SPONGIFORM ENCEPHALOPATHY ADVISORY COMMITTEE

63rd meeting held on 29 September 2000 at MAFF, Whitehall Place

Tape Index/Transcript

Members:	**Professor P Smith (Chairman)** **Dr C Bostock** **Mr R Bradley** **Professor H Kimbell** **Dr J Safar** **Professor C Masters** **Mr P Jinman** **Professor J Collinge** **Mr J Wilesmith** **Professor I McConnell**
Technical Advisors:	**Mr P Soul (MAFF)** **Dr M Dawson (FSA)** **Dr J Stephenson (DH)** **Dr A Wight (DH)** **Dr M Bailey (TSE R&S U.)**
Observers:	**Dr M Pitman (MRC)** **Dr M Wilson (BBSRC)** **Dr E Mitchell (DHSS-NI)** **Dr M Donaghy (SE)** **Dr D Shannon (CSG)**
Secretariat:	**Dr P Nash (MAFF)** **Mr A Harvey (DH)** **Mr G Austin (DH)** **Dr L Harbron (MAFF)** **Mr C Lawson (FSA)**
Also in attendance:	**Sir John Krebs (FSA- morning only)** **Ms S Leather (FSA- morning only)** **Mr A Hare (DH- afternoon only)** **Mr P Bennet (DH - afternoon only)** **Mr J Townsend (DH-afternoon only)**

Chairmans introduction

Peter Smith: Welcome everybody, can I just remind you before we start that these microphones record, they don't amplify so please do speak up and speak up if you can't hear what somebody else is saying. We've got a fairly full committee today and we've just had apologies from Roy Anderson and from John Wilesmith. We have a few new attendees, I'd like first to welcome Peter Soul who's attending his first meeting as MAFF's veterinary advisor to the Committee. He's the 'new' Danny Matthews. Danny has moved on to a new role as head of TSE research at the VLA, I think we've seen Danny around for longer than most of us have been around and he has made very important contributions to the committee, so I think it would be appropriate for us to wish Danny well in his new post and thank him for all the contributions he has made. We will I think be seeing him on occasions in the future, but Peter will be here on a regular basis. I'd also like to welcome Deirdre Cunningham who is the Director of Public Health Services with Lambeth & Lewisham Health Authority and she has kindly agreed to attend today's meeting to provide expertise in the area of public health. I'd also like to welcome Keith Jones who is the Chief Executive of the Medicine Controls Agency and is also a member of the EC Scientific Committee and he's joining us this morning, particularly for item 4 on the agenda. We will be having some other visitors this afternoon; Andre Hare and Peter Bennett from the Department of Health after lunch for the discussion on surgical instruments and Peter Cleasby, head of MAFF's rural marine and environment division and Philip Comer from DNV will join us for the discussion on the risk assessment with the use of small incinerators for burning SRM.
I should just update you on where we are with respect to the appointment of a new Chair. The position was advertised in the national press two weeks ago. I understand from the secretariat that they have been deluged with applicants (laughter) and prospective candidates will be considered in the near future to draw up a shortlist and interview are planned for the end of November, so who knows. I would also like to update you with where we are with respect to other vacancies on the committee. You recall that there are vacancies for expertise in public health following Mike Painter's departure and in genetics with Peter Goodfellow's departure. That is I think due to be advertised imminently. It has also been suggested that it might be useful at the same time to advertise for an additional position for a protein chemist. I would just really like to canvas the views of members as to whether this is an area of expertise that it would be of use to add to the committee at this time.

Harriet Kimbell: I don't even know what a protein chemist is.

James Ironside: Speaking personally, I feel that I have a rather poor understanding of protein chemistry and that this would be a perhaps a useful addition.

Adriano Aguzzi: I think that yes, considering how many times we have to deal with validations of tests of antibodies and also the structure of biology implications I think it would be extremely useful. I think this would be of real value for SEAC.

Peter Smith: Perhaps for Harriet's benefit you could just summarise what a protein chemist does.

Adrino Aguzzi: I guess that it is huge field. There is lots of specialities and we would have to brainstorm about what kind of scientist we would like to have joining us. In principle it would be a useful idea to have somebody that brings in technical expertise.

Chris Bostock: I think it is essential that one does have this sort of expertise on the committee but I would have though that to a large extent I think we already have that with Jiri Safar. I don't know whether you would define yourself as a protein chemist, bio-chemist, bio-physicist but you should certainly have most of the expertise required by someone that is classified as protein chemist.

Jiri Safar: Thank you (laughter) I think that in this field there is definitely a need for somebody who is strong I would define it as conformational chemist as a field of expertise, and I think that is really a good idea,

Peter Smith: You feel that it would add to your own expertise.

Jiri Safar: Yes I think that it is a good idea.

John Collinge: Yes I agree, it would be helpful obviously if they were interested in this rather unusual area of protein chemistry rather than but I think that general technical area of expertise would be useful.

Peter Smith: This would be a rather small number of people

John Collinge: Not that small, perhaps a dozen people.

Peter Smith: Ok that seems to be agreed, with that modification in terms of the qualification of the type of person we're looking for, hopefully those would be advertised soon.

Peter Nash: Yes, we could advertise the three posts together, fairly soon.

Harriet Kimbell: Could you actually direct it to the people you think would be useful rather than I know you have to advertise, but couldn't you contact individuals and say, come on sunshine, apply. Wouldn't that be a good idea?.

Peter Smith: Yes I think that's an excellent idea, at least it make sure it lands in front of their noses.

Harriet Kimbell: Well if John knows 12 people, you could send out 12 letters for starters!.

Peter Smith: Perhaps the secretariat could liase with John and others who know this field and send names to the secretariat of people who should be approached.

Peter Nash: Yes if you send us names, we will certainly send application forms to those people. that is no problem

Peter Smith: I think that's all by way of introduction, other than you will be aware that there has been considerable media interest in a number of items that we're due to discuss today, and we've discussed a little bit how this might be handled. It is our practice after SEAC meetings to hold a press briefing where there is a written document and we actually answer any questions that the press put at that briefing. That was scheduled quite a long time ago for the 19th October. That is a little time after this meeting, but we know from experience that it takes a little time to actually agree the press briefing once it's gone out to Members and changes have been incorporated, so the plan is to stick with the timetable of 19 October. But in the meantime it is possible that some of you, some of us, may be under pressure from the media because this meeting and some of the topics on the agenda are quite widely known and the date and the place of the meeting is known by some of the media so the suggestion is that members might like to resist the approaches with respect to one-to-one interviews discussing what was discussed at this meeting. Obviously, if you want one-to-one meetings to discuss other things that's up to you. But in terms of what's being discussed today, it is suggested that you might wish to refer enquiries 1) to the press briefing and 2) to the MAFF, DH, FSA press offices. Is everybody happy with that? It's easier said than done I know, OK.
I would just like to remind you before we start with the agenda items that any members with conflicts of interest should declare them when they speak on a particular item.

FSA review of BSE controls

Peter Smith: I would like to pass on to item 2 on the agenda which is the FSA review of BSE controls and Sir John Krebs has very kindly come along with Barbara Richards and Suzie Leather from the FSA and you've been circulated with a draft report and I think Sir John is going to introduce that and take any questions or comments.

