CONFIDENTIAL TO COMMITTEE MEMBERS MSBT 13/4
NOT FOR PUBLICATION

ADVISORY COMMITTEE ON THE MICROBIOLOGICAL SAFETY OF BLOOD AND TISSUES FOR TRANSPLANTATION (MSBT)

MINUTES OF THE MEETING HELD ON 27 OCTOBER 1997

Chairman :	Dr J S Metters
Members present :	Dr A J Cant Dr D W Gorst Dr D B L McClelland Professor P McMaster Dr P Mortimer Dr R J Perry Dr E A Robinson Dr T J Snape Dr T Wyatt Professor A Zuckerman
Also present :	Professor H Thomas (Items 1-6(pt))
Observers:	Ms C Corrigan (DoH) (Items 1-6(p)) Dr A Keel (SO) Mr W Kent (DoH) Dr A Mairs (NI) Dr F Rotblat (MCA) Mr M Skinner (DoH) (Items 1-6(p)) Dr W Smith (WO) Dr N Wingfield (DoH,RDD)
Secretariat:	Dr M McGovern Miss A Towner Ms G Skinner

1. Chairman's introduction and welcome

1.1 The Chairman welcomed members of MSBT, and Professor Thomas from the Hepatitis C lookback Working Group. Dr Mairs from DHSS Northern Ireland, was attending his first MSBT meeting. Also attending, for the discussion on CJD, were Ms Corrigan, who dealt with policy on blood, and Mr Skinner, DoH Secretary to the Spongiform Encephalopathy Advisory Committee (SEAC). Dr Wingfield was representing DoH's research directorate, and Mr Kent was attending in place of Dr Doyle dealing with policy on tissue for transplantation.

1.2 The Chairman introduced two new members of the Secretariat : Dr McGovern, and Ms Skinner who would be replacing Ms Towner.

2. Apologies for absence

2.1 Apologies for absence had been received from Dr Warren and Mr Forsythe, from absent members of the Hepatitis C lookback Working Group, and from Mrs Dhell (MDA).

3. Minutes of the twelfth MSBT meeting - 8 July 1997 (MSBT 12/6), and matters arising

Minutes

3.1 The minutes were agreed, subject to the following amendments :

* para 4.5 (first sentence): delete "electron-microscopy" and substitute "basic biology";

* para 5.13 (second sentence): "SAACTTI" should read "SACTTI";

* para 6.11 (last sentence) : delete the second "this" and substitute "first".

GBV-C/HGV

3.2 At the last meeting members had been asked to give any further comments to Professor Thomas, who would send any research bid to the Department's research directorate. Professor Thomas confirmed that the research bid had not yet gone forward.

Tissue banking

3.3 Mr Kent reported that since the last MSBT meeting, a submission on tissue banking had gone to Ministers. Their decision was awaited. Bone-marrow transplantation has been removed from the proposals. SMAC had no comments. Ministers had the choice of introducing primary legislation, which might mean a delay of some two years, or making secondary legislation under the Consumer Protection Act. The latter could be done this session, but involved some technical difficulties and could still leave gaps. Should Ministers decide to proceed with legislation, MSBT would have the chance to comment again during the formal consultation period.

3.4 Members were anxious to see early progress, and better control of tissue banking.

4. Hepatitis C Lookback.

4.1 Dr Robinson had provided paper MSBT 13/1 giving the latest information on the

follow up. The exercise was going well, although there was a gap between the number of components identified and notified to hospitals and the number of recipients identified by hospitals. It was probable that in a number of cases the patient records were no longer available, but this would only be likely to account for a gap of, say, two thousand. Dr Robinson was hopeful that by the next meeting there would be more detailed information on that aspect. There would be further thought given to elements which needed to be made quicker, now that poor responders had been identified.

