The Penrose Inquiry

Witness Statement of Prof.dr.W.G. van Aken, formerly Director of the Central Laboratory of the Blood Transfusion Service (CLB) of the Netherlands Red Cross.

The Penrose Inquiry – Heat Treatment to 1985

Re. Acceleration of existing pasteurization program

In 1983 Dr.P.Foster suggested to accelerate the pasteurisation programme of PFC to deal with the HIV/AIDS threat. The question is now if a decision to act accordingly, despite the absence of hard evidence about the nature of the agent responsible for AIDS, should have been taken on the basis of a *"worst case scenario"*.

Dr.Foster's suggestion was most likely based on the presumption that a micro-organism, such as a virus, is responsible for AIDS, that this agent is present in donor blood and that such an agent can be inactivated by heat, i.c. pasteurization. At the time it was not known if a virus was responsible for AIDS although there were speculations about the likelihood of a viral disease. It took, however, till 1984 before it was ascertained that HIV is responsible for AIDS. That the virus is present in donor blood was not known in 1983 although it was taken into account that, like other blood born diseases, the agent would most likely for some time be present in the circulating blood of infected people. How the agent would be present in blood, as a free particle in plasma, or bound to blood cells or both free and bound, was unknown. The heat sensitivity of the agent was also unknown. There were speculations that the agent might behave similar to certain hepatitis viruses, and therefore that heating might be an effective method for virus inactivation. But evidence for this was lacking.
Thus it was by no means certain that pasteurisation would be a method to improve the safety of plasma products like factor VIII concentrate.

However, for a "worst case scenario" it may be argued that although the evidence for efficacy of heating was lacking, pasteurization could still be tried provided that the potential negative effects would be manageable and acceptable. In 1983 it was well known that factor VIII (and other clotting factors) is quite labile at a temperature of more than 4˚Celsius. It was recommended that plasma, the source material of factor VIII, needs to be stored at 4˚C or below. If not, the recovery of factorVIII from plasma for fractionation or cryoprecipitation will decrease depending on the temperature and the length of storage. At the time factor VIII was the driving force behind the collection of plasma in many countries like Scotland which aimed to be self-sufficient. The initial attempts in several laboratories to use pasteurisation demonstrated that the yield of factor VIII was very low; only 10 % or less of the quantity of factor VIII present in freshly collected plasma could be recovered. If pasteurisation would have been introduced, this low yield would seriously compromise any attempt to create national self-sufficiency of blood and blood products. It should be kept in mind that patient organisations were most afraid about the lack of sufficient products for haemophilia treatment and were well aware about the risks of transmissible diseases.

A second negative effect to be considered is that neoantigens of factor VIII may form upon heating which would lead to inhibitor formation in patients receiving the pasteurized product.

Two instances are reported in the literature about neoantigen formation following the treatment with heat treated factor VIII.
Once a factor VIII inhibitor is present in patients with haemophilia the treatment is quite complex and requires very large quantities of factor VIII.

In 1982 – 1986 these considerations were part of discussions among fractionators in various countries. Some thought it was necessary to take action even though important evidence was not available. Others, like the Central Laboratory of the Blood Transfusion Service (CLB) in Amsterdam, acted in accordance with the published recommendations of haemophilia physicians in the Netherlands to restrict the manufacturing (and use) of factor VIII concentrates to have sufficient source material for the production of (freeze dried) cryoprecipitate. As a consequence CLB provided predominantly small pool cryoprecipitate (instead of factor VIII concentrates). It can be calculated that the risk of virus transmission by small pool cryoprecipitate is significantly less compared factor VIII concentrate which is prepared from very large pools of plasma. Furthermore, the yield of factor VIII from cryoprecipitation is much larger than when factorVIII concentrates are prepared.

Acceleration of the pasteurisation program by PFC would most likely have led to a low factor VIII yield and consequently fewer products for haemophilia treatment. To compensate such losses a very large increase in the collection of donor plasma in Scotland would have been necessary. In addition the risk of side effects, such as neoantigen formation by pasteurisation, would have made the treatment of a certain number of haemophilia patients more complicated. This leads me to conclude that although acceleration of the pasteurization program by PFC might have seemed an option in 1983, it is unlikely that (as part of a "worst case scenario") this would have provided a solution for PFC.

