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 heated 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.

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 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 a final product. Until recently, the most important contaminants were hepatitis viruses.

Considerable efforts are therefore made to ensure the health of donors, the absence of known infective agents in their blood, and the quality of the final products. 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 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 small number of haemophilia 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 competition.

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 a retrovirus, 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 treatment 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 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 haemophiliac 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 (HTVL III antibodies) to the putative AIDS virus, indicating previous exposure to either live or dead virus particles. It is not know at present what proportion of haemophiliacs attending the Northern Regional Centre have HTVL III 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 HTVL III antibodies are uncertain except to indicate previous exposure to living or dead virus. It is also uncertain as to whether antibody positive patients would be protected against further exposure to the AIDS virus.

Whilst the likelihood of contracting AIDS seems greatest from the use of commercial factor VIII, NHS factor VIII cannot be exonerated.

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 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 product 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 £43,000 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 acitivity incurr during the process, exacerbate the world shortage of the material. We believ however, that this is a problem for national and international health agencie 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.

Advice. Our advice to the Authority is as follows:-

1) On clinical grounds a change from using conventional commercial factor VIII t using commercial heat-treated factor VIII appears to carry little risk, but offers substantial advantages. It should be appreciated however that these advantages, although likely, are not proven. We cannot moreover exclude the possibility that even heat-treated commercial factor VIII concentrates do not transmit AIDS.

2) On clinical grounds we believe that the use of NHS factor VIII should continue and we note that from April 1985 this material will also undergo heat-treatmer We also advise the continued use of cryoprecipitate.

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

4) 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.

5) If the Authority is able to identify funds for the changes 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 DPhO continues to negotiate with individual companies for the most cost-effective supplier 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.

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