27/9/83

U.K. WORKING PARTY ON TRANSFUSION-ASSOCIATED HEPATITIS

Chairman

Dr. H. H. Gunson.

Dr. J. Barbara
Dr. J. Craske
Dr. B. Cuthbertson
Dr. R. S. Lane
Dr. D. B. L. McClelland
Dr. R. Mitchell
Dr. S. Polakoff
Dr. H. Thomas

Minutes of the fourth meeting, 27th Sept. 1983, 11.30 am at NLBTC, Deansbrook Road, Edgware, Middlesex.

ACTION

1. Apologies were received from Dr. Gunson; Dr. Barbara acted as chairman in his absence.

2. Minutes of the previous meeting were agreed subject to two corrections pointed out by Dr.McClelland i.e. 2.1. p2, item 5.2. Dr. James was to liase with Dr. Thomas and not Dr, McClelland; 2.2. p4, item 9; the parenthesis '(Dr. McClelland thought about fourfold in Edinburgh)' would be deleted, following the Secretary's misinterpretation.

3. Matters arising would be dealt with under the agenda headings.

4. AIDS

4.1. The current position was summarised by Dr. Craske.

In the USA there have been 18 factor VIII related cases though others are being investigated. Aproximately 20 'blood' associated cases are under review but we await a 'single-unit' transmission. In the UK the number of AIDS cases is still low and seem to be mainly 'imported' from the USA. There have been approximately 20 cases in the UK. Two of these were in haemophilia A patients.

One, diagnosed in April, is a 21 year old heterosexual male patient in Cardiff who denies drug abuse. His condition remains fair; his clinical picture is quite typical of AIDS. 1st March was taken as the date of onset and products used since 1st January 1980 have been reviewed (N.B. The

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longest documented 'incubation' period in the USA is 2¾ years).

The only risk factor with this patient is concentrate. Since Jan. 1980 he has received material from 9 batches of commercial and a similar number of NHS concentrates. Attempts will be made to trace other recipients.

The second case occurred in a mild (2%) 57 year old heterosexual male haemophiliac in Bristol, who denies drug abuse.

From 1973 he has been treated with cryoprecipitate and a few NHS batches. He had no commercial concentrate since Dec. 1981 when he had concentrate from 3 batches. 3 weeks after, he developed anicteric non A, non B hepatitis with an enlarged liver. In September 1982 he was found HBsAg positive and he has been a supercarrier until his death recently.

Deciding the onset of AIDS is difficult. In September his liver disease merged into several PUO incidents and EBV reactivation. After May '83, oral candidiasis and zoster on the right arm was diagnosed. There was a helper cell deficiency. He continued to deteriorate mildly till his death on 23rd Aug. 1983. At post mortem, pneumocytis pneumonia was found to be the cause of shadows on lung X-rays.

All batches of NHS and commercial concentrate and cryo since 1st Jan 1980 will be followed up and other recipients checked. Dr. Craske will discuss follow-up of the cryo donors with Dr. Fraser

Dr. Cras

Dr. Thomas suggested that HBV, non-A, non-B hepatitis and possibly EBV reactivation might reduce the T4/T8 cell ratios, but Dr. Craske felt that the absolute fall in T4 (helper) cells in the above case indicated it was indeed AIDS.

Dr. Thomas also mentioned that 30% of Royal Free haemophiliacs have raised T8 values whereas only a few have lowered T4 values. Recipients of low-purity factor VIII show the ratio abnormality, whereas high-purity factor VIII and factor IX recipients do not show abnormal ratios. Those concentrates

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with a high concentration of HLA class 1 protein are associated with reduced ratios (due to increased T8 values). Factor IX contains several orders of magnitude lower concentrations of HLA class 1 protein. Therefore immunization to HLA class 1 protein may raise the T8 value. Dr. Thomas also pointed out that several factors can immunosuppress haemophiliacs causing decrease in absolute T4 cell levels and lymphopenia, possibly causing a type of AIDS different from that in homosexuals.

So far, the incidence of AIDS is less that 1 per 1000 people at risk.

