CONFIDENTIAL TO COMMITTEE MEMBERS
NOT FOR PUBLICATION

MSBT 11/8

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

MINUTES OF THE MEETING HELD ON 25 MARCH 1997

Chairman : Dr J S Metters

Members present :
Mr J L R Forsythe
Dr D W Gorst
Prof P McMaster
Dr D B L McClelland
Dr R J Perry
Dr E A Robinson
Dr T J Snape
Dr R E Warren
Dr T Wyatt
Professor A Zuckerman

Also present: Professor H Thomas (items 1-6)

Observers:
Mrs J Dhell (MDA)
Dr P Doyle (DH)
Mr K J Guinness (DH)
Dr A Keel (SHHD)
Dr Ludlow (WO)
Dr F Rotblat (MCA)
Dr Toy (DH, RDD)

Secretariat:
Dr A S M Rejman
Miss A Towner
Mr M Harvey

1. Chairman's introduction and welcome

The Chairman welcomed members, including Dr Tim Wyatt and Mr John Forsythe who were replacing Miss Lord and Professor Williams on the Committee.

2. Apologies for absence

Apologies for absence had been received from Dr Cant, Dr Mortimer, Dr Mairs (NI), and from Dr Westmoreland and Dr Gillon (Hepatitis C look-back working group).

3. Hepatitis C look-back

3.1 The paper provided by Dr Robinson had been circulated as MSBT 11/6. Dr Robinson distributed an update of the current status of the look-back exercise. The previous second and third rows of the table had now been merged. Work to identify further recipients in the current first two rows had now ended and so these figures should not change in future. Dr Robinson added that the number of recipients who had died now stood at 3967. It was noted

that for England, Wales and Northern Ireland row 4, number of recipients followed up, did not include those who had died, bottom row, whereas for Scotland it did. The number of recipients who were negative was much higher than had been anticipated.

3.2 Dr Ludlow pointed out that Welsh figures differed significantly from the other countries and suggested that this could be due to a different approach by Wales.

3.3 Dr Toy asked whether some recipients could have received more than one component from an infected donor, so that the number of ~~donors~~ would be fewer than the number of recipients . Dr Robinson replied that this may sometimes have been the case.

3.4 The Chairman asked whether patient identification by hospitals (where outstanding), and referral to hepatology units, should be followed up by the NHS Executive. This matter was discussed at some length. Professor Thomas said some purchasing authorities were not prepared to fund treatment and Professor McMaster ~~said that other~~ said that treatment was covered by existing contracts, and that no further money would be made available. Dr McClelland said many hospitals did not have capacity for tracing; he felt this was an issue which required central direction. Mr Guinness said the Department would need to take a fresh look at what the Minister (Tom Sackville) had said about the treatment of patients identified through the lookback exercise in 1995. The Chairman felt the Department needed to look at how best to pass "encouragement" down the management chain where authorities or Trusts did not appear to have done all they could, especially where there was disregard of Ministers' views or where no additional funding was being made available.

3.5 Dr Warren asked whether there was any explanation of age-related differences in the data. It was pointed out that the chart on the age groups of recipients (page 5 of paper) should have an age group "5 to 10" - or, in September, "6 to 10" - and not "0 to 10" since all the cases had had transfusions prior to September 1991.

3. 6 Dr Robinson was concerned that the National Blood Service did not have information about quantities of blood held in hospital blood banks. She referred to a 1984 Department of Health circular which required all units to provide notification of donations on a monthly basis to the National Blood Service.

3.7 Committee members had anxieties about standards of record keeping in hospitals and whether this was contributing to the significant number of recipients who had not yet been identified or followed up. It was suggested that this might be improved if record keeping was included as one of the standard criteria for laboratory accreditation of haematology departments. It was reported that in recent years record keeping had improved. In 1996 a Council of Europe Recommendation on record keeping had been issued and the Secretariat would circulate this to members for information.

3.8 The Chairman raised a concern about funding of the Registry for collation of information gathered in the hepatitis C look-back exercise. Dr Toy confirmed that Research & Development Division had agreed to fund the Registry, which would be UK wide. Dr Robinson said this would help the Blood Service to link recipients with donors.

3.9 Dr Robinson had a further data sheet in respect of liver disease which she would pass to the Secretariat for circulation.

3.10 The Chairman concluded by suggesting the Committee should re-examine the subject after some six months had elapsed.

ACTION:

- DH to investigate appropriate follow-up action (paragraph 3.4)

- Secretariat to circulate Council of Europe recommendation (paragraph 3.7)

- **Secretariat to circulate information from Dr Robinson (paragraph 3.9)**

4. GBV-C/HGV

4.1 The Chairman referred to paper MSBT 11/2 containing an extract from a letter from Dr Mortimer about progress with the local study he was involved with. If, as this suggested, some 2% of blood donors were infected, quite a lot of units were implicated. Decisions were therefore crucial.

