product concentrates in Scotland in the period between the introduction of NHS heat treated products in 1984 and the supply of NHS products sufficiently treated to inactivate Hepatitis C.

I have been given the statement:

“Heat treated NHS Factor VIII (8Y) , treated at 80 degrees for 72 hours, was introduced in England in September/October 1985 but it was not until May 1987 that NHS heat treated Factor VIII (Z8) treated with the same protocol became available for clinical use in Scotland”.

I have been asked to consider the following questions when preparing my report:

Had you been treating patients in Scotland over this period, what would you have done? Would you have been concerned that there appeared to be a hepatitis-safe product available in another part of the UK that was not available for your patients?

### 1. Introduction

1.1 It has been known from the beginning of the history of blood transfusion that there is a risk of transmission of infection from donated blood. Large pool factor concentrates of factor VIII and factor IX were used widely from the beginning of the 1970s and it soon became apparent that there was a risk of hepatitis transmission. Initially hepatitis B infection was reported, partly because a test for hepatitis B had recently been described. For the same reason such infections began to decline as routine testing was introduced and donors positive for hepatitis B were rejected by the Blood Transfusion Service.

1.2 It then became apparent that a substantial numbers of patients treated with large pool concentrates were developing jaundice or asymptomatic abnormalities of tests of liver function without having the markers for hepatitis A or B infection (non-A non-B hepatitis - NANBH).

1.3 By 1983 it was suspected that coagulation factor concentrates, even those made from plasma of volunteer donors in Britain, transmitted NANBH to almost all patients receiving treatment for the first time<sup>1</sup> and this was confirmed by 1985<sup>2</sup>. At the same time the AIDS crisis began to dominate concerns for the haemophilia community. Against this background attempts were made to improve the safety of factor concentrates and reports began to appear on the use of heat to inactivate virus infectivity.

## 2. Product Availability

2.1 It is well known that there was insufficient factor VIII concentrate derived from donors within the UK to meet national demand. This shortfall was exacerbated by the reduced yield of factor VIII caused by the viral inactivation processes employed and by 1988 there was a world shortage of factor VIII of all types.

## 3. Clinical Trials

3.1 Clinical trials played an important part in haemophilia care in the 1980s and the results informed attitudes to management. Studies of hepatitis transmission were sometimes initially conducted in chimpanzees and the results did not necessarily reflect infectivity in humans. The results of trials were often available informally before publication but there was no pre-publication service as is now available with modern advances in computer technology. Following heat treatment of factor concentrates any residual infectivity depended not only on the method and severity of inactivation used but also on the qualities of the virus in question, the source of the plasma used to prepare the concentrate and the initial degree of contamination. Anecdotal reports of infectivity also spread through the haemophilia community, such as the rumour of HIV transmission by a heat treated commercial concentrate reported informally (and later verified) at the World Federation of Haemophilia (WFH) meeting in Milan in 1986.

3.2 The result was that it was difficult to know which concentrates were likely to transmit which viruses and clinicians were obliged to make their own judgements on product safety.

#### 4. UKHCDO Haemophilia Working Party Report for 1986/87

4.1 This report acts as a contemporary snapshot of the position on 15<sup>th</sup> September 1987<sup>3</sup>. It makes clear that “the incidence of symptomatic hepatitis related to blood products is falling”. It mentions “eight cases of non-A non-B hepatitis related to Armour heat treated Factor VIII in 1985”.

4.2 It concludes that “Pasteurisation of Factor VIII and IX using current techniques is unlikely to be complete (*sic*) effective in preventing transmission of infection”. It also mentions the cases of HIV infection in 1986 referred to in 3.1 above.

4.3 It suggests that “surveillance of hepatitis related blood products should be enlarged to include all infections, including HIV, so that information regarding the relative risk of infection related to different products can be collected”.

#### 5. My Personal Experience

5.1 I was aware of the risk on NANB infection caused by factor concentrates in the 1970s and early 1980s and was involved in the investigation of attempts to improve product safety.

5.2 In 1986 I published “Heat treated NHS factor VIII concentrate in the United Kingdom – a preliminary study”<sup>4</sup>. This was a series of case reports undertaken with colleagues at the Middlesex Hospital and at the Blood Products Laboratory at Elstree.

5.3 In 1987 I published “A prospective study of cryoprecipitate administration: absence of evidence of virus infection”<sup>5</sup>. This was a small prospective study of cryoprecipitate administration to patients potentially susceptible to hepatitis. Dr. John Craske was a co-author and was then virologist adviser to UKHCDO.