4.2 Professor Thomas reported that the pressure on hepatology departments was steady. A high percentage of cases involved intravenous drug use and compliance in that group was poor. A small proportion came for interferon therapy and this was likely to increase when the response rates for Ribavirin combined with interferon were known. In accordance with the guidelines, mild cases had not been treated, but these would now be reassessed for suitability for combined treatment.

4.3 A proposal was with RDD and the verdict would be known in December. Funding had been given for the HCV Registry and an epidemiology nurse had been appointed. Dr Wingfield would thank Dr Toy.

5. CJD and Blood/Blood Products Including Virally Inactivated Plasma

5.1 Paper MSBT 13/3 included CMO's statement on CJD and human transmission, and a note of DoH research directorate workshops on TSE infectivity in blood and blood products. A paper from the National Blood Service (NBS) on strategies to minimise the risk of transmission of new variant (nv)CJD by transfusion was tabled.

5.2 The Chairman introduced the discussion by reminding members of earlier MSBT discussions of possible CJD transmission through the blood supply and current media attention on the subject. Further action had been taken since CMO's statement of 6 October, in advance of the Watchdog programme on TV. Interest had been heightened by the visit of the European Parliament's Temporary Committee of Inquiry to the Churchill family, whose son was the first person to die from nvCJD. The Churchill's son had been a blood donor and they suggested that human to human transmission by blood/blood products might support an epidemic.

5.3 The Chairman said that the UK were free to take their own decisions on blood and labile components, at least until the Amsterdam Treaty, Article 129, was implemented in 2000. However, advice on blood products were given to the Commission by the Committee for Proprietary Medicinal Products (CPMP) and its Bio-Technology Working Party (BTWG). The UK had put a paper to them asking for advice on the action to be taken if a nvCJD patient were identified who had recently donated, and the plasma used to make products thought to be still on the shelf. The BTWG reaffirmed its advice on classic CJD that there was no need to clear the shelves, or recall. However in the case of nvCJD they advised recall of active blood products as a precautionary measure if an alternative product was available. This line had been endorsed by CPMP which decided to set up an expert working group to consider the position on exipients, including albumin in some vaccines. The UK would be represented.

5.4 The Chairman reported that Pasteur Merieux had decided to break their long-term contract with BPL for the supply of albumin, following a statement from the French equivalent of SEAC, the Dormont Committee. This effectively amounted to a ban on the import of UK blood products because of the potential risk of nvCJD.

5.5 SEAC had discussed the situation at length at their last meeting on 24 October, and concluded that it was impossible to say that no-one in Britain was incubating, or would in time develop, nvCJD. Professor Smith was carrying out a study for SEAC to assess the scale of any possible epidemic. SEAC considered that the new agent involved in nvCJD might be different from that in classic CJD, as the pattern of disease was different and it was found in lymphoid tissues, implicating the B lymphocyte in disease development.

5.6 SEAC had concluded that it was sensible to reduce any possible risk to recipients. They had recommended that a risk assessment be undertaken to inform a decision on whether or not to leucodeplete the blood supply as a precautionary measure. The Committee also recommended that planning for the introduction of leucodepletion should go ahead in parallel with the risk assessment, although final decisions on introduction would depend on the outcome of the risk assessment. These recommendations drew heavily on the NBS paper.

5.7 Dr McClelland, introduced the NBS paper on the feasibility and potential benefits of leucodepletion in reducing the risk of nvCJD. This reviewed measures in place to minimise the risk of possible transmission of classic CJD through donated blood, but the authors had been unable to identify any comparable measures which would be effective for nvCJD. There was no diagnostic test for nvCJD as yet and any screening test could take years to develop. The paper said that there was no evidence that processes to reduce viral infectivity would reduce the possible infectivity of nvCJD. The paper indicated that blood and blood products (including eg anti-D) were used in a very wide variety of clinical circumstances, and not limited to situations where life was at risk.

