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INFECTED BLOOD INQUIRY

EXHIBIT WITN2189030

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up to July 1985

5-16

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Lack of experimental animals - need to ~~evaluate~~ VALIDATE process in Humans for BOTH HIV + HEP

23. VIRUCIDALLY TREATED CLOTTING FACTOR CONCENTRATES

Introduction

Pro's of Heat-Treatment possible inactivation of organisms and viruses (for evidence of success - see below).

Con's of Heat-Treatment Plasma cannot be subjected to heat in the usual way. The albumin that it contains would solidify (cf. albumin in egg-white).

Factor VIII (or IX) is a trace protein in plasma and must be concentrated and purified and the bulk of contaminating proteins removed. In order to withstand heat "stabilisers" must be added; otherwise factor VIII biological activity would be destroyed. These stabilisers could also stabilise viruses. The conditions needed successfully to heat-treat factor VIII (or IX) were determined by tedious experimentation and are technical matters which could fill volumes to describe fully. It is facile to write on the ancient principles of pasteurisation. In general however, the following points could be noted.

a. albumin does not have such complex biological functions as factor VIII and heat-treatment for this was developed much more easily. Heat--treated albumin has been available for about 40 years and has a good track record regarding reduced transmission of hepatitis. Even so albumin was not subjected to critical assessments as required more recently for heat-treated products.

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b. heat-treatment is not one process:

Variables include:

i. moisture

dry heat (i.e. in freeze dried state)

heat in aqueous solution

all processes destroy biological activity and 'yield' of factor VIII but this is greater with increasing moisture.

ii. Temperature 60°C to 80°C

Conditions to heat successfully at 80°C were only recently (post HIV) developed.

iii. Time of heating - 10 hours - 72 hours

iv. need for stabilisers

v. need for purifications

vi. use of other viricidal or virus separation processes

Therefore Disadvantages include:

1. Alteration of factor VIII rendering it more likely induce factor VIII antibodies and resistance to treatment. This possibility was quite unassessed in 1980-1984.

2. Possible increased tendency to induce immune suppression.

3. Loss of yield and decrease in supplies

4. Batch to batch variation of effectiveness of process.

5. Lack of experimental animals - need to validate process in humans for both HIV and hepatitis. Well illustrated by 1st generation heat-treated factor VIII concentrate which still transmitted NANB hepatitis in spite of apparently successful trials in chimpanzees.

6. Need for licensing and requirement for different and time-consuming clinical trials (four years for development to licence).

Detailed Account

In July 1980 Tabor et al. (1980) reported on the removal of hepatitis B virus infectivity from factor IX complex by hepatitis immune globulin. This method was of theoretical use only because it

would have been impracticable for mass production of concentrates and its efficacy was not proven. However, in this paper the authors, who were experts on assessing blood products, said "Extensive but unsuccessful efforts have been made to remove HBV infectivity from blood and heat-labile plasma derivatives." They go on to state that ultraviolet light or beta propiolactone (see below) did not remove HBV infectivity.

In 1981 Tabor et al (1981) reported on the use of heat at 60°C for 10 hours in solution and claimed that it could inactivate HBV in antithrombin III preparation. (This clotting factor is more stable than VIII and IX and in any case the material was only tested in chimpanzees. This can hardly be taken as an indication that heat treated VIII or IX concentrate was available).

In 1981 Heimburger et al. (1981) of Behringerwerke AG reported in abstract form in a Supplement to the Journal "Haemostasis" that factor VIII concentrate could be heated in solution at 60° for 10 hours with reduced infectivity for hepatitis B in chimpanzees. The recovery of factor VIII was only about 8% of the level in the starting plasma. (This 27 line double column summary was published as an abstract in the supplement of a "second-line" journal and was almost certainly read by very few haemophilia doctors in UK. Nevertheless this

product was later developed as German heat-treated factor VIII "Hemate-P" which was in fact shown to be effectively sterilised for HIV and Hepatitis viruses - see Schmipf et al. (1987) reviewed below. This material has never been available in sufficient quantities to be used in UK and even now is very difficult to obtain. It's significance is perhaps to show that the technology was developing at that time, but it should be noted that 8% recovery from starting material would be unacceptably low).

This paper was published at length in a German Journal Arzneim-Forsch by Heimburger et al. (1981b.) with an English summary.

On 11 Jan 1982 [redacted] wrote to all HCD concerning the fact that four commercial manufacturers were planning to introduce heat-treated factor VIII and possibly factor IX concentrates in order to attempt to produce 'hepatitis-safe' products (see Appendix 2) We emphasised the need to assess these in clinical trials on previously untreated patients and that these were being planned. We advised against haphazard use of the unlicenced concentrates if they became available since the number of patients suitable for trials would be small and haphazard use would compromise proper assessment.