5.4 I contributed the largest number of patients to the UKHCDO study “Surveillance of Previously Untreated Patients for Possible Virus Transmission by BPL Factor VIII and Factor IX concentrates, 8Y and 9A”, an interim report for which was available on September 30<sup>th</sup> 1986. The report noted that this was not a strict protocol and that the data was inconclusive but compatible with infectivity of 0-14%. The full study was published in The Lancet on October 8<sup>th</sup> 1988 as “Effect of Dry-Heating of Coagulation Factor Concentrates at 80° C for 72 Hours on Transmission of Non-A, Non-B Hepatitis”<sup>6</sup> by the Study Group of the UK Haemophilia Centre Directors on Surveillance of Virus Transmission by

concentrates”. This paper describes 32 patients likely to be susceptible to NANBH who were treated with a total of 20 batches of a factor VIII concentrate and 10 batches of a factor IX concentrate, both heated at 80°C for 72 hours in the freeze-dried state. This was the 8Y concentrate referred to in the statement and questions that I have been given. The paper found no evidence of hepatitis transmission and suggested that this type of viral inactivation had “reduced the risk of NANB transmission from about 90% in untreated concentrates to a statistically determined rate of 0-9%”. Note that no claim was made that viral inactivation had been fully achieved.

5.5 I quote these publications to illustrate that in the period 1985-88:

- i) there was active investigation into the safety of factor concentrates, including the safety of cryoprecipitate that had not been virally inactivated.
- ii) there were still cases of NANBH and HIV infection due to transfusion of heat-treated factor VIII concentrates being reported in 1985 and 1986.
- ii) no claims had been made that any concentrate, however treated, was free of the risk of virus infection.

5.6 From 1984-1987 the United Kingdom was not self sufficient in factor VIII production and commercial heat treated factor VIII concentrates were being used in England (and probably Scotland) at that time. I recall vividly telephoning from Milan in 1986 as soon as I heard of the possible HIV transmission by heat-treated Armour factor VIII concentrate to warn my haemophilia centre in London not to use any of this product which might be in the centre’s stock.

## 6. An Independent Appraisal

On October 1<sup>st</sup> 1988 Professor P. Mannucci concluded in a Lancet Occasional Survey “Virucidal Treatment of Clotting Factor Concentrates”<sup>7</sup> :“To date published clinical studies indicate that viral inactivation by pasteurisation and, to a lesser extent, by vapour heating definitely improve the safety from hepatitis of factor VIII concentrates over that of unheated concentrates and concentrates heated in the lyophilised state at temperatures lower than 80° C. Other methods (such as solvent-detergent, super heating at 80°C, and monoclonal antibody techniques) might prove to be of equivalent safety, but the small numbers studied and the lack of details allow us, at the moment, only to say “presumed innocent””.

## The Questions

1. Had you been treating patients in Scotland over this period, what would you have done?

I would have used desmopressin (DDAVP) where this was appropriate for mild haemophilia A and von Willebrand disease.

Where necessary I would have used the concentrate that I believed, on the evidence available to me, was least likely to transmit NANBH (or HIV).

I would have considered the possibility of using cryoprecipitate for patients who were not suitable for DDAVP and whose exposure to blood products was likely to be very limited. Although the results of my small cryoprecipitate study were published in 1987, the work had been done earlier and by 1987 I believe that the use of cryoprecipitate for haemophilia A in England had largely ceased.

I would have used any NHS heat-treated concentrate that was available to me in preference to a commercial heat-treated concentrate, keeping the number of batches used for particularly vulnerable patients to a minimum. (This preference relates mainly to the risk of HIV infection)

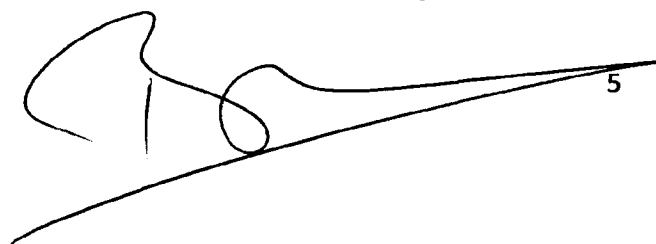
I would have used heat-treated commercial factor VIII where essential, especially for more significant bleeding episodes or major surgery where the use of substantial quantities of concentrate was anticipated.

2. Would you have been concerned that there appeared to be a hepatitis-safe product available in another part of the UK that was not available for your patients?

In my view there was no evidence in the period from 1984-1987 that any factor VIII concentrate was hepatitis-safe. I cannot recall exactly when I became personally convinced that 8Y was a safe product but it must have been after 30<sup>th</sup> September 1986 (the date of the UKHCDO Interim Report on 8Y and 9A) and before the publication of the Lancet paper of October 8<sup>th</sup> 1988. This point of view makes the question difficult to answer. Had it been my perception that a hepatitis-safe product had become available in another part of the UK which was not available for my patients then I would have been concerned.

Brian T. Colvin FRCP FRCPath

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5

## References

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