Sir John Krebs: Thank you very much Chairman and thank you Members of SEAC for giving me the opportunity to come and say a few words of introduction about the controls review. I'll just remind you, I've been through this before that I'll remind you the origin and process that lies behind the review. The origin is that we were asked by the Prime Minister at the end of March to undertake a stock-taking review of the current measures looking both now and the future of whether these measures were adequate to protect the health of the public and proportionate. In other words we were asked to look at the costs and the benefits. The process was, to remind you, that the FSA has been undertaking the review with the advice of experts, notably your acting Chairman, Peter Smith but also other external experts who's names are listed in the cover paper. That group has worked through the reviews and with the support of the FSA Secretariat Barbara Richards and her colleagues, has produced a draft, very much a first draft of the report. In parallel to this FSA group with the external advisors, we have been holding a series of public meetings with stakeholders, encompassing the range, from consumers groups through to farming and industry, health science and veterinary professionals. And in those public meeting the audience has been participatory and very effective input from a whole range of people in the audience. At the last stakeholder group meeting, this draft was discussed and a number of points made on it but I can say in summary, very simplistic summary, that the spectrum of people there, who ranged from the human BSE foundation to the abattoir federations and meat producers, had a degree of agreement about the kind of recommendations that we are making in this draft. The way forward from here is that we are going to hold a public meeting in York on the 9th October and then revise the report in light of your comments, comments from the stakeholders, the public, as well as chief medical officers from the 4 countries that I met on Monday, the chief scientific officer and the chief veterinary advisor. That report will go to the final meeting of the stakeholder group in November and a revised report will go to the FSA board on 9 November, to be commented on, approved or otherwise modified. In that intervening period we shall also have to take note of what comes out of Lord Phillips BSE inquiry which as you know was due to be handed over to Nick Brown and Alan Milburn on Monday. We in the FSA will also receive a copy so we will be able to study what the implications are of that report for this review, although just to remind you, that that report ends in 1996 and we are looking from 2000 forward. I very much welcome your comments, either now or if there isn't time subsequently in writing if there isn't time, on the following things; First of all your overall impression of the report, if it strikes the right balance is it accounting things in the right kind of language. I think particularly given that you are the experts on the science and the risk assessment of BSE, whether you are content with the scientific facts as they are portrayed, whether you think there are gaps in the information we have given. And then moving on to the recommendations themselves, as you will have seen, and I can explain to you now, with the three major controls; OTMS rule, SRM restrictions and MBM ban, we are not at this stage suggesting any

immediate changes in terms of lifting those restrictions. Of course if we did recommend lifting those they would then have to be discussed with colleagues in Brussels. We are going into a little more detail, we do envisage that in some stage in the future it would be possible to consider lifting the OTMS rule and that would relate to a declining incidence of BSE and the view that the current level of risk that is assessed by the Oxford model as being about 1-2 animals within 12 months of developing clinical symptoms entering the food chain but of course then the SRM removing most of the risk in those animals. But that level of risk animals could not be exceeded in the future with the lifting of the OTMS rule if the incidence of BSE had declined and I am doing some work with Neil Ferguson on trying to quantify when that risk threshold could be retained with a declining incidence of BSE and lift the OTMS rule in the future. What we say in the draft is that it would at least be 2002 and of course there being sufficient new information on the effectiveness of the August 1996 tightening of the feed ban to refine that calculation next year.

On the SRM controls, we see no case for lifting those restrictions on cattle, of course they are now being harmonised to European level as of 1 October which you have looked at. We draw up very strongly the point that were BSE to have been discovered in the national flock of sheep, the current SRM controls would be inadequate to draw up public controls. Therefore contingency planning by MAFF is an urgent manner if a theoretical risk were turn into reality.

On the MBM ban again, we see no case for lifting that ban, and accept your advice that intra-species recycling is undesirable and we've heard from both the industry and consumers the difficulty in guaranteeing segregation of the food, animal food chain which is relevant to the issue of perhaps separate lines of production for chickens being fed on porcine MBM. But we are not convinced that there is an adequate system of segregation or of audit of segregation. So those are the main conclusions in this first draft of the control measures.

There are just a few other points that I would very much welcome your views on . We draw out at the very beginning of the report the uncertainties of the whole science of BSE and emphasise that one is managing risk in the face of considerable uncertainty and managing it in a precautionary way to reduce but not eliminate risk. That approach has been welcomed by the consumerists on the stakeholder group and I would be interested to know if you feel that has been portrayed appropriately. We place considerable emphasis on the potential of diagnostic tests in the future for both further assessment of risk and also for management of risk. I would be interested on your views on that. We have a very incomplete section in paragraph 62 on future research needs because I think that one of the things that I would like to take the opportunity of in this report is to identify, from the FSA point of view as a user of scientific research, where the major gaps in knowledge lie that could be filled to help us with the risk management task. There is a section about the economic of the controls, which is slightly out of your central area, but I would be interested in your views on the concept of 'willingness to pay' which we will introduce as a way of trying to get a handle on whether the number of £450 million per year that is currently being spent on BSE controls by industry and by the public sector is

in any sense in the right ball park. And we'll be trying to think of a way of approaching that. And of course I am interested on your discussion later today on the new results on blood and the results from Chris Bostock's group and the implication of those for risk assessment in relation to blood in animal foodstuffs. There isn't a paragraph on blood in the draft at the moment, although right at the very beginning when we devised a list of issues to be covered, blood, gelatin and tallow was on that list, so we have it in mind to have a paragraph on blood and that would be very much influenced by your comments that you develop later on today. Thanks very much.

Peter Smith: We could spend a long time discussing this and I don't think that' s the plan this morning. What I would like to do is pick up the major areas that John has highlighted, particularly perhaps the recommendations as to whether SEAC may wish to question or make comments on. I have sent a number of detailed comments on this draft in which I think are not yet incorporated and I think you will be assembling those later on.

322- **Sir John Krebs:** Yes, obviously we will as you say, draw together all comments that have come in and do some revision. Shortly after the meeting on the 9th October, the public meeting so the public meeting will work to this draft and we will then revise it.

Peter Smith: OK, Ray, you look as if you're going to speak.

Ray Bradley: Good morning, I would just like to make a comment and ask Sir John about the statements in paragraph 49 relating to BSE and sheep and the other paragraph 54/2. What I find is that there is an inconsistency between these two. For example it says 'evidence of BSE in the national sheep flock if this was found, in which case the current controls would be inadequate and additional measures would have to be considered.' I absolutely agree with that, and not withstanding the blood, I'm not taking that into account at this point, because it is not really as you say in the report. But now we say in paragraph 49 first of all the BSE agent is more widely distributed in the bodies of sheep. We have not so much information about infectivity but about PrP at the moment. I know that the infectivity assays are coming along and I'm not denying that it is more extensive but we do no know its full distribution at the current time.

Sir John Krebs So do you think we are jumping to the conclusion.

Ray Bradley Yes. The doors are being shut a little prematurely until I think we have all the evidence. (It states that) It would be virtually impossible to remove all the affected tissues without destroying the saleable carcass. Well, when we know what all the tissues are, there are potential ways of doing this and I go back to the BSE epidemic wherein, at least for the export meat which

was agreed with our compatriots in the union, when we were originally allowed to sell that and currently under the date based export scheme, we took out all the visible lymphatic and nervous tissue. Now the industry is already looking at that in sheep. And one realises of course that this is a formidable task and whether or course it is achievable is another issue. But it would shut the door on that perhaps.

Sir John Krebs Yes thank you....

Ray Bradley: The next point is that in the next sentence it says 'if therefore BSE is shown to be in the national flock only sheep that could be clearly demonstrated to be clear from BSE and kept separate from etc etc ' Now we can't even do that for cattle, so how would you possibly demonstrate that every sheep that you are going to eat is disewase free. I think it's an overstatement and I think I very much support the more general view expressed in 54/2 and I think there should be a flexibility about the first statement..

Sir John I think one of the thoughts that was in our minds in para 49 was that if the MAFF breeding programme proceeds and if everyone is convinced that the genotypes selected are TSE resistant, there could in theory be a genotype way of defining which type of sheep are free and which are not.

