MEDICAL REPORT AND OPINION

Re: JPK 037

Stephen Robert **HALLWOOD** (dec.)

dob GRO-A 0

GRO-A , LIVERPOOL 1.

This medical report and opinion has been prepared from the following documents:-

1. copies of the complete hospital records from Liverpool Childrens Hospital (Alder Hay).
2. copies of letters from the patients G.P. to Alder Hay Hospital.
3. copies of the minutes of the U.K. Haemophilia Reference Centre Directors meetings.

The patient was diagnosed as suffering from severe Haemophilia A with a factor VIII level of < 1% normal, at the age of 4 months (letter Dr. Martin to Dr. Hullman dated 26.06.80). The family history was highly significant in this case, since the patient's mother was a known carrier, a maternal uncle had died of haemorrhagic symptoms due to haemophilia at the age of 7 years, an elder brother had severe haemophilia and subsequently a younger brother was born with severe haemophilia.

The young boy was first treated on 01.03.82 with U.S. commercial factor VIII concentrates. There is no documentation at that time to indicate that the treatment alternatives with single donor pool cryoprecipitate or NHS factor VIII

concentrates were ever entertained. During 1982, Stephen Hallwood was treated on 32 occasions with U.S. concentrate (Armour) and on 5 occasions with NHS material (factor VIII concentrate). This year proved to be the 12 months prior to 1985 that required the most frequent hospital visits necessitating infusions with factor VIII concentrates. During 1982 some 19,000 units of factor VIII were used to treat haemorrhagic symptoms. In 1983, 7 treatments were administered with U.S. commercial concentrates, and 2 with NHS concentrates, totalling in all approximately 5,500 units. In 1984, 4 treatments were given with U.S. commercial concentrates and 4 with NHS concentrates, giving a total of approximately 4,000 units for the year. The last treatment given during 1984 was on 02.12.84 with Armour factor VIII concentrate (Batch no. X 61311). This occasion was the only time this batch of unheated material was used. In 1985, Stephen was treated on 9 occasions with heat treated U.S. concentrates, on 2 occasions with U.S. unheated concentrates, on 2 occasions with NHS unheated concentrate and on 6 occasions with the earliest NHS heated factor VIII material (totalling approximately 10,000 factor VIII units). The 2 occasions when unheated Armour factor VIII were used were on 21.01.85 and on 22.01.85 for a spontaneous haemarthrosis of the left elbow. This unheated material was batch no. Y 88908 which had not been administered to the patient before, and was not used subsequently. To my knowledge, at other Centres, much of this unheated batch had been returned to the manufacturer, who subsequently heated the product in one of their facilities in W. Germany. The heated product with a modified batch number Y 88908(HT) was then made available for general purchase in the U.K. after 01.02.85. Home treatment with concentrates was started in this patient on 17.12.85. Although the child was seen on several occasions in 1985, the first documentation of blood sampling for antibody to HTLVIII was on 05.08.85, and the result indicating HTLV III seropositivity was

reported on 08.08.85. No previous negative results were obtained in this case rendering a possible date for the initial viral transmission difficult or impossible. It is of interest, however, that when the child was admitted to hospital in 1984, cervical adenopathy suggestive of a recent tonsillar infection was noted, but evidence for a generalized lymphadenopathy was lacking (letter Dr. West to Dr. Hillman dated 19.10.84). On 07.05.85, however, Stephen was admitted for abdominal symptoms and fever and was then noted to have cervical lymphadenopathy and an abdominal mass. Although his symptoms were attributed to an abdominal bleed, a diagnosis of mesenteric adenitis was considered. It is feasible that some of the symptoms and signs demonstrated on this admission could have represented a limited form of the early febrile illness associated with a recent infection by HTLVIII (HIV).

OPINION

This case concerns a young child with severe haemophilia who was treated from 1982 to 1985 with unheated U.S. commercial and NHS factor VIII concentrates for haemorrhagic symptoms. On 08.08.85, the patient was shown to have been infected with HTLVIII without a previous negative test result, presumably by transmission of the virus through contaminated blood products. The major issue in this case relating to possible negligence and causation rest upon the choice of therapeutic products used to treat haemorrhagic symptoms. The therapeutic policy adopted to manage this child is evaluated in terms of orthodox practice and knowledge of HTLVIII transmission from blood products at the time, and to the specific recommendations available in the medical literature and proposed by the U.K. Haemophilia Centre Directors Organisation.

Usage of Concentrates as opposed to Cryoprecipitate

There are two notable features of this case with respect to the adopted therapeutic approach. Firstly, there is no documentary evidence to suggest that single donor pool cryoprecipitate was ever contemplated in the management of this case, not even when the patient was initally treated. Secondly, there is evidence to indicate a defined preference to use U.S. commercial products (45 treatments) over NHS factor VIII concentrate (9 treatments) during the period 1982-1985 when initially only unheated, but subsequently heated products were available.

