Rorer International Pharmaceuticals

**Rorer Group Inc.** B0000016/1

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Subject: **SATELLITE MEETING**
**HEMOPHILIAC CENTER DIRECTORS MEETING**
**ST. THOMAS'S HOSPITAL, LONDON**
**17 MARCH 1986**

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TO: H. H. McDade
B. J. Miller
C. P. Murphy
R. P. Storm

I estimate that approximately 150 people attended this meeting chaired by Dr. G. Savidge. The purpose of the meeting was to look at the viral safety of AHF concentrates.

There was little discussion about HTLV-III inactivation, and most people assumed that all heat-treating was sufficient. Dr. Peter Jones did not attend. Apparently, the furor resulting from his statements has died down.

The following presentations were of specific note:

I. Dr. Eric Preston (Sheffield) - "Hemophilia: A Model for Liver Cirrhosis"

Dr. Preston, one of our MONOCLATE virgin patient investigators, concluded that hepatitis leads to progressive liver disease. He particularly took issue with the published work of Professor Manucci (Blood, 1982) and the unpublished comments from the Bonn center, both of whom believe that chronic persistent hepatitis is not a major problem.

Dr. Preston did dual biopsies on 10 patients over a period of years. Seven of the ten patients progressed from chronic persistent hepatitis to either chronic active hepatitis or to full cirrhosis. Although these patients had other risk factors, he concluded that the AHF concentrate was the problem. Other conclusions were as follows:

1. There is no dose relationship.

2. There is no correlation between liver enzyme and disease.

3. IgG levels do correlate rather well with disease.

II. Dr. Kernoff of the Royal Free Hospital, another of our MONOCLATE investigators, carried on from the platform that liver disease is a very serious problem resulting from AHF concentrates and acute NANB hepatitis.

Following is the listing of the incidence of NANB hepatitis from non-pooled plasma which he presented:

| | |
|---|---|
| U.S. Commercial | 28% |
| U.S. Volunteer | 7% |
| U.K. Volunteer | 4% |

Dr. Kernoff also estimated rates of attack from pooled plasma produced AHF to be as follows:

| | |
|---|---|
| U.S. Commercial | 100% rate of attack |
| U.K. Volunteer | 33% |

As support for this, he cited the published work of prospective virgin patient studies.

| | | | |
|---|---|---|---|
| Travenol | Hemophil T | 11 of 13 developed NANB | 84% |
| Armour | FACTORATE H.T. | 3 of 3 " " | 100% |
| Immuno | Kryobulin TIM + Chloroform | 1 of 1 " " | 100% |

He characterized all forms of dry heat-treating as "early attempts" which looked good in chimpanzee models, but did not work. The following table of heat-treating was then presented:

| Manufacturer | Method of Treating |
|---|---|
| Edinburg (Scotland) NHS Plant | 68°C 10 hours dry heat |
| Armour | 60°C 30 hours dry heat |
| Travenol | 60°C 72 hours dry heat |
| Cutter | 68°C 72 hours dry heat |
| Elstree NHS Plant | 80°C 72 hours dry heat |
| Immuno | 60°C 10 hours + chloroform |
| Biotest | Cold sterilization using β-Propiolactone and u.v. irradiation |
| Alpha | 60°C 10 hours wet Heptane solution |
| Behring | 60°C 10 hours wet |

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Dr. Kernoff went on to discuss factors other than the "treating" step which influence viral infectivity. Of the entire list, I believe the three having most significance to us are:

- surrogate clinical screening
- pool size
- fractionation method

I believe that we need to do more concerning Plasma Alliance. An informational/promotional piece is perhaps in order. I will discuss the possibility with Domestic.

Finally, he reviewed his experience with Alpha's PROFLIATE. The results were that 5 of 18 patients developed acute NANB. Four had been treated with one lot. His conclusion was that PROFLIATE was significantly safer than dry heat treatment, but not perfect. Alpha is currently reviewing the process used to manufacture the two lots and believe that the problem may be batch related.

III. Dr. Winkelman from Elstree, Dr. C. Rizza from Oxford and Mr. N. Pettet from Elstree sequentially reviewed the NHS "8Y" FVIII and "9A" FIX. Both of these are treated at 80°C for 72 hours.

There is clearly room to criticize their study on two points:

Batch size
Follow-up of patients

On the batch sizes, we believe their normal production lots are manufactured from 7-10,000 liter pools. Following is the listing of batch sizes tested to date:

| | | |
|---|---|---|
| 8Y | 1. | 700 liters |
| | 2. | 1416 " |
| | 3.-6. | 6000 liters @ |
| 9A | 1. | 1100 liters |
| | 2.-5. | 6000 liters @ |

The later batch sizes are approaching normal pool size, and they assured all present that there was no special selection of donors.

Concerning follow-up, Elstree admit that they have missed some test intervals with <u>many</u> of their patients. They were severely challenged for this; however, their response was that although the methodology may be challenged, to date, they have no seroconversion and no case of NANB in 17 "8Y" patients and 7 "9A" patients. Note there is discussion

about one 2 year old who had a single elevated reading; however, the child was not a true virgin.

The advocates of the Elstree plant complained that they were not receiving enough virgins to test and appealed to the nationalism of the audience. Their position is that the product is free of charge, and I quote ["better than Hemofil T and Armour Factorate H.T. although it remains to be seen as to whether it is better than the wet processes."]

According to Mr. Pettet, Elstree will produce 22.5 million units in 1986 and 70 million in 1987. By 1988, they expect to produce 100 million units which combined with Wales and Scotland's 10 million units will have U.K. self-sufficient. They are planning for all commercial requirements to be terminated by 1988.

**Conclusions:**

1. We cannot long endure our high priced product being referred to as the poor standard by which all other products are judged. Armour had over 50% market share in the UK which decreased to about 36% of the commercial market in 1985 and will further decline to the 25% range in 1986. I do not believe that the UK team--however good their relationships may be with the centers--can hold 25% share with Generation I.

2. C. Bishop is persuing a study with Dr. F. Hill (Birmingham) who believes that the protein load is perhaps as important as viral transmission. I believe that we should support this study with MONOCLATE.

3. If we are to be in business in the U.K. three years from now, we must (a) get major market share of the commercial market and (b) get some large percent of the NHS market, keeping in mind that the NHS product is free. The U.K. team has a proposal; however, it calls for the integration of viral inactivation studies, protein load studies and virgin patient studies. Long-term in the U.K., I believe that we will have to participate with Elstree somehow if we are to survive with AHF.

4. We should all be prepared to see a longer more detailed review of those data presented at Milan. I will discuss our rebuttals with our scientific group. If at all possible, we will try to reach the presenters before they speak and soften their impact, which should be felt in the U.S., Japan, and Germany.

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Loftus S. Lucas

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