Ray Bradley: Resistant, not necessarily free, and resistant about getting disease and until we know a little bit more about the research that is currently in hand. It is the infection that is the important issue, it's just a little bit ahead of time. Could I move onto another small point? This relates to paragraph 60 and this sentence 'if infected chicken tissues were then incorporated into pig feed it would amount to intra-species recycling'. Now, what I'm gathering here is that there has got to be feed getting into the chicken intestine and that if it had been MBM from pigs, manufactured from pig material which are not fed MBM, I wish to know if what you are thinking here really of a pig TSE generating itself and then after going through a chicken in the that being unaltered in the gut being returned to the pig. Well there is another possibility as I understand it at the present time, one is permitted to feed poultry MBM back to ruminant animals, so there is a clear answer to this which is also being discussed in the industry is that should a pig TSE develop then it would be rendered, going back to the poultry but then the poultry would not be able to go back to the pigs only to other ruminants. Thereby you have introduced a species barrier at each step. Now I am not wishing to debate at this point and I am sure that the others have different views but that is a mechanism for the species barrier issue can be dealt with. It may not be agreeable to others, that's a different issue, but I am just laying down the principles.

Prof Krebs: This particular sentence was one that was criticised by the stakeholder groups actually.

Ray Bradley: Oh right OK

Deidre Hutton: As you are on paragraph 60, I have a comment on paragraph 61 where it deals with the some forms of rendered tallow possibly being made into plastics and paint. Given that in paragraph 62 it says how experiments have indicated how difficult it is to inactivate the TSE agent, I would caution against their use. People, children, people with learning disabilities etc. actually eat paint and we have not iradicated other harmful agents from paint and I would suggest that prions are about the worst.

James Ironside: Just a quick comment on the end of paragraph 15 about the number of vCJD cases. Although I would agree that there is still considerable uncertainty about what future numbers might be, I think it could be premature to suggest that we are coming close to the peak of the epidemic in view of the recent evidence that the incidence is increasing. I can get you a copy of the letter of the Lancet which shows this. It is including in the information papers for this meeting.

John Collinge: I very much second that, not simply from the data from the CJD surveillance unit but from what we know about the range of incubation periods seen in these diseases in human's, particularly in Kuru and iatrogenic CJD. Particularly in Kuru we're seeing cases up to 50 years after the cessation of cannibalism and it would be truly remarkable if vCJD was going to go away in the next couple of years. We are looking at something that is going to be with us for a very long time.

419- **Diedre Hutton:** May I just come back to paint. Thank you very much for clearing that up. I think that what we're saying here is that it would only be used after the hydrolysis at 200 ^{0}C /40 bar pressure which is the way you make tallow derivatives, which are used in a whole range of things including pharmaceuticals. It's not going to be the tallow directly. Already scientific experts have decided that this process and tallow derivatives rather than tallow itself, are regarded as 'safe' so I think the risk factor from tallow derivatives in paint would be trivial. But I take the point about tallow itself.

Peter Smith: OK, are you happy?

Deirdre Hutton Well, I'm not an expert.

John Krebs: Yes, but it is the view that this process at 200 ^{0}C /40 bar pressure does render it safe.

Ray Bradley Yes

Chris Bostock : I would support the comments made by Ray on paragraph 49. I

would also like to add what may be seen as a trivial point but it relates to table1 where you list host and diseases and you distinguish man as being a host of vCJD but you don't distinguish between the hosts that are affected by BSE. Now it's a disease you're talking about and so that for a cat its actually Feline Spongiform Encephalopathy so there is an inconsistency. Either humans are listed as being infected by BSE or I think preferably you would try at least in some way to identify other species as having different diseases.

Ian McConnell: First of all I would like to say I thought it was an extremely good document for general consumption and certainly, once it's released, I would make it compulsory reading for every veterinary student in the country so that they realise that they should pay attention to this in the future and not hamster medicine. However having said that, I felt that in paragraphs 59 and 60 the case about intra-species cannibalism is I think is not made strong enough. I think that MBM and the use of MBM will be an issue that will come back again and again. As this really lay at the very heart of the amplification of this disease I think that one needs to be very strong and just to say it is unwise, I would say that intra-species cannibalism is wholly undesirable. I don't wish to put words into the committee's mouth but I felt that the arguments carried forward in paragraph 60 make the point that the reasons you don't do it is that it is difficult to police. However that's a secondary reason. The primary reason is that intra-species recycling of feed is something I would not which to wish to see come back.

Peter Smith It does sound as if you want to put words into the committees mouth. It's a suggestion anyway.

Sir John/Peter Smith: We actually did vacillate between being undesirable and unwise and I think we may have had undesirable at one stage in an earlier draft.

Barbara Richards I think we did in an earlier draft

Peter Smith I think it is something that the committee is particularly sensitive to because also this porcine MBM has been recycled back to us a number of times!

Sir John: That's not intra-species recycling

Peter Smith It's intra-committee recyling!

Harriet Kimbell: I was just wondering at your public meetings, were the members of the public who were there surprised at the extent to which there was, or had been in the past, recycling of MBM amongst farm animals and so forth.

Sir John Krebs No. It's not actually drawn out as a specific point but none of the people expressed surprise at that.

Barbara Richards No at none of the meetings. It may be raised at the public meeting in York. There will be a great many more people at that meeting.

Sir John: The public meeting at York will have 400 people at it. It's already fully booked out.

Chris Bostock: In relation to the arguements in para 44 and retaining it or finding other methods for relaxing it. It seems to me that if the arguments go roughly that the only cases of BSE in animals of 30 months or close to 30 months would be maternal transmission, then we would be basing the 30 month rule on the pathogenesis of maternally transmitted BSE as opposed to orally transmitted BSE on which all of our present information about pathogenesis is based. I am not sure that there is any way of resolving it, but certainly it may be that the progression of the disease to the maternally inherited infection would be very different to that in the food-borne infection,

Sir John: Is there any evidence that would relate to that?

C Bostock: I don't think that there is any evidence that would relate to that. There is no direct evidence that BSE is in fact maternally inherited, or at least that the infection is received through the maternal route.

Sir John: Are you saying that this would affect the rationale behind lifting the OTM rule in the future or is it an argument about having the OTM rule in the first place.

C Bostock: All I'm saying is that the premise on which much of the evidence to support the evidence on the thirty-month rule would be not applicable in the formal sense, because the infection will be derived through the maternal route. And I think one has to at least bear that in mind in terms of using that support or otherwise in what decisions are made

Peter Smith: Does that suggest, Chris that we should be, if it's not already been done, be thinking about looking at tissue distribution infectivity in BSE cases born after August 1996. We've got one case, presumably if there was maternal transmission we obviously can't do any studies of tissue infectivity during the course of the disease before clinical onset with respect to maternal transmission.

C Bostock: I think it is unlikely that you could think of a reasonable experiment to test this experimentally. But I would have thought that if there

are cases of BSE in animals born after August 1996 in which there is strong evidence that the mother was infected with BSE and therefore the animal was a candidate for maternal transmission, then yes I think it would be useful to have a look at infectivity distribution in tissues for comparative purposes. The animals that are being looked at so far have a very high probability of being exposed through MBM.

Peter Smith: We're probably not going to have animals in that category where there is strong evidence of maternal transmission, in the sense that if we know that the mother had BSE, then the animal won't be there because of the maternal cull. Given that we hope that any cases that are occurring born after August 1996 are most likely caused by maternal transmission, we can proceed on that assumption and look at the tissue distribution of infectivity on those animals.

C Bostock: One or two selective tissues, and certainly spleen, which if you like has now been confirmed to be free of detectable infectivity by cow to cow assay, I would think that could be one key tissue that could be looked at to see if their was a major difference in the pathogenesis.

Peter Smith: And studies of these kind are not in place?.

521- **Peter Soul:** No I don't believe they are

Ray Bradley: Could I just make some comments on what Chris said. I agree in what he's saying in principle but I would like to draw attention to the fact that in the maternal transmission it doesn't rule out an oral route first of all, because you could even have an oral route in-utero, but of the three kinds; you've got the in-utero, during the parturition itself and in the immediate post parturition period and this would only really apply to the first of those three.
I think there is a potential way of experimentally investigating it, although at the point that Chris said it I agreed with him, but I thought of a way to do it. Bill Hadlow did some studies by inoculating foetuses of unknown genotype in the uterus of the sheep and following them on thereafter and they didn't actually produce scrapie, but that may have been because of genotype problems. But what you could do here is either, orally or intravenously inoculate the foetus in-utero and then look at with BSE and then look for the infectivity of the tissues if and when the animal got the disease. I see that that is a possible way forward.