4.2 At the last MSBT meeting Professor McMaster and Professor Thomas had been asked to prepare research ideas. Professor Thomas said they would now need to take account of new developments, such as the material recently published in the New England Journal of Medicine (given out to members). As the editorial suggested, the link with hepatitis seemed less and less proven. However the study had been a short-term one of some 2 years. Longer-term studies (5-10 years) would be needed to be clear if problems would develop - perhaps a study of immunosuppressed transplant cases for GBV-C/HGV virus abnormalities and viraemia, and the effects of multiple blood transfusion ? A consortium of groups might be needed to ensure adequate material.

4.3 Professor McMaster agreed that accumulated data was needed to answer key questions. He and Professor Thomas had pursued rather different lines. He had focused on transplant patients who were immunosuppressed, and on key themes, in liaison with other units. He believed histology was the key. Some information would be available from retrospective studies, but this would be incomplete as most units did not keep records for many years. He mentioned concern among his colleagues that cases of grafts doing less well might be associated with GBV-C/HGV infection.

4.4 Professor Thomas said the virus was being transmitted frequently. There was no evidence of it causing serious disease, but this was over a short period. The only test currently available was PCR, and separate anti-body tests suggested recovery. We needed to find out if disease was caused in the medium/long-term. Multiple testing systems for hepatitis B, hepatitis C and HIV, with the subsequent addition of others such as GBV-C/HGV, might be the way forward.

4.5 Professor Zuckerman agreed. He was fairly certain that we would have moved to PCR techniques in 2 to 3 years. In the meantime we should collect further data. The agent was transmissible, but technology was not in place to evaluate the need for screening.

4.6 The Chairman reminded members that the Morland judgement (para 5.2 to 5.7 of minutes of last meeting) had highlighted the need for any position adopted by a committee to be reasonable in the light of the situation at the time. It seemed reasonable now for MSBT to say that it would set research in hand, as we could not carry out routine PCR testing currently and the long-term consequences of infection were unknown. Professor Zuckerman underlined the need for decisions to be properly minuted and agreed. In recently published Irish tribunal findings about the transmission of hepatitis C, the facts about testing in 1991 were wrong.

4.7 Dr Warren agreed that PCR testing was not yet routinely available, but wondered if we could be criticised for not building up now a centre which could do PCR testing as routine when it did become available. Professor Zuckerman believed current PCR technology was open to contamination and misinterpretation and that it could currently only be used reasonably at a few research laboratories, not generally. Dr McClelland thought that in the light of the European position there was little option but to take steps towards PCR testing, at least for hepatitis C. Dr Snape agreed. Although there were dangers in PCR testing without validation, with the rapid progress being made, within a year we would be routinely PCR testing for hepatitis C.

4. 8 The Chairman mentioned that while the hepatitis C look-back showed some 3-4% of patients had developed progressive disease, there had been no evidence of GBV-C/HGV so far. – how do we know – has it been specifically looked for we did look for evidence of marker for Hepatitis B.

4.9 Professor Thomas raised the question of whether GBV-C/HGV was the cause of fulminant hepatitis. Different people were putting forward contradictory views. Dr Mann's group in Germany had found some differences between cases of fulminant disease and other cases. If the link was proved, then an accelerated programme of PCR testing would be needed. But there was not evidence of much fulminant disease in the UK.

4.10 Dr McClelland thought the clinical epidemiological basis was incomplete. Pre-release PCR testing was not possible now, but pressures were such that the technology would be available soon. Professor Thomas thought it would first be applied to hepatitis C - there was currently no evidence that disease was caused by GBV-C/HGV. The Chairman said that if there were later to be evidence of significant disease following transfusion we would have no option but to say that PCR testing was needed as soon as possible.

4.11 Parallels were drawn with earlier debate about whether donors should be told results, when early hepatitis C tests had given a lot of false positives. If PCR tests were unreliable, we could not tell the donors the implications, or about transmissibility, but their insurance position would be affected. 2% of donors might be identified, and they might decide not to donate blood again until more reliable tests were available. Professor Thomas said that received wisdom was that no problems were caused. Professor Zuckerman agreed with the concerns raised. He felt that CMV was the best analogy- it was very common but did not cause serious disease. He believed the proposed MSBT position was secure until data, and tests for infectivity rather than antibodies, were available.

4.12 Dr Toy asked whether we could be sure GBV-C/HGV did not cause non-hepatitic disease. He referred to the possibility that SV40, present in early poliomyelitis vaccine, may now allegedly be the cause of unexpected illness many years later. Dr. Toy asked whether the presence of GBV-C/HGV anti-E2 antibody in blood indicated complete absence of infectious virus, and so indicate a non-infectious blood specimen. Prof. Thomas said GBV-C/HGV RNI and E2 have never both been found to be present in a single sample, but they were probably present simultaneously at the time of early seroconversion.

4.13 The Chairman thought that blood and transplant recipients should be treated as separate groups. Professor McMaster agreed. His colleagues felt that no precipitate action should be taken over what could be a minor matter. On the other hand we should not ignore the issue, but should take it ahead once evidence became available.