In the late 1970s and early 1980s, the majority of U.K. paediatricians treating infants and children with severe haemophilia considered cryoprecipitate obtained from single blood donations to be the therapeutic product of choice, but if not available NHS factor VIII concentrate should be used. These recommendations which had been in practice some years were quite explicitly expressed in 'AIDS and the blood' compiled by Dr. P. Jones and other practising clinicians - p.43 (1985) - 'In order to reduce the small risk of AIDS the present recommendation in Britain is that children under the age of 4 years should be treated with cryoprecipitate or small pool concentrate from carefully screened donors rather than with multi donor factor VIII concentrate, and with fresh frozen plasma rather than with factor IX concentrate. This recommendation might not be possible in the event of severe bleeding or the need for major surgery, or if a high level of clotting factor antibody is present. Older children who are severely affected should receive concentrates which have been heat treated'. At that time, this practice was deemed to confer a greater margin of safety from transfusion related viral diseases such as hepatitis B and non A non B hepatitis, on the grounds that treatment with a small number (less than 50 individual single donations) of cryoprecipitate preparations resulted in a reduced incidence of clinical and laboratory indices of hepatitis. In contrast, the donor pools of factor

VIII concentrates were derived from several hundreds or thousands of plasma donations (Pools from Elstree 3,500 donors, Oxford 500 donors, U.S. concentrate >10,000 donors - minutes p.5 U.K. Haemophilia Reference Centre Directors meeting, Sept. 1980). The increased morbidity in small children following infection with hepatitis B and non A non B hepatitis was an additional reason for choosing cryoprecipitate over concentrate.

Furthermore, sufficient amounts of factor VIII necessary to control haemorrhagic symptoms in such small children, were available in only a few single donor bags of cryoprecipitate, providing a safe and highly cost-effective approach to such cases. The somewhat larger infusion volumes with such treatments compared to the smaller reconstitution volumes of concentrates were not considered to disadvantage the increased safety aspects of this therapeutic approach. As small amounts of cryoprecipitate were usually required to manage such children, availability of the material from the local BTS was in general no particular problem, and orders could be placed in advance to ensure adequate supplies for individual patients. The side effects occasionally encountered with cryoprecipitate (rashes, asthma-like symptoms) were usually easily controllable with antihistamines, and did not impose a relative or absolute contraindication for its use. As the child required treatment in hospital for each bleed, often leading to subsequent inpatient management, any perceived additional convenience for using factor VIII concentrates cannot be considered a pertinent argument for their exclusive use over cryoprecipitate when the issues of safety and cost-effectiveness are also addressed.

The lack of consideration and disregard of the then current therapeutic recommendations for the treatment of children under the age of 4 years regarding

the use of cryoprecipitate in this case was negligent. Any argument that cryoprecipitate was in poor supply at the time is untenable since the material was being used in significant amounts for home therapy (minutes p8. U.K. Haemophilia Reference Centre Directors meeting, February 1981). The overwhelming use of commercial U.S. concentrates in preference to cryoprecipitate or NHS factor VIII is remarkable, particularly in a large city such as Liverpool known to have an active BTS with facilities for cryoprecipitate production and regularly supplying plasma to Elstree for fractionation. The lack of a well-defined therapeutic policy regarding preferential use of domestic plasma derivatives in children at this time was negligent, particularly since the factor VIII requirement in this case during 1983 and 1984 was so minimal (5,500 units in 1983 and 4,000 units in 1984) that special reserves of cryoprecipitate or NHS factor VIII could have been set aside. A reflection of the orthodox management of children at that time is apparent from the minutes of the U.K. Haemophilia Reference Centre Directors Meeting of May 1983 - p.2, when particular emphasis was placed upon use of domestic plasma derivatives.

'With regard to general policy to be followed in the use of factor VIII concentrates, it was noted that many directors have up until now reserved a supply of NHS concentrates for children and mildly affected haemophiliacs and it was considered circumspect to continue with that policy'. Although a slightly modified version of these minutes were circulated as recommendations to all U.K. Haemophilia Centre Directors dated 24.06.83, they were clearly not followed in this case. These recommendations for orthodox practice were reiterated in 'Aids and the blood' p.43 (1985).

During 1983 and 1984, both the mass media and the medical press were inundated with reports of AIDS cases in haemophilia and the potential dangers of large donor pool concentrates and by June 1984 (Sofai - Lancet i, 1438, Editorial BMJ, 288, 1782) it was clear the factor VIII concentrates in their then present form, transmitted HTLVIII. Following Levy's report (Lancet ii, 733) in September 1984, and an article in MMWR, 33, 589, heat sensitivity of HTLVIII was demonstrated in coagulation factor concentrates. At that time U.S. heat treated factor VIII products had just become available on a named patient basis in the U.K. In October 1984, 'Recommendations concerning AIDS and the Treatment of Haemophilia' were published (JAMA 252, 19: 2679) reporting the deliberations of the Medical and Scientific Advisory Council for the Haemophilia Foundation in the U.S. These were closely followed in December 1984 by the U.K. Haemophilia Centre Directors Organisation AIDS Advisory document to all U.K. Haemophilia Centre Directors. Both documents issued general recommendations for the use of heated concentrates and the discontinuation of therapy with U.S. commercial unheated material. At the first meeting of the AIDS group of the Haemophilia Centre Directors on 11.01.85, p4, the Reference Centre Directors unanimously agreed that all commercial factor VIII used should be heat treated and that some directors had even decided not to use NHS untreated material. Despite this information with which a competent practicing paediatric haematologist could be expected to be conversant, and a further report by Bloom in January 1985 (Lancet i, 336), which stated that at least 2 batches of NHS concentrate had transmitted HIV and urged the use of heat treated concentrates, Stephen Hallwood was given two infusions of unheated U.S. concentrate in January 1985 and two infusions of unheated NHS concentrates in March 1985. The infusion of these untreated therapeutic agents at these times

when heat treated concentrates were commercially available was negligent, and from the available data these treatments could have been the likely causation whereby HTLVIII was transmitted to the patient which subsequently led to the development of AIDS in this child.

GRO-C

G.F. Savidge, M.D. 26th March, 1992.

Director, Haemophilia Reference Centre