It was agreed that the chairman be asked to canvas directors to decide criteria for guidelines on follow-up of donors involved in AIDS transmission where only cryo was involved and also where cryo and concentrate were involved. Dr. Gunson

4.2. AIDS pamphlet.

Different Centres are trying different ways of presenting these pamphlets, ranging from inclusion with call-up cards through free availability on sessions to restricted availability on sessions. The effects of these different strategies will be compared and reviewed by the RTDs.

Dr. Lane presented the fractionator's view that a variable approach did not provide material of uniform specification but Dr. Mitchell pointed out the problems associated with any infringements of the integrity of the donor.

It was agreed to minute the preference of the working party for the choice of a uniform approach as soon as possible and within a fixed time period and to ask the Chairman to bring the preference to the attention of the RTDs. In the meantime it might be helpful if RTDs would provide details of how they get the AIDS information to the attention of the high risk groups of donors.

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Non-specific tests for AIDS.

Dr. McClelland pointed out that the distinction between a promiscuous non-promiscuous homosexual was not conclusive since it did not cover the promiscuity of the partner. The TPHA test may well be of value in indicating inclusion in a high risk group. It was therefore suggested that the AIDS pamphlet be made available to special clinics, since some donors would be patients at such clinics.

The anti-HBc test was also mentioned and Dr. Barbara commented that such a test had the value of association with hepatitis B and non-A, non-B hepatitis as well as AIDS. However, it provided problems because of the need for anti-HBs testing, apart from logistical problems.

Dr. Howard said that reports from Japan of the value of β microglobulin tests have not been confirmed though the α and γ interferon levels appear to rise during the progression to AIDS.

4.3. Council of Europe's AIDS meeting.

Dr. Barbara presented Dr. Gunson's summary; Members of the council are being circulated with a draft which makes the following four recommendations for each country:

4.3.1. Aim for National self sufficiency in blood and products.

4.3.2. Aim at minimising cross-border transfer of blood.

4.3.3. Avoid the use of coagulation factor products made from large plasma pools. This will pose problems in the U.K. due to considerable product losses during Q.C. procedures; in the U.K. this approach or use of accredited donors might be applicable to patients with 'low immunity' (e.g. babies) or 'infrequent users' (e.g. mild haemophiliacs at operations).

4.3.4. Provide information on AIDS to all donors so that high risk donors exclude themselves; methods of providing this

ACTION

information were not specified. Also inform physicians and selected recipients, of the potential hazards of haemotherapy so that blood (or its products) is not given unnecessarily.

5. Items 5, 6 and 7 on the agenda were deferred to the next meeting.

6. Immunoglobulins.

6.1. Anti-HBs IgG supply.

The supply is still extremely low; since several of the donors who provide the plasma may be in the 'high risk' group for AIDS, the supply may be further jeopardised.

Dr. Craske commented that in the USA all high risk donors have been recommended (in a B.O.B. directive) to donate plasma only, to be used in IgG production.

Dr. Craske will provide the secretary with a copy of this recommendation. However, some members of the B.O.B. are not completely satisfied with this and it was noted that follow up of recipients of BPL intravenous IgG at Northwick Park showed evidence of non-A, non-B hepatitis infection. This occurred even though the product had undergone ethanol fractionation, although the final stages of intravenous IgG preparation differed from intramuscular IgG preparation. Dr. Craske

Dr. Lane is examining the data in detail, but he summarised it as follows: 12 patients received i.m. IgG for 6 months and 12 received i.v. IgG for 6 months; these groups were to cross over to receive the alternative IgG. Both preparations came from large pool batches though not necessarily from identical ones. In the i.v. group 12/12 patients showed hepatitis. Three had symptoms (2 with jaundice) though ALT rises were mild. The incubation period was approximately 3 weeks to symptoms and 6 weeks to the first ALT elevations, suggesting a 'short incubation' non-A, non-B hepatitis. In the i.m. group, no

transmission was noted. There is little data available in the literature on ALT determinations following i.m. preparations given intramuscularly, let alone intravenously - presumably a much more direct route for infection. Although i.v. therapy involves higher doses than i.m., the preparation of the latter appears to be intrinsically safer, providing the existing method is adhered to exactly. This is especially relevant to considerations of the safety of IgG from high AIDS risk donors.