4.14 The Chairman reminded members that MSBT was not a grant-giving committee. Any proposals for research would be passed to DH's research division for consideration.

4.15 Mr Forsythe suggested studying renal patients, even though liver disease was not their primary disease. They were immunosuppressed, and there were more renal than liver transplant patients in the country. The Chairman suggested that Mr Forsythe might join Professor McMaster and Professor Thomas in drawing up proposals. It was suggested that Dr Gorst should join the group so that they could consider bone marrow transplant recipients. They should send their joint proposals for studies to the Secretariat, who would send them to members for written comments. The proposals would then be passed to DH's research division for consideration, although any key points would be discussed at the next MSBT meeting.

4.16 The Secretariat distributed copies of 4 items from journals which Professor Thomas had supplied.

4.17 It was asked if there was any possibility that anti-body screening would be effective. Professor Thomas said that with hepatitis C and GBV-C/HGV patients no correlation had

been found with viraemia. With anti-E2 there was a negative correlation - if the antibody was present GBV-C/HGV was not. Most haemophiliacs got rid of GBV-C/HGV infection, whereas with hepatitis C it was the other way round, and it increased.

4.18 Summarising the discussions, the Chairman said that the evidence that the GBV-C/HGV virus was causing real problems seemed to be diminishing; it was less of a problem than was at first thought. But we could not be certain of this; studies were needed to prove it. Until there was more reliable evidence of epidemiology and natural history, it seemed that GBV-C/HGV probably did not cause long-term problems. There was question over whether it was implicated in fulminant hepatitis. There was no routine PCR test at present. Studies were needed to find out whether the effects of the virus were serious; there should be long-term follow up of both transfusion and transplant recipients. On the information available it seemed that MSBT could properly take no action at this stage, other than putting plans for research in hand.

ACTION : Professor McMaster, Professor Thomas, Mr Forsythe and Dr Gorst to draw up joint proposals for studies, for the Secretariat to send to members (para 4.15)

5. Minutes of the tenth MSBT meeting - 18 November 1996

5.1 The Chairman reported that no written comments had been received on the minutes (paper MSBT 10/14).

5.2 Dr Robinson wished to clarify that the protocol referred to in paragraph 10.1 (line 5) was a protocol on bacterial contamination.

6. Fresh frozen plasma

6.1 The Chairman referred to paper MSBT 11/3, and in particular the notes under "action required".

6.2 Members assumed that a licensed product would be on the market before long, perhaps in the autumn. It was understood that the manufacturers had said that their long-term view was that if they ended up fractionating UK donor plasma, they would not also supply a commercial product in the UK. While the summary table in MSBT 11/3 showed that Octaplas used paid donors, the company claimed that they used unremunerated donors from Austria and Germany. This needed clarification. It was suggested that German delegates at EU meetings had said that all their plasma donors were paid expenses of 50DM for donating.

6.3 Copies of an article from the British Journal of Haematology about SD treatment of cryoprecipitate (cryo.) were distributed to members. It was pointed out that cryo. was used for sufferers from Von Willebrands (VW) disease or as a source of fibrinogen, and it was not virally inactivated. At page 195, the article suggested that SD treatment affected VW clotting factors. It was suggested that 8Y was probably the product to be used instead. If SD were to be used for FFP, not virally inactivating cryo. would be difficult to justify.

6.4 Dr Perry advised that Scotland had a virally inactivated fibrogen product which was about to enter trials, and would be validated. Dr Snape suggested this might be used also in England, if Scotland could produce sufficient supplies. Dr McClelland suggested the use of 8Y or a comparable product for VW cases.

6.5 The Chairman asked for members' views on the third action point in MSBT 11/3. If a product was licensed prior to the next MSBT meeting in July, should the BTS proceed immediately to introduce the SD treatment of plasma, or await further discussion at MSBT ?

6.6 Dr Wyatt feared that, as with BSE, public acceptability was being put before science. He did not consider the risks great, but also agreed with Dr Robinson that doing nothing was not an option. Methylene Blue treatment might be an alternative in the future. Dr Gorst supported the measure as inevitable; although it could hardly be justified on scientific grounds, there was enormous pressure. Dr Warren agreed. He had some concerns about pool size, but these might be resolved through the proposals on gene amplification.

6.7 Dr Snape posed the question of whether the BTS should make any untreated FFP available once the virally inactivated product was available. The Chairman thought MSBT had a limited role in this issue. Although there was a duty towards the NHS and also to other patients, he doubted that a decision by MSBT should be used to stop clinicians using the non-treated FFP if they wanted to prescribe it for particular patients.

6.8 While Dr Snape suggested an analogy with the position in 1984/85 when BPL took the decision to not to make untreated factor VIII concentrate available, Professor Zuckerman believed the science to be quite different. He was concerned that the product was described as "virally free plasma" in MSBT 11/3. Dr Rotblat said that when the product went on the market there would be warnings about the increased risks in some respects, such as parvovirus and hepatitis A (before PCR testing), and it would be made clear that the product should not be used for neo-nates. The documentation, which drew on BTS information on FFP, would indicate that the risks had to be weighed against the benefits.