C Bostock: There clearly are experiments going on with maternal transmission of sheep with BSE but I think the problem there is experimentally orally infected sheep have a different pathogenesis and so I think in this case it would not be appropriate to read across.

Peter Smith: OK. Other comments?. If not John, I don't know whether you want to say anything in conclusion?.

Sir John Krebs: Well really just to reiterate my thanks to SEAC but also to you Peter, because you've been contributing fully and made major comments on the earlier stages of this on behalf of SEAC, you've been making very important input. So thank you all very much and I'll take away the comments from today to build into the revised draft that we'll produce later in October. And if as you say there are any more comments that come out of your discussions after I've left the room or people think of, if you could send them to.....Would it be best to send it through the SEAC Secretariat?

H Kimbell: Do you think that anyone from SEAC is going to attend that meeting in York? Are there going to be minutes of that meeting in York that we could see?

Sir John: There certainly are minutes of the stakeholder meetings and they are put on our website and we could distribute them to SEAC members if anybody would like to see them. Are we planning to take any of the public meeting Barbara?

B Richards: We will try and take some sort of note but we're probably going to go into breakout groups if it's possible depending on the number of people. So it may not be a formal minute of the whole meeting, it may be a summary of the points raised in discussions.

Sir John: I think the answer is yes, Harriet and we'll make it available. If any member of SEAC wants to attend even though I've said it's fully booked up, we will create a space. We've placed an ad in the national dailies today and our helpline was jammed first thing this morning and the 300 slots that were left from the 400 places were all gone by the time I left the office at 10 o'clock this morning so there was a lot of interest in it.

Peter Smith Thank you very much for coming along. OK so if I could encourage Members to send comments through the secretariat. There were quite a few points of detail that needed correcting and similarly I am sure you will have others, particularly on the factual areas. We've got an almost private discussion now. Chris lawson is here to take notes as to whether there were any things that we wanted to discuss without John and Suzie present with respect to the report. My fear when this whole process was set up was that it was a potentially very difficult position for this committee because if this report ended up by saying well basically SEAC has got it wrong then that would have put us in a very difficult position. I read this as not saying that but in fact that there is no proposal really to change anything that we have written and recommended, so I am reassured by this process and I think that it re-enforces

some of the things that we were concerned about, including porcine MBM recycling where we've had a slight battle with and this will enforce our assessment. But, other comments.

Ian McConnell: I think it is particularly good on the uncertainty, I mean it really does get across that although everyone would wish there to be more precise information it is a very uncertain epidemic and that comes across I think very well.

Colin Masters: I think you should welcome the emphasis they are placing on research, particularly on diagnostic tests. To link any variation to the OTMS ban with improved diagnostic tests certifying that the national herd is in fact free of BSE would be very good.

Peter Smith: You mean not change anything until those diagnostic tests are available?

Colin Masters: No, until the scientific.....

End of Tape 1 Side A- Tape 1 Side B

....suggests as best we can that there is no sub-clinical circulating in the OTM.

Peter Smith: Previously there had I think been talk of having some form of public debate when discussing the revisions to the OTM rule, which this committee would not necessarily initiate but would certainly contribute to. I would still see a role for that in moving things forward in the face of the uncertainties.

Peter Smith: OK. so if you've got any specific comments do pass them through the Secretariat to Sir John's group.

CJD update

Peter Smith: The next item is the CJD update which James is going to introduce.

James Ironside: I hope that you can see, you have in your documents a copy of the graph of the cases of CJD arranged by the disease onset. you have received a copy of the latest figures and tabled this morning is a paper related to the analysis by Nick Andrews. So just to say where we are officially, there are 67 neuropathologically confirmed cases and six probable cases where neuopathological diagnosis will never be available. The biodata in these cases is rather unvarying. The mean age of death still 29 ranging from 15-54 and the

onset 14-53, consistent with the median duration of illness which ranges from 6 to 39 months confirmed. Of the confirmed cases, 36 are females and 37 males. Of all the cases tested, all are methionine homozygous at codon 129 of the PrP gene.
Then we also have the probable cases. At least 7 are still alive, 4 are dead and they died in this year so we are still in the process of reviewing the material from these cases. In these the mean age is rather younger and includes the youngest patient so far with a disease onset at aged 12. Of the 11 probables, 5 are male and 6 female. We have DNA analysis on 6 of these and there are again all met homozygotes. Of these 11 most of them have a disease onset in 1999, one in 1998 and 2 in 2000. That is the situation in these cases.
I turn to the paper by Nick Andrews that we considered at the last meeting and which has subsequently been published in the Lancet. The paper covers all the cases mentioned above (84 definites and probables). The trend continues to be significant with a increase of 27% for onset and 36% for deaths (per year) so the situation really hasn't changed much since the last presentation. That's really all I have to say about that. I have another case which with the Chairman's permission I would like to present,

Peter Smith: Any questions on what James has presented so far?

Chris Bostock: The difference in the increasing rate in the onset compared to death. Does that mean that the clinical phase is getting shorter?.

James Ironside: No that's not certain. The clinical duration seems to be linked to the ages of the patients. By and large the younger patients tend to have a longer duration so that's probably partly explains some of the difference seen. I don't think formal analysis proves that the clinical phase is shortening.

Peter Smith: Another point I think is that the diseases are being diagnosed sooner so the interval between onset and diagnosis is shortening.

Peter Jinman: Is it also true that sporadic CJD is increasing at the same rate?. I have seen some of the figures and over the years the number of cases seem to be going up too.

James Ironside: No, they're not increasing at this rate. Since the surveillance project began in 1990 the numbers of sporadic cases in the UK have increased, but they have not increased any more than other European countries that are doing surveillance with similar methodology. So that is probably an effect of improved ascertainment and better diagnosis.

Adriano Aguzzi: It worries me a little that the histopathological definition criteria for variant CJD was established at the time when there were only a handful of cases. The glycotyping criteria was established when there was a

few more cases, but not that many. Are you seeing any evidence of there being a shift. Are there discrepancies for example between life expectancy and histopathology which may perhaps be an indication of some of these patients may already be second passage of vCJD into humans?. The second question is, can we be sure that, or are we doing something to see whether, the pathological criteria that was originally defined still enable us to see all the cases that are there.

James Ironside: OK, I think these are important questions and these are ones that exercise us constantly. In the cases that are listed here, I don't think there is any evidence that the neuropathological features are changing and in the cases where we do have done glycotyping, and John can perhaps comment on this, I am not aware on any changes in these particular cases.
The other question was could some of these perhaps be iatrogenic vCJD cases showing the same features. Well, that I guess we can't formally exclude this, but there is nothing to indicate this in the disease phenotype either clinically or pathologically that this is the case. The other question that you are alluding to is I think, would we be able to recognise a case of BSE infection in a patient that wasn't a methionine homozygote. I think that's a good question and I don't have an answer, except to say that we have a very high index of suspicion for any case that doesn't fall into what's recognised as the spectrum of sporadic CJD. And one of the problems we have of course is that the spectrum of sporadic CJD is wide with the identification of a number of sub-types. We investigate any unusual case, including full transmission studies.

Ray Bradley: Could I just ask James about numbers of cases in other countries and do we know if those countries which have already reported cases have adopted the same kind of procedures, or even investigating things like surgical instruments and that sort of thing, in the same way as the UK has done.

James Ironside: There have been cases of variant CJD confirmed in Ireland although one case lived in the UK for a number of years in the 1980's and there are two confirmed and one probable suspected case in France. I have reviewed the pathology of all these cases and they are very similar to the British cases and the analysis done on the PrP typing by the French in particular so I think that evidence suggests they are the same. Regarding the approach to surgical instruments, certainly France and Ireland are concerned not only about surgical instruments but about blood and blood products which they are taking seriously.