In the event heat-treated commercial concentrates were not available in substantial quantities until late 1984.

In 1982 — Heinrich et al. (1982) of Biotest GmbH reported on clinical evaluation of the hepatitis safety of beta propiolactone and ultra violet light treated factor IX concentrate. This procedure causes 50% loss of yield of factor IX and is not suitable for factor VIII. Although this method is effective this preparation of factor IX has never been available or used, as far as I know in this country.

In Sept 1982 — Gerety and Aronson (1982) wrote that "... alteration, denaturation or inactivation of proteins and residual β-propiolactone in products are additional concerns that would have to be addressed before this combination of treatments can be applied to plasma derivatives."

In Feb 1983 — Prince et al. confirmed the HBV viral inactivation by beta propiolactone/UVL and they outline other precautions and requirements for a safe product, but this paper did not fully address these problems.

11 July 1983 — (Circulated September 1983) [redacted] on behalf of the HCD Hepatitis Working Party summarised the status of hepatitis-reduced products and described those from five manufacturers. Only one of them (Hemofil T) was available for Clinical trials in UK.

He points out that the infective nature of AIDS is the most likely theory but that the nature of the agent is not known nor if it is inactivated by any of the processes used more or less successfully (or unproven) for hepatitis.

He points to ethical problems with assessment of heat-treated products:- "Since the only way of ensuring the susceptibility to non A non B viruses is by using patients who have not previously received factor VIII or IX concentrate, a choice will have to be made between using heat-treated products from commercial sources, which might carry a small risk of AIDS transmission, or using NHS concentrate which appears to carry a 100% chance of transmitting non A non B hepatitis. (See Appendix 3)

In March 1984 [redacted] wrote to HCDs that studies on Hemofil HT indicated an attack rate of 63% for NANB Hepatitis and that altogether eight 'hepatitis-reduced' products on trial, all except NHS were produced from USA plasma. We asked that directors inform Oxford Secretariat if they planned to use the products and emphasised the importance of using them against a clinical trial exemption certificate. Otherwise for use on a named patient basis means that the doctor not the Pharmaceutical company is liable for compensation.

This document (Appendix 4) indicates that products were available but that those made from USA plasma carried the putative risk of AIDS. (At that time the effect of heat on HIV was not known and NANB hepatitis was not inactivated in Hemofil T).

In 1984 Gerety (1984) reviewed virucidal and virus removing processes for clotting factor concentrates. Available data indicated that heat inactivation of hepatitis viruses could be accomplished.

Yoshizawa et al. (1984) in chimpanzee experiment found that nonAnonB hepatitis virus was inactivated by beta propiolactone.

In August 1984 Hollinger et al. also found that a dry heat-treated factor VIII concentrate (Hyland USA) showed reduced risk of hepatitis transmission in chimpanzees.

It should be noted that experience (Colombo et al. 1985), that a dry heat-treated factor VIII concentrate transmitted hepatitis to humans even although chimpanzee tests had indicated that it was 'safe'. Chimpanzee tests are not a reliable indicator of hepatitis safety in humans.

In Sept 1984 — Levy et al. (1984) in a paper in Lancet indicated that infectious retroviruses were inactivated in factor VIII concentrates heated in the dry state at 68°C for between 72 and 96 hours.

13 Oct 1984 — The National Hemophilia Foundation of USA revised its recommendations for treatment of haemophilia and strongly recommended changing over to heat-treated products with the understanding that protection against AIDS was yet unproven (Appendix 5).

This information was published in MMWR of 26th October 1984.

In Dec 1984 — An Editorial in the Lancet which was written by me recommended use of heat-treated factor VIII concentrate but left the question of heat treated factor IX concentrate open because of lower incidence of HIV seroconversion in haemophilia B in USA and UK and doubts on safety of heated factor IX concentrate.

In Dec 1984 — HRCD's drew up revised guidelines for treatment making recommendations in line with Lancet Editorial. These were circulated to HCD's in early January 1985. (Appendix 6).

24 Jan 1985 — [redacted] wrote to HCDs on supplies of heated factor VIII concentrates pointing out that heat-treated material would be at first merely the current

product heated and that supplies would be available over next three to four months in reduced amount. He wrote that solubility would be marginally impaired (in fact some was virtually insoluble and I did not consider that it was suitable for home-treatment - ALB).

They stated that a new product 8Y would be available later in the year, in which both HTLVIII and hepatitis viruses would be inactivated. (Appendix 7)

In Jan 1985 — In a letter to Lancet Stephan (1985) of Biotest claimed that beta-propiolactone inactivated LAV and is useful for factor VIII concentrate.

In Jan 1985 — Spire et al. (1985a.) claimed that LAV was inactivated by heating in liquid medium at 56° for 30 minutes. (However this is different from factor VIII concentrate). The virus was not inactivated by gamma rays or ultraviolet light.