6.9 Dr Robinson said a lot of FFP was used. NBS single unit Pooled A licensed virally safer FFP could become available at the same time as BPL untreated FFP, with its residual risks. There could be a high cost differential Dr McClelland said that discussions in the group had suggested that the risk of using BPL FFP were likely to be very low. If in 6 months time a safer product was marketed, it would seem difficult not to provide for that option, even though science alone did not seem to justify a change. Costs being about double was a problem.

NBS

6.10 Professor Zuckerman thought the legal profession would take a different view, as they had over the question of heat-treated versus recombinant factor VIII. The Chairman noted that to date all legal action against HAs or SoS had failed, on the basis that the SoS's duty of care in the NHS Acts law was qualified by a proviso "in so far as he judges fit". It was, however, a difficult decision and he could understand the argument that it would be ethically hard for clinicians to chose an allegedly less safe product if a safer product was available.

6.11 It was confirmed that the commercial product would be accompanied by a sheet showing its characteristics. SACTTI was preparing a similar sheet regard existing FFP, which he thought should help clinicians judge which product to use. The Chairman pointed out SACTTI's lack of formal standing. The Chairman also mentioned that the SPC would give information about the new product. Dr Rotblat said that the SPC statement would make the risks clear. She underlined that the SD process did not deal with non-enveloped viruses.

6.12 The Chairman felt that clinicians should be given the choice about which product to use. MSBT had not in the past given clinical guidance to clinicians about which patients should be given a particular treatment and he felt that they should not do so now. That would amount to a clinical practice document. He felt they should say only that if a licence was given, the blood service should have some SD treated product available (whether from UK donors or from other sources), but must not get into the position where this was the only product they could provide.

6.13 Dr Perry suggested that licensing implied that the product was safe. The Chairman doubted that total reliance should be placed on this. Dr Rotblat confirmed that a licence would not be granted if the product was felt to be unsafe, but reiterated that information

would show the balance of risks. Dr Perry felt we were considering an even safer version of an already very safe product. PCR testing could provide an alternative route to that planned.

6.14 Dr Forsythe thought a choice should be retained and both products should be available. The science did not all point one way. Perhaps more information for clinicians was needed. Dr Rotblat said that would be provided by the SPC. The product would have a user leaflet with it, and there would also be a patient leaflet.

6.15 Dr Robinson asked whether the NBS should develop a SD product. The Chairman advised that on the basis of MSBT's discussion the blood service should not wait, but should start making arrangements now for the SD treatment of some UK plasma, giving clinicians a choice.

6.16 Dr Thomas also suggested some guidance or distillation of information for clinicians. The Chairman reiterated that this would be an extension of MSBT's role. It was not for MSBT to advise clinicians on that choice or to draft guidance to them. The major financial implications mentioned by Dr McClelland were a matter initially for the blood service.

6.17 Dr Robinson repeated that the blood service, with help from SACTTI, were preparing an information leaflet on their product setting out the balance of advantage. They might also consult Mr Forsythe.

6.18 Dr Gorst suggested updating existing guidelines on FFP. Dr Perry thought the decision on FFP implied a decision in respect of fibrogen, and encouraged the BTS to take action on that. The Chairman said that BPL would need to decide whether or not to follow Scotland and produce its own product.

6.19 The Chairman summarised MSBT's advice to the National Blood Service that they should make preparations to provide a SD product once a licence was given, so that clinicians had a choice of product available to meet individual clinical needs.

7. CJD : Blood and blood products

7.1 The Chairman pointed out that the UK was free to decide on donor exclusion criteria and other matters relating to the safety of blood, but was bound by EU decisions as regards blood products. The issue of CJD was topical because the MSBT meeting coincided with a closed WHO meeting on the subject, and there was press interest in research being carried out by Paul Brown which was due to be reported at that meeting. Dr Stephen Dealler was suggesting we were about to face an explosion of CJD infection transmitted through blood/blood products. MSBT needed to consider if they wanted to modify their advice as regards blood, and also to advise SEAC of their position.

7.2 Dr Robinson said that Dr Barbara, Dr Will and Dr Flanagan were representing the UK at the WHO meeting. The impression the press had gained was that plasma fractions had transmitted CJD in humanised mice. Dr Dealler felt he had a duty to warn the public if their safety was at risk, and was wanting to discuss with the BTS various suggestions for stopping inappropriate use of plasma.

7.3 Initial UK reports from the WHO meeting were that there were two sets of experiments. One set of experiments involved spiking human blood with highly infectious hamster derived prion. The other set of experiments had involved blood from mice which had been subjected to passage of human CJD by intracranial inoculation. The blood of the mice had become infectious after 8 weeks, and CJD had developed after 16 weeks. Various components from both these experiments had been tested and each had shown some level of transmission of CJD by the intracranial route only. Paul Brown's conclusion was that more information about epidemiology was needed; there was no evidence of blood transmission in humans so far, although the theoretical risks had been considered for several years.