Harriet Kimbell: I think it was the case that we were told that, someone had told us before that there had been corneas transplanted into people that had been taken from the CJD patient…..

James Ironside: Yes, that's right…

Harriet Kimbell: Have people who had those corneas got the disease

James Ironside: These corneas were transplanted from a women who died of sporadic CJD and diagnosis was not made until after the transplants had been done. To my knowledge, one of the corneal transplants has subsequently been removed the other one has not been removed so we have a controlled situation Scleral material was also used in other patients and that has also been removed. As far as I am aware the recipient of the cornea which has not been removed does not have CJD. She is still alive, but elderly.

Adriano Aguzzi: There is still a question. Of all these cases how many of them how many of them were glycotyped so far

James Ironside: Not all of these 73 cases have been glycotyped. I think roughly half of them probably have and we are doing this for our own diagnostic purposes in Edinburgh and we supply John with material. I should just say that we are running into difficulties with issues of post-mortem consent. These are issues arising from the review going on in Bristol concerning the retention and use of brains and other organs. Undoubtedly, we are having difficulties in firstly getting consent for post mortems, secondly getting consent to remove the brain and thirdly getting consent to use the material for research purposes. If these difficulties continue this will hamper our investigations particularly regarding atypical our unusual cases. The families generally are very co-operative with us but there is a particular difficulty in this regard.

Adriano Aguzzi: The reason why I am hammering on this point is because I assume you are also glycotyping sporadic cases, so I wonder whether you are seeing any atypical glycotypes. The reason why I am asking is because we have seen such a case recently with a pattern that is not typical vCJD pattern, but with a most prominent diglycosylated band but not correlated at histopathology eg no florid plagues etc. I was wondering if you had seen similar things because the question is of course what are the real case criteria definition for vCJD.

James Ironside: I think that the case definition criteria is very good for BSE infection in methionine homozygotes. I think that for other cases, we do have to keep an open mind about this. John will know because he was present at a meeting in Austria earlier this year when a case from the Netherlands was presented. A woman who had sporadic CJD, which the glycotype picture at autopsy, although interesting not at biopsy, was approaching the pattern that you would except from vCJD. That is the only one that I am aware of. In the UK we personally have not actually seen this kind of sporadic case, but maybe

John wants to comment.

John Collinge: Yes I would agree with James. I can't tell you the exact number of glycotypes we have done but it is probably about 20-30 new variants, including the ones James has sent down and autopsies that have been done in London and the patterns are remarkable consistent. The is the standard errors when you plot these things out are quite remarkable and we can't distinguish between them. There are very tight distributions which is why we were able to indicate to you that your case lay well outside that distribution. We've looked at one French case, the original French case, which is again indistinguishable from the British cases so it's a very tight picture that we're seeing. These are all in methionine homozygotes. The work we published in 1997 on transmission of variant CJD to mice expressing the human valine isoform suggests that we may see a different pattern in that genotypes of individuals. There is one patient that we've seen recently at St Mary's that we're investigating in that regard, and there is an unusual glycoform pattern. I've discussed this with James and our investigations are not complete and I'd rather not say anymore about that until they are.

James Ironside: The other thing I would add is that in the few cases where we have looked at different areas in the brain, there does not seem to be significant differences.

Colin Masters: At our last meeting James, the figures were 20-30% and now were 27-36% . Is this a real increase?

James Ironside: I'm not an epidemiologist or statistician. I would invite the Chairman to comment.

Peter Smith: I'm certain it won't be statistically significant. It's a real increase in the estimate but I don't think it's a significantly different change from what we've seen before.

Ray Bradley: James, I'm not asking about individual cases but I'd just like to ask how we as a group might respond to questions put to you at meetings about this supposed neurological condition in the baby of the patient who did have CJD that has been in the newspapers a lot. What is the answer we should give when asked.

James Ironside: Well I would say that we don't discuss individual cases. This is a good answer but John perhaps knows more about it

John Collinge: The mother and baby have both been investigated at St Mary's and I think the correct answer is that we don't cover individual cases. There has been a lot of misleading things in the media as usual but I have been

discussing with colleagues about whether we should write a case report to perhaps help settle some of these issues, but that is a question to be discussed with the family.

Ray Bradley: But I think what can be said at this stage is that in the figures that are released by the surveillance unit, the age range of cases excludes that infant having been officially classified as a case.

James Ironside: And of course if I can just remind members that there is of course the separate paediatric surveillance system and I can also remind Members, and this is also confidential, but this is not the first incidence of a CJD patient giving birth to a baby. It has happened before with one of the first cases and that child is alive and well but that is ……

Peter Smith: That's very confidential, I don't think that is known to the media?

James Ironside: No well, it has been known to the media in the past, it was raised in the past but it's beyond the attention span so to speak.

Peter Smith: OK please go on to your next bit because I think that that's ….

James Ironside: Yes, John's just reminded me that the family did mention this in their evidence to the BSE inquiry so that may come out in some stage…..alright, I'd like to present an interesting case which has some relevance to our discussion. Variant CJD in a geriatric patient. I don't know if you know the details, but this is a case that has just been diagnosed and it's not included in these figures yet. The patient's date of birth GRO-A 24 , unmarried, no children, presented in February 1999 with behavioural problems, withdrawn, some speech difficulties, driving erratically and memory loss. The GP that referred her to the hospital diagnosed senile dementia and there was no neurological signs and the patient was suffering from memory loss. Clinical investigations were unremarkable, the patient was then referred to a psychiatrist who suspected that there was an organic psychosis and also raised the possibility of multi-infarct dementia, which is a form of cerebral vascular disease. The patient essentially deteriorated over the following months and began to be very unsteady and fell on a number of occasion and was admitted to a psychiatric geriatric nursing home in August with dementia and he died on the GRO-A last year. The autopsy was requested by the clinician and permission was obtained and the brain was referred to the regional pathology centre. On the 10th July this year the preliminary examination suggested that this was indeed a human TSE, the suspicion being that it was CJD/GSS so the brain was referred to us at the end of July and this month we confirmed the diagnosis of vCJD. The neuro-pathology is very similar to all the other cases we have seen at that stage and we will use DNA extracted from [???] to find the genotype, but if we have problems, I will refer this to John.

The physician dealing with the case is currently on holiday and the relatives have not yet been informed of the diagnosis so this is one of the case not yet in the official figures but they will be. Because the physician is on holiday we have not been able to survey the hospital case notes with the usual care to actually chart the neurological features and I guess some debate how well some of the neurological features have been recorded. But the broad features of the history is not very dissimilar.
Clearly this case will skew the statistics and it's untidy in that sense and I don't know whether we need to have a prolonged debate about it now but obviously it is the first case of variant CJD to be diagnosed in an elderly patient and we must therefore ask whether it is the first case to occur in this age group, 20 years older than the oldest to date. In view of my other comments, I have to say that most other suspicious older cases have been identified and investigated by autopsy. We have some studies that DH funded looking at the pathology in sporadic CJD and other dementia's across the UK and in this study of the elderly, neurological disease across the board are examined. We can debate this when we have more information particularly on the gene type at codon 129 in this case. So this is a preliminary presentation but because the case will be out shortly and then announced, I thought it best to present this to you now.

Harriet Kimbell: Will you be investigating his eating habits and medical treatments and all the rest of it in the same way as you do for the others?.

James Ironside: Yes we will do. Because he wasn't married and doesn't have children, the siblings are the nearest relatives and unless.....

John Collinge: Obviously we would be very happy to help with anything you want. Finding the PrP gene from fixed material is not straight forward as you know. There's less than 50% success rate. I just wondered whether you might investigate whether there are any blood samples taken during the hospital admission and whether they are still stored in any of the chemical pathology labs. That would might make life a lot easier, both to exclude an inherited cause here and also to determine a codon 129 genotype.