5.8 The paper suggested that the scientific basis for leucodepletion was very fragile. In animal studies disease transmission was demonstrable through intracerebral inoculation of white blood cells but not intravenous injection. Work from Switzerland, about to be published, was suggesting that the presence of circulating B-lymphocytes cells was necessary for transmission nvCJD and disease development. This was the rationale for suggesting leucodepletion of the blood supply.

5.9 The appendices dealt with the practicalities and efficacy of validated methods of leucodepletion, the limits of detection of white blood cells by conventional optical techniques and the need to develop and improve quality assurance. The paper indicated that leucodepletion could be incorporated into the blood processing in UK blood centres though there would be substantial costs for hardware disposables and labour.

5.10 The Chairman said the paper had been most helpful in suggesting that techniques were available which could be integrated into current blood banking practice. MSBT now needed to decide what steps the National Blood Services should be taking to implement leucodepletion, and whether any action should be taken to reduce risks while the planned risk assessment was being undertaken.This also prompted two important questions; should particular categories of patients be given leucodepleted blood as a priority? and

could there be a single vesting date for leucodepletion? The Department would need to make recommendations to Ministers quickly.

5.11 A number of other questions were raised including the action to be taken where a donor was known to have, or suspected of having, nvCJD, and where some products from the donation had not yet been used. In such cases, could Ministers justify allowing those products to be used? While CPMP had advised on blood products, what action should be taken in the case of blood and labile components? Should any action include cases where nvCJD was suspected as well as those where it was confirmed? If unused labile components were withdrawn and plasma traced, should recipients be told, and patients who might be holding unused stocks ?

5.12 Dr Wingfield recognised that modelling systems were imperfect since experiments could not be undertaken in humans. The planned risk assessment would be based on what little hard data existed and as such would have wide confidence limits and hence wide estimates of risk. The Chairman added that all the experiments done so far had been across the species barrier. There would be no species barrier with human blood transfusion, so human to human transmission was likely to be higher than if human blood were tested in mice. SEAC had been advised that there were a lot of unknowns, eg whether there many or few cases, whether patients were infective before developing symptoms. Mr Skinner said that the risk assessment would be undertaken by management consultants, Det Norsk Veritas (DNV) experienced in assessments of risk in environmental matters, and would take about two months. In view of the range of facts given, the findings would be a range of risk, rather than firm outcomes.

5.13 Dr Snape doubted the validity of risk assessment when nvCJD transmission through blood and blood products was only a hypothetical risk. The burden in plasma pools, and the effect of fractionation and inactivation processes, were not known. He said that evaluation rather than practical work was in progress on "partitioning" of prion proteins and that only a few of the methods suggested in the paper were likely to be effective.

5.14 Dr Robinson was concerned about the additional burden which leucodepletion would place on the blood services. They were already having to deal with reorganisation, and NAT testing. The Chairman recognised the considerable burden any new measures represented for the National Blood Service.

5.15 Dr Mortimer asked why it was apparently being assumed that cellular components represented more of a threat than plasma, how reliable the data were and how effective were the systems. The blood service paper suggested that leucodepletion removed less infectivity than was assumed in the research directorate paper. Dr Wingfield agreed that evidence had yet to be produced as experiments were hard to do but that what evidence there was pointed to transmission by white cells/buffy coats. Dr McClelland said the white cell data in Table 1 of the blood service paper were based on red cell and platelet work at his own centre, and were achievable but that they had no experience of filtering plasma until recently. He added that they knew the systems were effective at removing the granulocytes but were not sure how good they were at removing lymphocytes. While the data seemed quite good, they might not represent all that could be achieved.

5.16 Members expressed concern about the absence of firm data on which to base decisions and emphasised the importance of further research. Dr Cant suggested that studies in humans should be considered, and there might be scope for further work on new donors and nvCJD. Transmission seemed to require a considerable prion load, which the risk assessment should reflect. While injecting animals intra-cerebrally transmitted infection, other methods of transmission were less consistent. He wondered if there had been studies of the infectivity of different fractions of blood from infected animals.