7.4 The UK experts considered that there was a need for further work related to critical inoculation routes, such as intravenous injection. It was very unreliable to extrapolate from mice to the human situation. Dr Robinson thought there was little new development. No haemophiliacs world-wide had been reported as developing CJD. However, the media had gathered that CJD might be transmissible by plasma and plasma products.

7.5 The Chairman recalled that previous experimental work had shown that buffy coats transmitted CJD.

7.6 Dr Rotblat said that CPMP had been aware of the WHO meeting, but not of the full content of Paul Brown's paper. At a CPMP meeting the previous week the general feeling had been that CJD was not transmitted by blood products, but the focus of CPMP had been on whether to recall batches of blood products because donors were later identified as being at an increased risk of CJD.

7.7 At the Council of Europe, there was agreement on exclusion criteria for donors, except as regards dura mater recipients.

7.8 Problems had arisen over the interpretation of the previous CPMP line on product recall. Where 2 donors had subsequently been identified as being in risk groups for CJD, an immunoglobulin product had been withdrawn in the US and France had followed suit. (The product had not been on the UK market.) The latest CPMP meeting had therefore endorsed a recommendation from their Bio-Technology Working Party intended to clarify the position. It still maintained that there was no evidence of transmission of CJD by blood products, but there was a theoretical risk and insufficient data to rule this out completely. CPMP had now made it clear that while plasma pools where a donor was subsequently found to have CJD were not to be recalled by the Member State concerned, if a product was withdrawn in the US or in any Member State, that withdrawn product should not subsequently be exported to an EU Member State, whether from the US or another Member State. (FDA practice was to withdraw in the US products where a donor or relative of a donor was subsequently found to have CJD.)

7.9 The US policy could lead to shortage of a product. The Chairman mentioned a case where Canada had withdrawn a product and asked the UK for a replacement product. However they chose not to buy the UK product when they realised the UK did not have the same rules as they had for withdrawal.

7.10 Dr Snape noted that within the UK there was not the same rigorous system of advice to fractionators, including the transfusion service, which would enable us to guarantee that a product was free of CJD.

7.11 Members were concerned as to how to respond to questions from the press and others about such matters as the blood service's policy on CJD and blood. The Chairman said that existing blood service guidelines deferred relatives of CJD sufferers, and individuals who had been treated with human pituitary growth hormone or human gonadotrophin of pituitary origin from giving blood. He asked if members remained content with this, and with not excluding also recipients of dura mater, as some of Europe did. This was because of the difficulty of identifying dura recipients among would be blood donors, as they might well not be aware that dura mater had been used.

7.12 Dr Perry was content with the present position on blood products, and thought the parallel position on blood was to make no change. The Chairman supported this view. If MSBT decided to change its advice on blood, we would need to look again at blood products, and whether to take a more stringent position than CPMP.

7.13 Dr Rotblat thought that the Commission's DGV were planning a meeting which would consider the implications for blood. As Mrs Silvester was unable to attend, it would be helpful if an alternative UK official, eg Dr Rejman, could be invited, but it was noted that

the Commission would decide who should be invited to the meeting.

7.14 Answering a question from the Chairman, Dr Rotblat confirmed she was not aware of any gene amplification techniques which were relevant as a test for CJD.

7.15 Dr Perry questioned whether a recipient should be told if (s)he had received blood from a donor who had subsequently developed CJD.

7.16 Dr Robinson asked about the proposals considered by SEAC for further experiments as to whether particular components can transmit CJD. Dr Toy said that the joint MRC/DH research advisory group thought there was very low risk of transmission of TSE infection through blood or blood products, although this might need to revisited in relation to new variant CJD. The group had not been particularly impressed by the Minor/Williamson proposals. However the joint DH/MAFF funding group meeting on 7 April would prioritise research proposals, and then advertise for bids to carry them out.

7.17 The Chairman noted that MSBT, SEAC and the Research Advisory Group all had an interest in CJD and blood. In view of the public sensitivity it was important there should be no difference between MSBT's and SEAC's lines. MSBT should therefore set out its position and convey this to SEAC indicating that they would be interested in any comments SEAC might have. The research group, covering both animals and humans, would be prioritising research proposals, and blood would need to be high up on their list. (In passing it was noted that following EC intervention abattoirs now had to filter off and destroy blood, as it was suggested this might be a potential risk of infection.)

7.18 Dr Wyatt asked if blood from new variant CJD patients was being used in any current experiments. Dr Toy said this was being done in America, using blood from UK patients, injected into squirrel monkeys.

7.19 A number of members asked for advice, and to see question and answer material, on how to respond to questions about this issue, including about what measures were being taken to find out if infection was transmitted by blood/blood products. It was agreed that the Secretariat would send them material supplied by their research colleagues which gave details of the role and membership of the DH/MRC Research Advisory Group, and research currently being funded, which were already public knowledge. However, firm information about new research could not be given until after the 7 April meeting.