James Ironside: Absolutely, we are doing that and so far there is no record of anything being kept unfortunately. All we've found are some wet tissue from other organs, unfortunately not the tonsils because it is not of course routinely examined in post-mortem and we've haven't received those yet.

Prof Smith: The nine month delay between the autopsy and the neuro-pathology result, is that typical or is that unusual?

James Ironside: I think my answer to that was that both in pathology and neuro-pathology there is a shortage in terms of medical and technical staff and some departments are under -resourced. So once the case had been studied we

were notified almost immediately.

Peter Smith: And, neuro-pathologically this was more or less identical to the younger cases?

James Ironside: Excepting all the Adriano's caveats about the neuro-pathological features, it has all the neuro-pathological cases identified in the other cases. We are doing some more detailed work to actually look at and quantify some of these subtle changes, but it is only a couple of days since the case was diagnosed.

Deidre Hutton: I was just wondering whether this raises the possibility that there is considerable confusion in older-age victims with dementia and that there may have been undetected cases are treated like dementia…

James Ironside: Clearly that's a possibility, yes.

John Stephenson: Yes, to briefly mention this, and just to answer that question, obviously this is a situation which has been on the mind of the DH for some time. Apart from the nationwide study, which James has been exemplary in co-ordinating, he has managed to recruit just about all the neuro-pathologists in the UK into this study. We have also commissioned two contracts with Marco Desiree of Oxford and Jim Lowe at Nottingham to look at all of the samples in their pathology department, to go through them again with a fresh insight to see if this problem of under-diagnosis is indeed a real problem. I went to see Marco and Jim in the last few months and so far they have not detected any great under-diagnosis but this is ongoing. And as James has said their departments are also under-resourced so they cannot move as fast as we would like.

Harriet Kimbell: Is James going to update us on Leicestershire at all?

James Ironside: All I can say on Leicestershire is that we are still awaiting further information from the studies that Dr Monks is initiating and Hester Lord from UMIST is dealing with in close liaison with the group in Leicestershire. Those have not been completed yet so really there is not any more information about that at present. As far as I am aware, there have been no more confirmed or suspected cases since the last meeting occurring in the area. I was referred a case of a young man who had died of a psychiatric illness of unknown type and a post-mortem was performed and there are at least parts of the brain to examine but what I see in that is not a case of CJD of any type.

Peter Smith: Ailsa, I don't know whether it's appropriate at this time to say something about the meeting with the CCDC's and what might happen in

future about one similar situation in Leicester and two with respect to education

Ailsa Wight: Yes there are a number of issues raised by the Leicestershire case not least in relation to defining a cluster and what we need to do is to make sure that everything runs smoothly and everyone who needs to know has the right information at the right time. I met with Peter and other colleagues from the CJD surveillance unit earlier this week to consider how we might make arrangements routinely for making sure that public health committee hear about any cases coming though really at the stage when they become clinical cases. And we're just in the process of working with the CJD surveillance about getting some sort of proposal. We hope that the spin-off from that will be actually we get identification of clusters in a timely way because each case that comes through will be notified to the appropriate people so they will have all the information that the CJD unit has [????????]

Peter Smith: I think there has been concern that local public health officials have found out about situations through the media and have been embarrassed by this. Obviously there are issues of confidentiality so the discussion is ongoing as to how public health officials may be notified at the same time without compromising confidentiality associated with the surveillance unit.

Ailsa Wight: Nor indeed compromising the investigation that the St Mary's team carries out in all cases which is a national study and it was thought very important that a balance is struck between compromising their work and the needs of the local community

Diedre Hutton: Can I just say that I think that is very welcome from the CCDC perspective. They are actually use to maintaining confidentiality, particularly in terms of HIV infected health care workers etc. and that they can be trusted.

Peter Smith: Yes, it was just the mechanism by which they are informed that I think was the issue and I think the proposal was that the surveillance unit should suggest to the person who notified the case to the unit that they also notify the public health people. I suppose we don't know when this is going to become public.

James Ironside: No, I think that the clinician concerned is back some time around the end of next week, so I would guess in the next couple of weeks.

Peter Smith: I guess as we've not really known why it's only been in young people this shouldn't surprise us, but it obviously will lead to a lot of speculation and comment and opens up a whole large section of the population to being an 'at risk' group who might previously have felt secure.
OK, if there's no other questions or comments we'll move on. We've got a number of items now related to recent publications. The first of these is the

publication from John Collinge's group which provoked quite a lot of media attention, John, I don't know whether you want to say something about what you see perhaps as the implications of those findings. I am particularly thinking of two key issues; do they have any implications with respect to the control measures we have in place and secondly for research that ought to be ongoing.

Discussion of recent scientific publications

John Collinge: I brought some slides along but I'm not sure about how much detail you want to go into.

Peter Smith: Well I think we'll assume that everyone has read your paper, so anything in addition to that, I mean if you want to give a rapid overview of your interpretation of it… I say that but I know not everyone always does that.

Prof Collinge: Well from my point of view the interesting things scientifically are that it's challenging our interpretation of what we mean by species barriers in that species barriers are normally measured in one of two ways either; by a change in the incubation period in the first and subsequent passage in a new species or by comparative endpoint titrations between two species. But both of those rely on having clinical endpoints, so if you have no endpoints i.e. if the mice don't develop a clinical syndrome, the interpretation has often been that there's an excellent species barrier there.
But what I thought I meant by a species barrier and I guess is the more biologically important and certainly more important from the public health viewpoint is not that there isn't a clinical disease but whether inoculation of an animal with prions of another species actually triggers replication of prions within that new host. That seems to be the more important way of thinking about the species barrier and in this case it is what's happening with animals. This strain of prions has been around for a long time and first really identified by Richard Kimberlain in a series of studies in the 1970's -263k, also referred to as sc237 and it was the strain that Prusiner used on his seminal studies on the species barrier in 89 and 90 published in Cell, where he shows that inoculating conventional mice doesn't seem to do anything, but when you make such mice transgenic with a hamster gene they then become highly susceptible and they all die with consistent short incubation periods which are inversely proportionate to the expression level of the transgenically expressed prion protein in those animals.

So here we are seeing that although the inoculated animals don't develop a clinical syndrome and they apparently die of old age or intercurrent illness along the way and the duration of their life is not different from those in the control inoculated animals, a significant proportion of these animals, and indeed the ones that have gone on longest, have high levels of PrP scrapie in their brains. These are not difficult to detect. The levels of PrP scrapie in their brains are very similar to type levels of PrP seen in clinical end points in these

type of animals. Indeed they have high titres, the sort of titres that may been seen in end stage disease in mice.
So it does question in a sense what we mean by species barriers and does lead us to look back at some things that have been done in the past in that regard.

The other scientific issue that has been raised it that this adds further evidence to a number of things that have happened before that I have tried to cite in here suggesting that PrP^{Sc} or indeed prions themselves, whether or not that is the same thing, may not be neuro-toxic or may not be highly neuro-toxic. If these mice can tolerate high levels of prions and high levels of PrP^{Sc} in their brain without clinical syndrome, it does raise the question about what is actually killing the mouse. So these are some of the interesting scientific points.

We've speculated a bit about what we think might be worth exploring and what hypotheses we're currently exploring in that regard with respect to prion neuro-degeneration. From a public health point of view I guess it emphasises the point that I and others have made for some time on this Committee, which is that we ought to consider the fact that there may be sub-clinical forms of these diseases in addition to pre-clinical forms and we all know that these diseases have extremely long incubation periods and therefore animals may die or be killed before they show signs of the disease. To some extent, this is a semantic problem in what you are calling these things. When you are dealing with a disease with a very long incubation period which, when crossing a species barrier, may be approaching the life span of the species concerned, whether you are calling that pre-clinical or sub-clinical is a little semantic. Operationally we try to define an infection in the animal which does not show any clinical signs during a normal lifespan as being potentially a sub-clinical state and of course such sub-clinical carrier states are essentially routine in other forms of infectious disease which we are much more familiar. So it is not surprising that there may also be asymptomatic carrier states of prion diseases too. Now, whether this is something that's unique to this strain of prions in these hosts, or whether it requires the crossing of species barrier to induce this sub-clinical state is not clear. Its general applicability will, of course, have to be explored further. But it does raise the possibility that there might be sub-clinical states of BSE in cattle or BSE in other species. This is an important issue of course because this is a lethal human pathogen and that's what we're interested and we want as far as possible to exclude it from the human food chain. So that, I think is the 'take home' message from the public health point of view.