6.2. Immune plasma from 'gay' donors.

The question of how to deal with such donors remains open; the distinction between 'promiscuous' and 'non-promiscuous' is blurred and takes no account of the partner's habits.

The possibility of non-specific tests aimed at identifying donors in high AIDS risk groups was raised by Dr. Lane. These (e.g. TPHA) might be done at BPL although some centres (like Edgware) already use TPHA instead of the less specific cardiolipin tests. Anti-HBc testing for anti-HBs donors was obviously inappropriate.

The fact that the AIDS lesion might cause high titres of antibodies to appear in the plasma was noted.

6.3. Mouse monoclonal antibodies as alternatives.

Dr. Thomas reported that 10 ng of mouse monoclonal antibody appeared protective in chimps. with no anti- mouse response; he will be undertaking field studies in Malaysia; nevertheless these were still only preliminary results and the problems with human immune plasma still required attention until such time as monoclonal reagents might become available.

6.4. Chemical/enzyme treatments of intravenous IgG preparations.

It was noted that some commercial intravenous IgG preparations finish

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the processing precedure with chemical or enzyme inactivation steps, but results of trials are awaited and commercial companies are currently following recipients who have received such preparations. It will be of interest to compare the effect of agents like pepsin, used in commercial products, with the 'gel/column' approach at BPL. Possibly the differences in final processing steps at BPL between i.m. and i.v. preparations removed a denaturing step or allowed 'break through' of other suppressed virus activity.

6.5. CMV IgG.

Dr. Lane reported that anti-CMV IgG for i.v. use had been withdrawn although it will be prepared for i.m. use. High titres of anti-CMV may be associated with donors from 'high-risk' populations generally (and specifically with the CMI lesion caused by the AIDS agent).

6.6 HBIg for babies.

The data from Northern Ireland showed that some white mothers were HBeAg positive HBsAg carriers. The working party felt that if the particular screening system in operation in a given region detected such mothers, their children should obviously be offered HBIg. However, the highest numbers of HBsAg positive mothers will come from countries of high hepatitis incidence and this is the most obvious group to be tested.

Dr. McClelland would prefer to offer HBIg to children of all HBsAg positive mothers, but Dr. Polakoff pointed out the problem of supply; she will provide the secretary with a copy of a breakdown of HBIg cost-effectiveness

Dr. Polakof

6.7. Meeting to consider IgG problems.

Dr. Lane asked if Dr. Gunson would consider organising a meeting to review the problems associated with IgG.

Dr. Gunson

ACTION

The working party did feel however that the question of i.v. vs i.m. preparations constituted a separate topic from that of the safety and supply of i.m. IgG preparations.

One immediate step suggested by Dr. McClelland was that he and Dr. Craske would review the B.O.B.'s recommendations of IgG and circulate the working party with this, within the next month. Dr. McClella / Dr. Craske.

Dr. McClelland also wished to recored his feeling that consideration of alternative sources of IgG (i.e. monoclonals) should be a priorty.

The problems associated with i.m. IgG include:

Identification of high risk groups and whether donors should be questioned about homosexuality though this was contrary to the statement in the AIDS leaflet.

Funding for screening and selecting donors for high titre antibody provision. Such procedures and practices like plasmapheresis were not currently taken into account in costings. If centres were not to receive credit for plasma in terms of fractionation potential (i.e. if the plasma was to be reserved solely for IgG preparation) the funding imbalance would be worsened.

The ethics of boosting donors to improve anti-HBs yields.

7. Donor sessions in prisons.

Members asked if the chairman could provide details of which Centres took donations at Prisons. They realised that the definition of 'prison' ranged from 'closed' to 'open' prisons. The working party felt that prisons should be considered in the context of a 'high-risk' population in terms of several of the transfusion-transmitted infections and as such should be avoided as a donor source. Dr. Gunson.

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8. Date of the next meeting.

This was kept open pending the chairman's decision on whether to convene a meeting to consider IgG specifically. Dr. Gunson

Dr. J. A. J. Barbara.

Secretary to the Working Party.

MH/JAB/10th Oct. 83.