7.20 Dr Robinson reported on progress with the research follow up study of CJD patients who had been blood donors being undertaken by Dr Will. Approval had been obtained from the Lothian Ethics Committee, on the strict understanding that the work would be anonymised and that no attempt would be made to trace recipients or tell them they had received CJD-implicated donations. Dr Will had a control group of patients who were CJD-free but had a history of donating blood or receiving transfusions. The study would be "blinded" with only the CJD Surveillance Unit knowing which patients had received implicated donations. Hospital and NBS staff would not know which were the control cases. Hospital involvement would only go as far as haematologists, whose co-operation would be sought on a one to one basis.

7.21 The names of donors, controls and recipients to be followed up were being given by Dr Will to the English or Scottish BTS. So far England had received 100 names and addresses. 47 index CJD cases had been identified among people who had given blood after 1980 where recipient records were likely to be available, so the study seemed viable. England also had details of some transfusion recipients; more names for both groups were to follow. The Chairman said recipients would be followed up by flagging their names in the NHS Central Registries, so any deaths would be notified.

7.22 Dr Robinson felt there was particular urgency to identify recipients of blood from donors with new variant CJD. There were three new variant CJD patients known to have

given donations.

7.23 Dr Robinson had taken advice and believed that in the present state of knowledge it was legally and ethically acceptable not to inform recipients of donations from donors who subsequently developed CJD. This would need to be reviewed if the position changed, eg if diagnostic tests or treatment became available. The likelihood of transmission was low and also since the study was blinded those responsible for the care of the recipient would not know whether he had received blood from a control or an implicated donor. The Chairman felt that the conditions imposed by the ethics committee could be cited in defence of this line.

7.24 Members asked about MSBT's response to questions about what was being done about CJD blood transfusion donors, and whether we would be following up new variant CJD cases. The Chairman suggested at present the reply should be that this was being considered - as no actual studies were yet in progress. To the second part we could say we were planning to undertake follow up.

7.25 Dr Warren asked what we would do if it should became known that there was pre-clinical infectivity. The Chairman thought MSBT should hold to its existing position on deferral of those who might pose a risk. Dr Warren also raised the question of deferring recipients of blood donations from CJD patients. It was suggested that this would involve breaking the conditions set by the Ethics Committee.

7.26 On the question of dura mater, the Chairman commented that while the UK would prefer to defer dura mater recipients, MSBT had taken the view that this would be very difficult to implement, since dura mater (which came from cadavers) was used for various surgical procedures, not only neuro-surgical work. Members recognised the difficulty of the issue, which MSBT had considered carefully in the past. The issue was a practical one of finding a reliable way of identifying patients who had received dura mater grafts for non-neurosurgical procedures. Dr Robinson said that donors who had had neuro-surgery would be deferred from donation in any case.

7.27 Dura mater had come under the Medicines Act. The Chairman said that one licence for an earlier dura mater product (as a medicine) had been withdrawn. Members were however not sure that licensing could guarantee the product was safe. It was uncertain which EU-based controls were now in place. Mrs Dhell agreed to provide material on whether dura mater was now covered by the Medical Device Directives.

7.28 Dr Rotblat felt that some other Member States had decided on the deferral in dura mater cases without recognising the difficulty of identifying them. It seemed fairly clear that deferral would shortly be agreed by Europe despite these practical problems.

7.29 Dr McClelland saw a need for a system of recording and auditing, as in the case of other tissues, particularly as dura mater was arguably the most dangerous tissue. The Chairman agreed, saying that dura mater was high on the EU list of tissues at risk of transmission of TSEs.

7.30 Dr Snape thought the question would need to be addressed, and robust defence given, when other Members States and North America were operating a dura exclusion. It was hard to defend the UK acting differently. The Chairman noted that, unlike some other countries, the UK was reluctant to agree to measures which sounded good in theory, but where there was no obvious means of implementation. If the EC or WHO could develop practical criteria to identify dura recipients, these would be worth considering. Dr Rotblat said the UK had asked how other European countries had achieved implementation, but had received no sound answer and so had defended the UK position.

7.31 Dr Robinson, asked if it had been shown that dura mater transmitted CJD only if used intracranially, as that would make exclusion easier. Some members thought that was the case. Dr Robinson, and the Department of Health, agreed to check if there was any relevant

evidence. Dr Toy and Dr Rotblat warned that even if records did not show any such cases that was not conclusive, Dr Rotblat suggesting that the use of dura mater was not always included in hospital records. The Chairman said that Dr Will's records included all operations.

7.32 Dr Wyatt asked how much dura was used. Mrs Dhell undertook to find out.

7.33 After extensive discussion members the Chairman asked if MSBT wished to change its position on blood donation, while agreeing with the CPMP position on blood products. Members did not propose any change. The Chairman noted that MSBT would now set out its position to SEAC to ensure there was no difference in their stance. The Secretariat would provide information to members as promised, including about the research in progress. MSBT would return to the topic at its next meeting.

