

NOTES ON THE FOURTEENTH MEETING OF U.K. HAEMOPHILIA
CENTRE DIRECTORS AT OXFORD R.H.A. - 17th OCTOBER 1983

Heat Treated FVIII concentrates

1. Heated Dry Product

... would be available on the basis that it is no worse than the existing product.

I asked whether any **viral inactivation data** was available ... such data may be available in due course but would probably follow the general availability of the product and therefore be retrospective.

... Neither Dr Boulton, Dr Ludlum or myself considered it appropriate to discuss publicly the details of our current 'clinical trial' on heat treated FVIII.

1. AIDS

US Situation

Haemophiliacs 15 cases

Of the 15 transfusion related cases none have Kaposi's Sarcoma - **all opportunistic infection** - attractive to speculate more than one factor involved?

U.K. Situation

Details of haemophiliac cases (A1 and A4) are contained ... and the follow-up protocol is to be circulated in due course.

This protocol will **broadly identify all patients who have received implicated FVIII who will be subjected to clinical follow-up every three months for eight years.**

Spouses of patients who received FVIII will also be followed.

Choice of control group for the above study not defined as yet but is considered critical to the study.

2. Hepatitis

NHS material **is not better** than commercial product, with respect to disease transmission.

An agenda of the meeting is attached. Major points of interest emerging from the morning session were brief discussions on B.P.L. ATIII concentrate and 'non infective' FVIII concentrates.

ATIII

Terry Snape summarised the current situation with regard to the B.P.L. anti thrombin III concentrate. He suggested that there were two options available and sought a response/preference to these options.

1. Pasteurised ATIII Concentrate

This product contains no FXI activity as it is destroyed in the pasteurisation process.

It has been trialed in two patients to date. One of these patients is in Glasgow.

Preliminary data indicates a half life of approx. 24 hours and both patients have normal L.F.T.'s after 2-3 months. Monitoring is to be continued. No attempt has been made to assess the efficacy of the pasteurisation process using model viruses.

2. Unpasteurised ATIII/FXI Concentrate

This product was offered as an alternative since it is the precursor of the above product and thus retains FXI activity. This product has not been used in any patient trials.

No definitive conclusions were drawn from the discussion though haemophilia directors undertook to consider the options and convey their comments to Dr Lane.

HEAT TREATED FVIII CONCENTRATES

Terry Snape similarly sought haemophilia directors' views on two options regarding heat treated FVIII products.

1. Heated Dry Product

No technical details were presented though it was implied that the existing product would simply be heated in the final container as with the Travenol product.

Subject to demand, Terry Snape indicated that such a product could be available within 2-3 months and would be available on the basis that it is no worse than the existing product.

I asked whether any viral inactivation data was available on the process (e.g. vaccinia data) to which Terry responded by saying that such data may be available in due course but would probably follow the general availability of the product and therefore be retrospective.

2. Pasteurisation in Liquid State

Terry indicated that such a product would be a more scientific approach to infectivity but pointed out that at the current rate of/

of progress its availability would be a long term prospect (unspecified time scale).

In general discussion of above options Dr Crashe pointed out that limited experience (Travenol) of heated dry product was not encouraging. There also emerged a general fear and fateful acceptance that the production of non-infective products would lead to a reduction in availability of N.H.S. concentrates (i.e. loss of yield). Terry seemed to reinforce this view quoting figures of up to 25% loss in yield over the existing product. I pointed out that, while hard data was not yet available, developments relating to other aspects of the overall manufacturing process upstream of any heating process may partly or fully offset any yield inherent in pasteurisation. I quoted, in particular, Peter's publication on zinc and calcium. Neither Dr Boulton, Dr Ludlam or myself considered it appropriate to discuss publicly the details of our current 'clinical trial' on heat treated FVIII.

Despite the unvalidated nature of B.P.L.'s short term solution there seemed to be a general feeling in favour of a heated dry product since such a solution would 'do no harm'. It was suggested that B.P.L. manufacture a limited scale batch of heated dry product with a view to conducting a small clinical trial in virgin haemophiliacs (or at least those with no previous exposure to concentrates and who have normal L.F.T.'s).

AFTERNOON SESSION

The afternoon session was devoted to reports by working parties. Comprehensive written reports were circulated (attached). Additional points of interest from oral presentations are as follows:

1. AIDS

USA Situation:

	<u>No. of Cases*</u>
Homosexuals	1428
I.V. Drug Abusers	336
Haitians	108
Haemophiliacs	15
Others	115

*according to N.I.B. criteria

*Of the 15 transfusion related cases none have Kaposi's Sarcoma - all opportunistic infection - attractive to speculate more than one factor involved?

There is a generally poor patient/product follow up in U.S.A. due to poor records of batches infused.

There is a total of 21 cases of transfusion associated AIDS in the USA. Superficial statistics as follows: (incomplete)

Male:Female	9:6
Age	53 (16 - 67)
Alive - Dead	7:8
Incubation	18 months (12 - 38)
No. of Donors	20 (2 - 42)

Crude/

Crude interpretation of these figures provides the following risk statistics.

Transfusion	-	1 in 500,000 at risk
Haemophiliacs	-	1.2 in 1,000 at risk
Conclusion	-	Serious disease in haemophiliacs a low possibility??

U.K. Situation:

Twenty two patients have N.I.H. diagnostic criteria for AIDS - many through contact in U.S.A.

10 patients have so far died.

Details of haemophiliac cases (A1 and A4) are contained in Appendix B and the follow-up protocol is to be circulated in due course.

This protocol will broadly identify all patients who have received implicated FVIII who will be subjected to clinical follow-up every three months for eight years.

This follow-up will include the following investigations:

Hb ESR

W.B.C. - absolute lymphocyte count (IMPORTANT)

Platelets

IgA IgG IgM

Direct Coombs Test

Microbiology - throat swabs, urine, faeces
serum - viral antibodies

Immunology - in-vitro transformation
skin tests
T cell subsets
K Cell

Possible Predictors - Lymphadenopathy - Histology
Microbiology (cultures)

Cryoprecipitate Donors

- Trace
1. Donors.
 2. Recipients of red cells.

Spouses of patients who received FVIII will also be followed.

Choice of control group for above study not defined as yet but is considered critical to the study.

2. Hepatitis (Appendix C)

N.H.S. material is no better than commercial product, with respect to disease transmission.

In a small study using an 'accredited donor' pool, manufactured by B.P.L. one, in eight recipients have so far developed signs of NANB hepatitis. So far this study is of two months duration and unfortunately B.P.L. cannot determine the pool size used to make the batch.

3. Antibodies (Appendix E)

Apart from fleeting references to phospholipid work (T. Barrowcliffe) Appendix E is a comprehensive summary.

4. Von Willebrand's Disease

Appendix D represents comprehensive summary.

5. FVIII Assay

Dr Rizza confessed to little activity and proposed that the working party be wound-up after one more year.

Dr Barrowcliffe presented data on the 11th British Standard.

VIII:C	0.73	
VIII:CAS	0.95	
VIII:RAG	0.91	
VIII:R. R.to F.	0.91	U/ml
IX	0.57	
ATIII	0.83	

Good interlaboratory agreement.

No significant difference between 1 and 2 stage assay systems.