Prof Smith: So the potential implications are in all species, but in particular man, cattle, sheep, pigs and chickens…

Prof Collinge: Yes, but that needs to be experimentally determined. Obviously all we've done is look at the parallel between hamsters and mice. But this is the barrier by which most experimental work has been done, it's the barrier on which Prusiner built most of his transgenic studies, it's not any old barrier, so this came as a great surprise to us of course. We weren't intentionally doing

these studies to begin with. We sort of stumbled on it, so it's rather a surprise but I think it means that one does need to look elsewhere, particularly in those areas of public health concern, i.e. what's happening in cattle, what's happening in sheep, and at a more speculative level, what's happening in pigs and chickens, I think does need to be thought through.

Prof Smith: Can I put words in your mouth?. What I'm hearing is that it is not obvious that this would lead to any immediate changes with respect to the control measures that are in place in the sense that they are based on the notion that they are all based on the assumption that there is pre-clinical infection which would encompass sub-clinical infection in the way that you are describing it. But there might be areas in which there is a need for further research to investigate this as a possibility.

Prof Collinge: My own view in terms of the measures in place is that they ought to be adequate, but they may well have a bearing on any future changes that we may wish to make, as we were discussing with Sir John Krebs earlier. I think following on from the comments Chris made earlier about the potential different pathogenesis of maternally transmitted cases, you could argue equally that there might be a different pathogenesis of sub-clinical diseases. Indeed in a sense by definition it is different pathogenesis. For instance there may be different tissues affected which may result in there being different routes of natural transmission. So I think it does need to be thought through as a separate case.

Chris Bostock: The idea that the incubation period goes beyond the natural lifespan of the animal has been around and accepted for a long time. I think that the first person who published that was in 1975, so I don't think that necessarily the idea that an infection in the animal can proceed but the consequences of that infection are not realised until after the death of the animal is not a new concept. Indeed in Moira Bruce's report, along with the transmission of vCJD to mice, she had a control group that were inoculated with sporadic CJD and had a very similar situation to this. The older animals were clearly infected and they had signs of pathology very similar to the sorts of results assembled here with Hamster scrapie in mice. Indeed, Stan Prusiner's paper that you quoted did get some non-transgenic animals going down with infection when challenged with this strain of scrapie.

End of Tape 1 Side B - Tape 2 Side A

Prof Collinge: Can I just come back on that. As you say, I do discuss Alan Dickinson's 1975 paper and I think that to some extent it is a matter of semantics, but I think there is an important difference here. You could argue that incubation periods may extend beyond the normal lifespan, but you can't follow the mice into the afterlife, so that is inevitably speculative. It is question of titration. These animals have infectious titres in their brains that are similar

to titres seen in end stage clinical disease, and I am not aware that that has been reported before, either in studies by Alan Dickinson or Moira Bruce, with her apparently classical CJD transmissions. You are seeing here mice that have died of old age with titres in their brain comparable to end stage clinical disease, and that is really the difference here. We are not talking about animals that have low prion titres in their brains and if they had lived for another hundred days, they would have gone on to develop a sufficient titre to produce a clinical syndrome. That is really the point that I am arguing about sub-clinical disease. This really might not be any different from an asymptomatic carrier of typhoid. It may have high titres that are able to infect other, but never develop disease themselves.

Prof Bostock: OK, but we arguing about issues that are quantitative aspects rather than the principles. It seems to me that the principle has been accepted in all of the discussions that I have been involved in, and presumably you before I was a member of SEAC. The possibility of animals carrying infectivity, yet not showing signs of infection is likely to be the case.

Prof Collinge: I agree, and this has been discussed by SEAC a number of times before.

Prof Masters: The message I got from this paper is that it is surprising that what you have discovered has not been discovered earlier, and with more sophisticated and sensitive detection techniques such as immunostaining and more careful analysis with classical histopathology. Translating back to the bovine situation, one would ask if we have really exhausted the levels of sensitive analysis in the cattle population to be sure that there is in fact no sub-clinical and pre-clinical infection in the bovine herd. I am not at all clear that this sort of analysis has been done yet.

Prof Aguzzi: I think that this is a very important topic and in fact I think that the situation may be even more widespread than John and Co are discussing right now. For example, or lab has report in '97 and again in more detail in '99, that immune deficiencies can induce a state of chronic prion carrier, with histopathology and massive deposition of prion protein and infectivity, but never an outbreak of clinical symptoms. So I guess the conclusions of all these studies taken together is that species transmission as well as particular immune states may lead to the establishment of chronic subclinical infection.

080- **Mr Bradley:** I have a number of comments. Firstly, I agree with Chris on the principle, and actually Nick Barlow followed this principle in his original oral challenge of mice with BSE, and he sub-passaged at the end of their lifespan to determine whether the mice were subclinically infected. In that particular model, using CRH mice, it did not. Hence the principle is well known.

The other point is that what would be more important than studies examining what happens at the end of the lifespan, would be to examine the pathogenesis of this particular model system and the time at which infectivity is detected and what tissues are infected. This is important if you relate the result back to cattle. Old cows, where this phenomena might be most important, would still be subject to the SRM ban, so I think the risk to public health is minimal. However the risk to animal health may not be except by virtue of the feed ban and the rendering system etc., and that could be important for MBM for pets for example. We have the OTMS which protects against this at this particular time. The more important issue to me is the issue about chickens and pigs. In view of the fact that we have had the feed ban since 1996, which appears to have been pretty secure, and the fact that the experiments we have done with BSE in these particular species showing no demonstrable infectivity following bioassay of clinically normal animals, does John still think that pigs and poultry are still a significant risk at the current time?. Historically it is a different matter, but unless we are proposing that maternal transmission occurs in pigs and in poultry, (there appears to be little risk). We haven't mentioned eggs. If poultry are getting it now, what about eggs?. I think that this is so extremist that I can not envisage it.

138- **Prof Collinge:** As is usual on this Committee, I am not able to quantify the risk. This is a scientific study of some interest about the species barrier , and I think it would have been irresponsible of us not to point out that the result has some consequences. What is not new, and I and other have argued this for some time, is that the way to answer this question is by proper cross-sectional studies of cases going through abattoirs, which would hopefully provide us with rapid reassurance that there isn't occult disease passing into the food chain. We are not talking about anything that is technically difficult. It requires detecting PrP^{Sc} in a sample of animals from the various food species going through abattoirs, and I think arguments about transmission experiments in pigs, poultry etc. are secondary. We can discuss how useful we think that information is, but what I would really like to know, both as a scientist and a consumer, is that we have biochemically tested and screened animals destined for the food chain using a simple test which has been around for a long time but just needs to be put into a commercial scale. Then we can hopefully be reassured that there is no preclinical or sub-clinical forms of disease in these species and we can move on. However I think I would like to base knowledge of that on experimental data rather than mathematical models or argues from very limited numbers of transmission experiments with single inocula and no relevant positive controls. I would really like to know that it is not there, and one can easily do this.
Can I just say that the MRC and imperial have formed a spin-off company to develop diagnostic tests based on work we have done in the MRC unit, so I have a commercial interest in the development of diagnostic tests. I have raised this before and written to all government departments concerned.