Tissue banking

7.34 Dr Warren asked about progress on procedures for tissue banking generally. The Chairman said that while he had no progress to report currently, there would be progress to report at the meeting on 8 July.

ACTION :

- **Mrs Dhell to advise if the medical devices directive applies to dura mater (para. 7.27). and to try to find out how much dura mater is used (para. 7.32)**
- **Dr Toy to provide material, via the Secretariat, explaining the research being undertaken (para. 7.19)**
- **Secretariat to pass on material to brief members, including that on research (para.7.33)**
- **DH and Dr Robinson to check for any evidence that dura mater transmitted CJD only if used intracranially (para 7.31)**

8. Introduction of gene amplification techniques

8.1. Dr Rotblat introduced paper MSBT 11/5. It appeared that proposals coming from Europe were more practical than in the past. The Bio-Technology Working Party of CPMP wanted to introduce gene amplification techniques, and had in mind to apply them first to hepatitis C as being most robust. Mini-pools were envisaged to avoid having to discard larger pools. While there were still some problems with application, some commercial firms were already applying the technique to hepatitis A and C. Efforts were being made to prevent manufacturers claiming that the products were therefore safe. (There had been an incidence of transmission of hepatitis A, in Germany even though the pool had been tested and found negative.)

8.2 Progress was being made in meetings between the Working Party, industry and national fractionators. CPMP itself would discuss the question, including feasibility, in April or May. The MCA were keeping UK fractionators informed. The Working Party was also looking at other viruses, with the position on Hepatitis G being kept under review. Some political, and some more tangible, problems were being identified.

8.3 Dr Rotblat also mentioned that an attempt was being made to write monographs for the European Pharmacopoeia.

8.4 The Chairman thought the introduction of the techniques was inevitable, the only question being the timing. Dr Snape said they had succeeded in getting timescales included in

the paper which seemed attainable. It had also been a significant achievement to obtain recognition that the process was more relevant to cellular components than to plasma-derived products. Plans therefore needed to take account of the implications for recovered plasma. Application to cellular components would follow almost inevitably, based on knowledge of pool components.

8.5 Dr Perry agreed we were succeeding in building sound common sense into the European proposals. The timescales proposed had been offered by UK and other fractionators to avoid CPMP imposing unrealistic dates. Introduction of the process was inevitable. The remaining question was whether we were content with the NBA and SNBTS plans for implementation.

8.6 The Chairman noted that if CPMP decided to introduce the techniques the UK had no choice but to follow suit, for blood products. The same did not apply to labile components. But there was potential for embarrassment if labile components were treated differently, and officials would need to consider how to handle this with Ministers. Mr Forsythe agreed that recipients could be disturbed if blood were not treated in the same way as blood products. He also would also wish the test to be done in time for organs from dead donors to be used for transplantation.

8.7 Dr Robinson thought there was a greater impact on blood than on blood products and that we could be criticised if we did not get down to testing individual donations. Those working on this with the NBS were very excited by the prospect, seeing this as the forerunner of a major change in the way in which screening was carried out. Combining algorithms with serological screening could give a much safer end product. If we did introduce the technique it could be used for the release of fresh components too, as was already being done in Germany. NBS experts were working on how the necessary very quick turnround could be achieved.

8.8 Dr Warren wondered whether it was realistic to expect the NHS to deliver reliable PCR testing for transplanted organs, even though MSBT's aim was to avoid treating organs differently from tissues. Professor Zuckerman agreed there were difficulties in a diagnostic setting, in the absence of national or international standards, and foresaw great problems in achieving implementation by 1998/99. Results from different European laboratories differed widely.

8.9 Members were advised that the international SOGAT group, meeting at NIBSC, had been trying to agree on standards and appeared to be getting closer to agreement. A major problem was whether any pool which tested positive should be excluded or whether a minimum level of infectivity was acceptable.

8.10 Professor Zuckerman was sure that PCR, or a variation or other gene amplification technique, would be introduced in due course, perhaps in 2 or 3 years. But questions remained. For instance, what was the level of transmissibility where a surgeon was hepatitis B positive ? Also, the systems available commercially did not give the same results, and laboratories seemed unlikely to be able to cope with the costs and the training involved.

8.11 The Chairman said the discussions suggested that to introduce the technique at all required agreement on standards, and the proper application of quality control. Any proposals from CPMP would need to be tested against these criteria. Dr Snape said that fractionators had reminded CPMP of the need for standardisation and quality controls to be built in, and their points seemed to have been taken on board, eg by SOGAT. The target dates which had been secured would help. He reported that progress had been slowed down in the US because the FDA had recently blocked mini-pool screening by commercial manufacturers, saying that special permission had to be obtained.

8.12 Dr Snape felt that an April 1998 implementation date was the latest CPMP was likely to accept. The UK could make a commitment on quality control and standards applied by the

BTS in relation to hepatitis C, but he was not sure if that was true of the rest of Europe. The Chairman referred to the principle that goods should be exchangeable within Europe.