May 1985 — Mosseler et al. (1985) found that wet-pasteurised Hemate P in Germany did not induce antibodies to HTLVIII in a small group of 18 patients.

June 1985 — Mannucci et al. (1985) warned against over interpretting Mosseler's data because of small number of patients studied.

June 1985 — Levy et al. (1985) confirmed previous work on heat inactivation of ARV claiming heating at 68°C for over 48 hours was effective. Results indicated that heating in dry state at 68°C for 72 hours or in wet at 60° for 10 hours should kill up to 10^6 viruses per millilitre. (It should be noted that Levy worked in collaboration with Cutter Laboratories whose scientific staff were co-authors).

In July 1985 — Colombo et al. (1985) showed that NANB hepatitis occurred in 11/13 patients treated with factor VIII concentrate heated in dry state at 60° for 72 hours (Hemofil T). Preliminary information had been circulated to HCD's in March 1984 (see above and Appendix 4).

In July 1985 — Preston et al. (1985) reported 2 cases of NANB hepatitis after use of Armour Factorate HT (dry heat 60° 30 hours).

In Sept 1985 — BPL started general issue of its new 8Y heat treated Factor VIII (dry heat 80° 72 hours) (Appendix 8)

In August 1985 — McDougal et al. (1985) reported that heating factor VIII and IX concentrates in accordance with manufacturers regimens inactivated HTLVIII/LAV. Specific manufacturers were not stated.

In Sept 1985 — Kernoff et al. (1985) reported that a heat-treatment protocol for factor VIII with heating in a heptane slurry ("wet" heating) before final freeze-drying - Profilate (Alpha) was more effective than dry-heating in inactivating NANB hepatitis virus.

In 1985 — Hilfenhaus et al. (1985) of Behringwerke reported that heating at 60° for 10 hours in liquid (as in Hemate P) destroyed surrogate retroviruses (HIV not tested).

October 1985 — Petriacciani et al. (1985) reported experiment to show that LAV/HTLVIII was likely to be killed in then licensed (in USA) heat-treated factor concentrates.

In Nov 1985 — Piszkiewicz et al. (1985) reported that alcohol precipitation step in fractionating factor VIII reduced HTLVIII/LAV virus content.

Gazengel (1985) reported no seroconversions in 21 patients given unheated Autoplex (USA factor VIII inhibitor bypassing agent) and suggested that alcohol treatment had destroyed LAV/HTLVIII.

In Feb 1986 The Department of Health and Social Security Expert Advisory Committee on AIDS reviewed possible seroconversions after heat-treated factor VIII which were reported by letter by [redacted] He claimed that the events had occured in patients treated in USA and Holland.

Heat treated products were reviewed

who noted interalia that Hoechst (Behringwerke) Hemate P was not available in UK.

noted that three seroconversions to HTLVIII after use of heat treated factor VIII had occurred; two of them with Factorate (Armour) in a batch known to contain plasma from an infected donor.

In March 1986 White et al. (1985) reported one case of seroconversion after heat-treated factor VIII.

In April 1986 Van der Berg (1985) reported another seroconversion to heat-treated factor VIII.

In April 1986 Van der Meer (1986) reports on absence of seroconversion in haemophiliacs (18 patients) treated with dry heat-treated factor VIII.

March 1986 Prince et al. (1986) report on a new method for sterilising concentrates by exposure to solvent and detergent.

In 1987 — Mariani et al. reported three seroconversions to HIV in patients treated with heated factor VIII and IX concentrate.

In 1987 — Kernoff et al. (1987) confirmed his 1985 letter to Lancet (Kernoff et al. 1985) that factor VIII concentrate "wet" treated in heptane slurry had reduced risk of transmitting NANB hepatitis.

In 1987 — Carnelli et al. (1987) found substantially similar results to Kernoff et al. above. Risk of transmission of NANB hepatitis reduced to 20% or less.

April 1987 — Schmipf et al. found that wet heat treated Hemate P (Hoechst-Behringwerke) did not transmit hepatitis.

January 1988 — [redacted] reported to HRCD's on a meeting in Atlanta in which 20 cases of seroconversion to HIV In patients treated with heat-treated factor VIII worldwide were reviewed. Although only 7 cases were confirmed the cases mostly involved dry heat-treated 60°C for a short period of 30 hours i.e. Factor-ate (Armour) even when it was produced only from HIV--screened donors (Appendix 1)

In July 1988

These and later surveys were published by CDC (MMWR 1988) 14/18 apparent seroconversions due to products dry-heated at 60°C for 30 hours. They recommend for HIV and NANB hepatitis products heated in aqueous solution, solvent/detergent treated, or newer technology products.