Re. Commercial products – clinical trials

The question was put forward: "Should PFC have been encouraging clinicians not to let their patients try the commercial heat treated products?"

The arguments which were used by Dr. Cash to state that "the NHS fractionators should do nothing to support commercial rivals" are not known to me.

The situation in my country may have been different from that in Scotland. As a national fractionation institute and supplier of plasma products CLB provided information about its own products. Furthermore the haemophilia physicians were regularly (every 3 months) informed about the logistics of the supply of concentrates and cryoprecipitate. During these meetings new developments to improve the virus (AIDS) safety of plasma products were presented. The physicians treating haemophilia patients felt that the first priority of CLB and the regional blood banks was the provision of sufficient cryoprecipitate.
CLB did not encourage clinicians to stop or decrease commercial products; it did not give an opinion, negative or positive, about those products.

In January 1983 the association of physicians treating haemophilia patients agreed on the following advice concerning haemophilia treatment:

1) if possible use cryoprecipitate (notably for newly diagnosed patients and children of less than 4 years);

2) if factor VIII concentrate needs to be used, prescribe factor VIII concentrate prepared from plasma of Dutch donors (use commercial concentrates only in case of a severe side effects following the use of Dutch concentrate);
3) for the treatment of haemophilia B patients use only factor IX concentrate prepared from plasma of Dutch donors.

This advice was published in the Dutch Medical Journal and in the magazine "Factor" which was distributed among members of the haemophilia foundation in the Netherlands.

There was one blood bank in the Netherlands which used a different policy: here the use of commercial heat-treated factors VIII concentrate was recommended and such products were distributed. The other blood banks prepared and supplied only cryoprecipitate.

Re. Commercial products – Hyland (*Hemofil T*)

The question was put forward: "Do you think that there is potentially an argument that such heat treated products (*Hemofil T*) should have been adopted in the UK in advance of locally produced products?"

In 1982 Hyland started its marketing campaign of Hemofil T (heat treated factor VIII concentrate) in the Netherlands. In March 1983 this product was licensed in the US. In Augustus 1983 Hyland received a license from the Dutch Ministry of Health to import *Hemofil T.*
Hemofil T was developed to prevent transmission of hepatitis B and hepatitis Non-A/non-B hepatitis (NANB). The effectivity of the heat inactivation method was tested in a few chimpanzees. It was reported that these animals did not develop NANB hepatitis following the administration of heat treated factor VIII concentrate (Gomperts, E.D. Am.J.Haematol. 1988, 70, 393-395).
In October 1983 some experts mentioned unofficially that NANB hepatitis was observed in so-called "virgin patients" (i.e. patients not treated before with plasma products), following the use of *Hemofil T.* It took till 1985 before these observations were published in the Lancet by Colombo et al (Lancet 6 July 1985, page 1-3) [LIT.001.0369]. In their study 84% of infants and children who were exclusively treated with *Hemofil T* developed NANB hepatitis.

If the marketing efforts of commercial companies such as Hyland would have led to introduce such a product for haemophilia treatment in the UK it would subsequently have created uncertainty and critique when it was shown that the claim of non-transmission of NANB hepatitis proved to be unjustified.

I believe that the adoption of heat treated products was justified when it was established that the agent responsible for AIDS was inactivated by the heating procedure.
In view of the relative unsafety of commercial plasma as source material for the manufacturing of clotting factor concentrates like factor VIII it was prudent not to introduce commercial factor VIII concentrate until it was shown that such products were safe. There were alternative products like cryoprecipitate available which because they were prepared from small pools of plasma from non-remunerated donors were less risky than factor VIII concentrates prepared from very large pools of remunerated donors.

To answer the question, I believe that the adoption of commercial heat treated products in the UK in advance of locally produced products would have been justified once there was

sufficient and reliable data from clinical studies demonstrating the safety and efficacy of such commercial products. *Hemofil-T* did not meet such criteria.

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