8.13 Dr Perry was concerned that matters were moving far too quickly and before technical problems had been resolved. It was inevitable that the technique would be applied to plasma. But this should not be introduced until a validated mini-pool system was in place at blood centres, or there would be a large-scale loss of pools. There were inbuilt controls in the timescales offered. The Chairman reminded members that if CPMP introduced the system we would have no choice, even if controls were not in place. Dr Snape thought CPMP would require testing of pools, but that our system of testing pools of samples rather than of donations would meet this requirement.

8.14 The Chairman reiterated the need for proper quality controls and standards, and a practical system which could be operated by blood centres. He also pointed out that DH would need early warning of costs, followed later by details, from the NBA. The NBA and the SNBTS would need to produce plans for practical steps for introducing testing of mini-pools.

8.15 Dr Rotblat said that a period of national consultation would follow the April/May CPMP meeting. She confirmed that NIBSC were represented on the CPMP Bio-Technology Working Party; the UK can feed in question of standards and quality control. There was debate about whether all tests must be negative or whether a cut-off point would be acceptable. Professor Zuckerman advised that there was still no generally accepted standardised technique for hepatitis B after some 5 years. The points highlighted by the Chairman must be put across within Europe.

8.16 Dr Gorst asked if red cell recipients would be told if hepatitis C infection was found in later pool testing. Mr Guinness said that the blood service plan was to test before release. The Chairman understood that CPMP envisaged that mega-pools would be tested, but did not intend to extend testing to individual components. Others were concerned that some 10% of mega-pools would fail, but Dr Rotblat pointed out that we could achieve the goal how we liked, eg using a mini-pool strategy to achieve the specified end. It was also easier to identify individuals from smaller pools. Dr Perry said that mini-pools should be used for economic reasons, and they enabled the patient to be told, which he understood was being done without any problems in Germany.

8.17 The Chairman said that the UK had the world's leading centre in NIBSC. They should work with CPMP to achieve validated standards and quality control measures On the practicalities, the NBA and SNBTS had plans which would take us so far, and would allow the identification of individual donors. He reminded them of the need for details and for costs to be supplied to DH. Tissues were the outstanding problem. Would BTS need to be the ones to test donors, since they had a good testing system ?

8.18 Dr Robinson had in mind that one blood service laboratory in each of the 3 zones might carry out the tests and try to get a fast enough turn-round to include blood components, although the details had yet to be worked out. They wanted to use a small number of other centres where quality controls could be applied, not just BPL. Dr Snape said it had been planned that BPL should deal with blood products; but this was before tissues were considered. Professor Zuckerman agreed there should be just a few testing centres, perhaps at PHLS or university laboratories. Once standards were in place, the Royal College of Pathologists could be asked for recommendations, as very sophisticated technology was involved.

8.19 Dr Warrren pointed out that both facilities and personnel were needed and that accreditation took time. Professor McMaster was concerned about whether the same standards were to be applied in transplant cases, the potential loss of organs, and how quality controls would be applied particularly at busy times when guidance could be forgotten, The Chairman pointed out that existing MSBT guidance allowed clinicians to depart from the

normal guidelines and use infected organs in life and death situations, despite the recognised risks. It was added that, unlike organs, tissues could generally be tested at leisure.

8.20 Dr Robinson would take up Dr Wyatt's suggestion of contacting Colin Roberts who was doing some related work. who's Colin Roberts.

8.21 The Chairman summed up by suggesting that the Secretariat should set up a smaller meeting to decide how to take this issue forward. He also reminded those concerned that fractionators needed to liaise with the blood transfusion service, and that the costs provided in the papers should be pursued. Dr Rotblat said she would send the CPMP proposals to MSBT members when they became available. They could send her their comments.

ACTION :

- Secretariat to set up a smaller meeting to decide how to take this issue forward (para 8.21)

- Dr Rotblat to send the CPMP proposals to MSBT members for comment when they become available (para 8.21)

9. Any Other Business

HTLV

9.1 The Chairman reported that the few comments so far received on the draft report were largely content with its accuracy. It was agreed members could have a further ten to fourteen days from the date of the meeting in which to comment.

Paper 11/1 (progress reports) & Paper 11/4 (Screening Blood Donors for new Viruses (HHV - 8))

9.2 There were no substantive comments. The Chairman asked for any comments to be put in writing to the Secretariat.

Guidance notes on the processing, storage and issue of bone marrow stem cells

9.3 Dr Rejman advised that the document had now been published and copies circulated to consultant haematologists. A copy had been passed on to the Human Fertilisation and Embryology Authority.

Draft good practice guidelines for the prevention and control of blood borne virus infection in renal dialysis and renal transplantation units

9.4 Comments had been received from several members of MSBT including Professor Zuckerman and Dr Wyatt. These had been passed on to the Secretariat of the responsible working group. The future of the guidelines was now under discussion.

10. Date of next meeting

10.1 The Chairman said the next two meetings would be held on 8 July and 27 October, as previously notified.