5.17 The Chairman thought that epidemiological studies in humans were impractical as incubation might be as long as 30 years or even more. SEAC had been concerned that even the animal work would take at least 2 years, and about the prospect of a major epidemic if early action was not taken, as had happened with BSE in cattle. Dr Mortimer said that while he understood this very well, he still favoured properly targeted research, to avoid the risk of being confronted in the future with justifying the action taken. The Chairman said that the research was in progress and that accumulating animal data suggested white blood cells and possibly plasma were implicated in TSE transmission.

5.18 In the light of the Pasteur Merieux decision not to renew its contract for UK albumin with BPL and the implications of this for excipients, Professor Zuckerman asked in how many other products UK albumin was used. Dr Rotblat confirmed that human albumin was used as an excipient in many products including some vaccines. This would be part of the remit of the CPMP working group.

5.19 Members discussed the use of UK human albumin as an active and an excipient in relation to its long shelf life and B lymphocyte content. Dr Perry pointed out that while current wisdom was that present viral inactivation measures were not effective against nvCJD, paragraph 96 of the research directorate paper suggested that scrapie was very substantially reduced in infectivity by conventional inactivation processes, although some infectivity remained.

5.20 Dr Robinson asked whether the new CPMP advice meant abandoning the NBA/CJD SU blinded epidemiological study of classic CJD and nvCJD.

5.21 The Chairman confirmed the need to follow CPMP's advice on blood products. The CPMP working party would also look at scientific issues. When the blood services were informed of suspected cases from any source confirmed by the CJD Surveillance Unit they would have to trace recipients. He and members agreed that it was important to continue the nvCJD lookback without informing the recipients of implicated product.

5.22 The Chairman recognised an apparent inconsistency in following the CPMP advice on blood products but not telling patients, once traced, when labile components had been given to them. The Lothian Ethics Committee had been asked to review their earlier decision that recipients should not be told. Written confirmation was awaited, but it was understood that they had upheld the existing line.

5.23 Dr Rotblat said that for commercial products, the investigation would be put in the hands of the licence holder if that were a commercial company. Dr Snape said that BPL and PFC had tracing procedures in place ending in consultation with DoH/MCA. The

blood services could trace material supplied to Haemophilia Centres, but not so readily to individual haemophiliacs. When approached, in relation to product recall, patients would want to know why questions were being asked. The Chairman asked if MSBT's advice was still to avoid casting a shadow over the lives of recipients of nvCJD implicated products, when no positive steps could be taken.

5.24 Dr McClelland considered that labile blood components were much more likely to be infective than licensed blood products and that it was fairly simple to identify their location, date, and clinician responsible for the transfusion. There were precedents for consulting clinicians in these situations. Following discussion the Chairman said that MSBT's view seemed to be that patients who received implicated products should be traced but not told on the basis of the current science.

5.25 It had been suggested that recall might not be appropriate if a long time had elapsed since the person with nvCJD donated blood. However if the interval was shorter and it seemed likely that products might still be on the shelf these should be searched for and recalled.

5.26 Dr Gorst was concerned about keeping information from patients, given the growing climate of openness. Dr Robinson said that the Haemophilia Society had already written to the NBA asking whether any implicated plasma had been used in the manufacture of Factor VIII or Factor IX, whether any such products would be withdrawn and, and whether the patients who had used them would be told. The Chairman again referred to the advice of the Lothian Ethics Committee.

5.27 Dr Cant reminded members that for the hepatitis C lookback MSBT had advised that patients be told, where diagnosis and positive action were possible. He said that the NBA should be open with the Haemophilia Society, explaining the reasons why patients, in the light of the low risks, and the absence of steps that could be taken to help them might not be told. Members agreed with this position but that this should be reviewed in the light of any new evidence.

