NEWCASTLE DISTRICT HEALTH AUTHORITY

REPORT OF AN AD-HOC GROUP TO CONSIDER THE USE OF HEAT-TREATED FACTOR VIII CONCENTRATE

At the request of the District Administrator (Mr. C.Spry) and the Chairman of the Hospital Medical Committee (Dr. C.B. Henderson) we met on December 4th 1984 to consider the necessity and implications of using heat-treated factor VIII concentrates in treating patients attending the Health Authority's Haemophilia Centre at the Royal Victoria Infirmary.

Background. The Haemophilia Centre at the Royal Victoria Infirmary cares for patients with haemophilia in the Northern Region. This condition is due to a genetic defect in the production of one of the coagulation factors (factor VIII) required for the normal clotting of blood. Consequently patients with the disorder are at risk of severe bleeding either spontaneously, after minor injury, or after surgery, depending on the severity of their condition.

The mainstay of treatment of patients with haemophilia is to administer factor VIII intravenously either as human factor VIII concentrate, human cryoprecipitate, or animal factor VIII. For clinical and practical reasons most patients with haemophilia are treated with human factor VIII concentrate: 30-40% of the material used in the Haemophilia Centre is UK-derived factor VIII obtained free of charge from the National Blood Transfusion Service, but the remainder is purchased from a variety of commercial sources. All human factor VIII preparations, however, are obtained from donors. Although both NHS and commercial factor VIII concentrates are satisfactory forms of replacement therapy, material from both sources has the potential to transmit infections from donors to recipients. This danger is aggravated by the fact that factor VIII concentrates are prepared by pooling plasma fractions from a large number of donors: consequently, even a very small number of infected donations can produce widespread contamination of the final product. Until recently, the most important contaminants were hepatitis viruses.

Considerable efforts are therefore made to establish that donors are healthy, that they do not have known infective agents in their blood, and that the quality of the final product is satisfactory. For a number of reasons, NHS factor VIII is substantially less likely to contain infective agents than that obtained from commercial sources which is ultimately derived from donors in North America. Whilst it has been the policy of the Health Authority and the Haemophilia Centre to use NHS factor VIII wherever possible, supplies are limited and it is anticipated that the UK will not become self-sufficient before 1986. We believe that this date may also be overoptimistic.

Consumption of factor VIII concentrates, and their cost, within the Authority, over the past few years are shown below:

	Units (million)	Cost (£)
1982/83	4.9	279,000
1983/84	4.1	275,000
1984/85 (end October)	3.8	301,000

Annual fluctuations in usage (reflected in the number of units used per year) are due to the development of inhibitory antibodies in some patients, and the large quantities required if even a small number of haemophilic patients require major surgery. The increase in costs are due to price rises of the commercial products. The RVI pharmacy department, in consultation with the Director of the Haemophilia Centre, have made substantial efforts to obtain commercial factor VIII at the most economic price but the world-wide shortage of the material does not provide much scope for price negotiation.

Acquired Immunodeficiency Syndrome (AIDS). This disease has only been recognised for the past four to five years. Recent evidence suggests that it is caused by one or more retroviruses, and that infection with the agent results in depression of the immune system. Consequently, patients are susceptible to overwhelming infections from other viruses, bacteria and fungi. Knowledge of the natural history of AIDS is very incomplete, and there is no known effective treatment for patients suffering from the disorder. Epidemiological evidence, however, has shown that it may be transmitted during homosexual and (less commonly) heterosexual intercourse, and by transfusion of blood containing the putative AIDS virus. The disease appears to have a median incubation period of 2 years but it may be as long as 5 years in some individuals.

90 individuals are believed to have died from AIDS in the UK including 2 heterosexual haemophilic patients. Because of the known haematogenous transmission of AIDS, haemophiliacs are at clear and special risk of contracting the disease. 74% of haemophiliacs in the USA, 53% of West German haemophiliacs, and 34% of London haemophiliacs have antibodies to the putative AIDS virus (HTLV III & LAV) indicating previous exposure to viral antigen either as live or dead virus. It is not known at present what proportion of haemophiliacs attending the Northern Regional Centre have anti-viral antibodies but this information will be available soon: there is no reason to believe that the incidence will be less than that in London haemophiliacs and we know that one patient has contracted the disease in Newcastle. The clinical implications of the presence of anti-viral antibodies

are uncertain except to indicate previous exposure to living or dead virus. It is also uncertain whether antibody positive patients would be protected against further exposure to the AIDS virus. At the present time there is no test for the AIDS agent which can be used to screen factor VIII preparations for potential infectivity. Whilst the likelihood of contracting AIDS seems greatest from the use of commercial factor VIII, NHS factor VIII cannot be regarded as completely free of risk.