5.28 The Chairman said that in the case of human growth hormone (hgh) a decision had been taken nationally, after specific advice from the ethics committee, not to advise recipients. Two years later, it was decided that they should all be traced, and told. In a case before Mr Justice Morland, hgh recipients who did not in fact develop iatrogenic CJD, were now seeking damages for psychological harm, because of the information given to them. This case would have implications for nvCJD as well other 'worried well' situations.

5.29 Dr Wyatt agreed that patients should not be told, but raised the question of their position in relation to subsequent blood and tissue donation by exposed recipients. The Chairman indicated that this would be a decision for Ministers (in all 4 countries) following considered advice from MSBT and a submission from the Department.

5.30 Dr Perry said that it was questionable to assume that old material would not still be on the shelf, and that limitation of recall would set a dangerous precedent. If recall was agreed in principle, there should be no time-limit. Dr Snape suggested this might be limited by the licensed product expiry date. Dr McClelland thought that recall should be

attempted in all cases of products with a long shelf life but not for those that were used up quickly such as Factor VIII and Factor IX. Dr Rotblat said that in the US recall was carried out in all cases of classic CJD, even though no implicated product remained.

5.31 Dr Rotblat added that the MCA avoided recall of products distributed to patients if possible, but could not do so if a risk was involved. Usually the physician prompted the recall by reporting problems or adverse events. Recall from the centre was a different high profile exercise, and usually made front-page news.

5.32 Professor Thomas said he was not concerned that recall might spark public debate and that problems could arise with anything less than transparency. The Chairman agreed that Ministers were likely to take a similar view, and say that if nvCJD cases were identified there should be a recall of implicated products, and that patients should be told why.

5.33 Dr Keel asked for clarification about direct notification of cases to the NBS by the UK CJDSU. The Chairman agreed that this should be the case and advised that any difficulties might be discussed with the SEAC Secretariat.

5.34 Dr Robinson said that information given to the NBA was currently done so as part of the blinded NBA/CJDSU study. Any decision to follow up nvCJD cases actively would alert clinicians to them, as well informing the patients themselves in the case of product recall. The Chairman said there were new considerations now that more active intervention would be seen to be put in place.

5.35 Dr McClelland said that if they got a report of a suspected case at present they notified the transfusion centre and the CJDSU, but asked if they should now also trace recipients, to the level of the clinician, without telling the patient.

5.36 The Chairman confirmed Dr McClelland's summary. However, he added that if Ministers were to decide that unused product should be recalled from patients then they would have to be advised of the reason. Dr McClelland questioned the logic of informing recipients of licensed blood products where there was probably a low risk, but not recipients of labile components where the risk was likely to be greater. However the Chairman suggested that the decisive factor was whether we could do anything about a situation. In the case of labile blood products already used we could not but for licensed product still in circulation we could recall on precautionary grounds.

5.37 Members discussed the public health implications of people who might have given organs or become blood donors and how recipients of the implicated blood and organs might be monitored. The Chairman advised that this would need to be kept under review and advice developed by MSBT. The Ethics Committee had advised against telling the recipients on the basis of benefit to the individual, though not on the wider public health aspects.

5.38 The Chairman did not favour flagging up names of those potentially infected with nvCJD on organ donor or blood donor registries. CPMP advised that products should not be withdrawn if the donor died of classic CJD rather than nvCJD. Although the diagnosis and type of CJD was often not clear until the post-mortem stage the precautionary

measures for nvCJD cases should be applied to suspected cases too.

5.39 Dr Mortimer suggested further discussion of the research paper in MSBT 13/3. The Chairman said that MSBT had originally intended to focus on that paper, but this had been overtaken by events. Members would come back to the subject again when there were further developments. Dr Wingfield confirmed there were no time-critical issues in the paper for MSBT.

5.40 Dr Wingfield said that most of the data in the paper were now known, though some of the results of the experiments were yet to be published. The particularly confidential part of the research paper was that headed "unpublished work". The Chairman said that the position on leucodepletion was likely to change when Ministers had received and considered advice from SEAC/MSBT. What was put into the public domain would then require careful handling.