Heat-treated factor VIII concentrates. A number of manufacturers of factor VIII concentrates possess Clinical Trial Certificates for the preparation and administration of heat-treated factor VIII. Heat-treatment of factor VIII was initially introduced in order to inactivate at least some of the viruses causing hepatitis. Heat treatment has also been shown to inactivate some retroviruses and it seems likely, on theoretical grounds, that heat-treatment will inactivate the AIDS virus. The use of heat-treated factor VIII, however, poses five potential problems:

1) No heat-treated commercial factor VIII is currently available with a Product Licence. For the time being, therefore, any use of commercial heat-treated material within the Authority must be carried out under the "named-patient" provisions of Section 8 of the Medicines Act. Informal discussion by one of us (MDR) with the Licensing Authority indicates that there are no objections to this course of action.

2) Heat treatment of factor VIII results in some loss of biological activity. On theoretical grounds, therefore, factor VIII degradation products produced by the heat treatment might produce adverse effects. Informal discussion by one of us (MDR) with the staff of the National Institute for Biological Standards suggest that, in practice, such problems have not arisen.

3) Heat-treated factor VIII from commercial sources costs substantially more than conventional material. At present, manufacturers of heat-treated factor VIII are quoting prices of 12p./unit or 14p./unit, compared with 8p./unit for non-heated factor VIII. Substitution of heat-treated commercial factor VIII for conventional commercial products would increase our costs for factor VIII by approximately £61,000 during the current financial year. Over a full year we estimate that at currently quoted prices the additional costs of changing completely to heat-treated factor VIII would amount to £150,000 to £250,000 per annum depending on usage.

4) Substantial stocks of conventional commercial factor VIII are held by the Authority and by patients in their homes. The stock value of material in the RVI pharmacy (28.11.84) is £33,149. Manufacturers have, however, indicated that they will accept this material for credit, or for heat-treatment.

5) Use of heat-treated factor VIII will, because of the loss of activity incurred during the process, exacerbate the world shortage of the material. We believe, however, that this is a problem for national and international heatlh agencies which should not prejudice the treatment offered by the Health Authority to haemophiliac patients within the Region. In offering our advice to the Authority we have therefore not taken this into account.

Conclusion and advice. Our conclusions and advice are as follows:-

1) From the available evidence a change from using conventional commercial factor VIII to using commercial heat-treated factor VIII appears to carry little risk, but offers substantial advantages. It should be appreciated however that these advantages, though likely, are not proven and we cannot exclude the possibility that even heat-treated commercial factor VIII concentrates do not transmit AIDS.

2) We believe, on balance, that the use of NHS factor VIII should be discontinued until after April 1985 when material from this source will also undergo prior heat-treatment. One of us (P.J.) has received assurances from the Director of the Blood Products Laboratory at Elstree that the Authority will be able to "role over" its allocation of NHS factor VIII concentrate until after April 1985. The temporary discontinuation of NHS material, over the next three months, will not therefore have any financial implications over a full year.

3) We advise the continued use of cryoprecipitate.

4) In the light of available knowledge, we cannot identify groups of haemophilic patients who would be likely to benefit from heat-treated commercial factor VIII, or who would be likely to be at special risk from conventional commercial factor VIII, apart from those without previous exposure to any factor VIII concentrate.

5) In formulating our advice we have not taken into account the economic consequences of changing to heat-treated commercial material. We believe that this decision must be for the Authority and its Officers.

6) If the Authority is able to identify funds for the changes that we believe can be justified on clinical grounds, we further recommend that:

a) the Health Authority inform the Licensing Authority (Medicines Division, DHSS) of its intention to use commercial heat-treated factor VIII on a "named patient" basis.

b) The District Pharmaceutical Officer continues to negotiate with individual companies for the most cost-effective supplies of heat-treated material.

c) The position is reviewed at the end of the current financial year when further scientific and commercial information may have become available.

Professor Michael D. RAWLINS (Chairman, Drug & Therapeutics Sub-Committee, Professor of Clinical Pharmacology)

Dr. Peter JONES, (Director, Haemophilia Centre)

Professor R. MADELEY (Professor of Virology)

Dr. A.G. BIRD (Consultant Immunologist)

Dr. Michael SNOW (Chairman, Cross-Infection Sub-committee, Consultant Physician in Infectious Diseases)

Mr. P.HOPLEY, (District Pharmaceutical Officer)