5.41 The blood service paper discussed virally inactivated plasma. In March, MSBT advised the blood service to make preparations to provide an SD product, once a licence was given. The NBA were negotiating a contract for SD treatment of UK plasma by Octapharma using pools of up to 1,000 donors. Dr Robinson said , in the light of developments on nvCJD, and the lack of knowledge the NBA were now suggesting methylene blue(MB) ultra violet light treatment of individual plasma donations. They would not in any event have been able to provide the SD product for all cases and indications from clinicians about potential demand had ranged from nil to 100%, averaging about 20%.

5.42 The idea of a mixed economy in plasma was confusing clinicians who were looking for guidelines, and guidance about what product to use for which patient. They were concerned about the legal liability of using an unlicensed product ie FFP instead of a licensed one, and about the price differential given that the SD product was expected to be 20%-30% more expensive. Dr Robinson understood that BCSH would be happy to produce guidelines, including the priority to be given to groups such as neonates.

5.43 The Chairman said that any guidance from DoH would need to be based on the recommendations of clinicians and that if they were willing, BCSH should be asked to advise on such guidance.

5.44 Dr McClelland, and clinical colleagues did not like the concept of pooling plasma where this could be avoided and therefore supported the new single donor approach.

5.45 Dr Robinson suggested that if the UK did not go ahead with their contract, Octopharma would market their own product here, presenting it as a non-UK product, and therefore safer. Dr Snape thought that, if Octaplas were to be licensed for use in the UK, the implication would be that UK donor plasma was unfit for use.

5.46 The Chairman said that if Europe should decide to ban all UK blood/blood products this would raise the question of how we could justify giving them to UK patients. SEAC had advised that we should not abandon providing a UK blood service, as the risks of doing so were so great.

5.47 The Chairman said the Department would now press ahead urgently with a submission to Ministers, taking account of MSBT's views, and keeping in touch with the territorial departments.

CPMP paper on plasma-based products

6.1 Following the issue of the paper to for comment on 28 August, members had been advised that their comments on the guidance note would again be sought at this meeting. Dr Rotblat advised that no comments had been received so far from any of those on the wide distribution list, and that as discussion in committee would be difficult, submission of comments by 1 December could be the best way forward. Dr Snape observed that in some places in the document the meeting's previous agenda item was relevant, and references to classic sporadic CJD needed to be changed to reflect the position on nvCJD.

6.2 A number of points, and questions, were raised in discussion which Dr Rotblat suggested be submitted in writing. She advised that an agreement on GAT testing seemed now to have been reached. The CPMP Chairman had taken the view that plasma pools which had not been GAT tested should be withdrawn, but had now accepted the view that GAT testing did not improve safety, but quality, and that withdrawal of untested pools should not be required. Excipients in products after 1 January 1999 would have to come from GAT tested pools.

6.3 Dr Robinson stressed her concern that it should be made very clear to hospitals, which would bear the extra testing costs, that the extra testing was a requirement not an NBA choice. The Chairman agreed that a central statement was needed, possibly from the MCA, of the start date and the fact that the UK had to abide by the decisions of the European authorities.

Any Other Business.

Autologous transfusion

7.1 The Chairman advised that CMO favoured the development of autologous transfusion, and sought the committee's views. There was increased interest in this in Scotland, where there had been a pre donation service for about 10 years. The process was expensive.

7.2 It was reported that there had been a very good consensus conference on autologous transfusion in Edinburgh 12 months ago. Risks and benefits had been identified, including the need for operations to be done to time. The general view of those present was that autologous transfusion could be valuable if the arrangements were properly targeted and managed. The issue would be addressed again when the blood service had emerged from the various other current matters exercising them.

Date of Next meeting

8.1 The next meeting would be on **28 February 1998.** Thanks were given to Ann Towner for her work with the Committee and best wishes expressed for the future.