Prof McConnell: This is a hamster inter-murine TSE which is without clinical signs, but it is not without spongiform pathology. You quote that several mice show the histopathological features of TSE and include a picture showing classic pathology. I think that is important because one is a true marker for persistence of this disease in a species that you might be worried about, and as far as I can see from work done which examines histopathology, there isn't a widespread latent infection in the cattle population if we take the histopathology data from the OTMS survey showing 18 positives in 4,000 animals tested.
Had your paper showed that you got PrP staining and no spongiform change, that would be very worrying, but the fact that you do get spongiform change indicates that this is a very important marker to pay attention to and if it is absent, then we can perhaps take some comfort from that.

209- **Prof Collinge:** It is a proportion of animals that show pathology, and it a question of how extensive the screening using classical histopathology was. My understanding is that the diagnostic histopathological technique for BSE suspects only involves a examination of a single section through the obex, which has always caused me some concern, given the variability in the pathology in these diseases and the continuing uncertainty about whether there is only one strain of BSE. If there are different strains of BSE which different pathogeneses, then one would expect to see different lesions in the brain which you might not necessarily see through a single section of the obex. I think it is a little misleading to compare comprehensive neuropathology using the latest techniques done by a very distinguished histopathologist with examination of a single brain area in a large processing suite.

220- **Prof McConnell:** When you say several mice exhibited pathology, how many is several?. 50% of the mice are western blot positive, but how many exhibit spongiform change?.

Prof Collinge: I can't tell you off the top of my head, but I think that about half the ones that were looked at that were PrP^{Sc} positive also had characteristic pathology. You will appreciate that the mouse has quite a small brain, and one can't do everything with every mouse. the picture shown was probable the best example of pathology seen. The others were probable not so marked as that.

Prof Masters: In the same data set that you have just referred to, a second immunoassay for levels of PrP show quite a number of cattle with more than three standard deviations of elevated PrP in their brains, and that always worried me. This was a year ago. If that turned out to be representative of sub-clinical PrP^{Sc} accumulation in these cattle, we would then be in the situation that John is describing of sub-clinical infectivity.

Prof McConnell: Would you have this type of data without any spongiform pathology?.

Prof Collinge: Well you might. We have certainly seen that in humans.

Prof McConnell: But you don't have this in this paper?.

Prof Collinge: But these are mice. We don't know what we see in cattle. We haven't identified sub-clinical prion disease in cattle, so how do we know what it looks like. We can predict that there would be PrP^{Sc} present, but the histology varies enormously between species and with different stain combination and routes of exposure. How do we know what we are looking for in cows?. I think that one can predict that by doing a PrP^{Sc} immunoassay we would detect it, irrespective of how it looked histopathologically.

Mike Dawson: On that OTMS survey that you are discussing at the moment, western blot was done routinely on samples taken from the brain stem using the prionic tests, and results corresponded with the histopathological examination. Granted, it was not done on other samples of brain and focused on the medulla. It was also done blind by Prionics.

Prof Masters: It was the DELFIA test that showed the increased levels compared to NZ cattle.

Mike Dawson: Yes, but I think at that stage, the DELFIA test had not been validated by the EU.

Prof Collinge: We have also been looking at the NZ cattle and comparing it with UK, and there do seem to be higher levels of PrP^{C} in UK cattle that we have looked at.

268- **Dr Bailey:** As part of the R&D update, I was going to present the results of the DELFIA test on OTMS1. Do you want that doing now in view of the discussions that have taken place?. If not, we will be coming back to that one.

Prof Kimbell: I would just like to support what John is suggesting, and I am wondering as a Committee if we should flag up that we think that there ought to be more abattoir testing on a random basis to see if we can detect [sub-clinical disease]. It does seem to be something that ought to be done.

Prof Smith: We do have that on the agenda later on, and we might explore that.

281- **Chris Bostock:** I would just like to comment on the discussion and say that one can choose specific models for these diseases which have virtually no

PrP^{Sc} but extensive pathology at the time of death, and conversely, there are models with no pathology but extensive deposition of PrP^{Sc} and everything in between. I think one has to recognise that there is huge variation in the detailed pathogenesis and PrP deposition. I agree with everything that has been said about long incubation periods in terms of crossing species barriers, in terms of the possibility that the incubation period may exceed natural life span, as is the case in this paper.....

Prof Collinge: Can I just interrupt there. We don't know that this is the case. We don't know that these mice would have gone on to develop disease. We can't follow these mice into their after life. We don't know what would happen if they lived another 100-200 days. You are assuming that if they had lived long enough they would have developed a clinical syndrome, but the point of this is that they have titres in their brain that are comparable to end stage disease in clinically affected animals, but they haven't developed a syndrome. This is really the fundamental point and we need to clear about that. We are not talking about animals that have not quite got there and if they had lived for another 100 days they would have displayed clinical signs. They have the titres in the brains that would have caused disease if they had been inoculated with mice strains.

312- **Prof Bostock:** Of course it is speculation, but you can take strains of mice that were unhealthy and died earlier with a defined genotype, and compare them with a strain with a longer life. You can do experiments in those two strains of mice; the first will die of natural causes before they come to disease, and the later will develop a clinical TSE because they live longer. You can address that type of thing experimentally. I think it is unnecessary....

Prof Collinge: But will the short life span mice have the same titres in their brains as the ones that died later of clinical disease?.

Prof Bostock: The fact of the matter is that you get incubation of these diseases, you get increasing levels of infectivity and the animals may die of a TSE before they die of natural causes, or it may die of natural causes. The point I was trying to make was that in those cases where you get transmission within species, which is I assume what we are taking about in the case of BSE, in most models, you either infect the animal or you don't. For example if you infect a VM mouse with 301v, it will die with a defined incubation period according to the dose that you give it. If you get to the end point of dilution, then you get to a point that the mouse either dies or it doesn't, and you can then leave it for may hundreds of days until it dies of natural causes and there are no indication at all that it is carrying signs of infectivity, either through sub-passage to another mouse or PrP deposition, or pathology. So I think there is a different situation when these agents are recycled with the same species when you know that the agent creates clinical disease within a different period. In the case of cattle, the peak incidence at 4-5 years. So the idea that a large number of

animals may have sub-clinical disease has to be put within that context.

Prof Collinge: I am getting a little confused about what you are arguing. You are quite rightly pointing out the enormous variability within these models, and I do have a problem understanding why there is such resistance to screening in abattoirs for a limited amount of time to reassure ourselves there is nothing there and to make sure that a lethal human pathogen is not entering the human food chain. If this was any other infectious disease....

351- **Prof Bostock:** I am not against screening, but I am against the notion that there is a large number of animals incubating this hypothetical sub-clinical form.

Prof Collinge: I haven't said that. I have mentioned nothing about numbers. I am just raising this as a theoretical possibility.

Prof Smith: Can we defer this discussion s until later when we discuss abattoir surveys.

Mr Bradley: I would like to add something to what Mike said, and as a prelude to what will be discussed later. Firstly, it is not only us that have found cases of BSE as a result of immunodiagnostics during surveillance. The Swiss have found positives in both abattoir animals and fallen stock, the French have found cases, although they are targeting surveillance at fallen stock or animals for emergence slaughter. There animals are not important because they are not entering the human food chain. The important ones are the ones that we are eating as John says. Hence the EU has initiated a compulsory program to investigate casualty animals and fallen stock beginning on 1/1/01. Some countries have already started it. However this may be the wrong target in terms of public health protection. If that is what this Committee thinks after we have debated the issues, then I think we should get the message over to the EU. The public health of the people in this country may be compromised from imported material, and currently we may be eating this on a false premise of security because they do not have the same control measures abroad as in the UK.

Prof Smith: It is true that the mathematical modelling of the epidemic assumes that there is pre-clinical infection, but not sub-clinical infection as you are suggesting. Our predictions have been based on the assumption that there is not a state of infection that will not eventually develop disease. The feed controls in place, irrespective of whether there is sub-clinical infection or pre-clinical infection, should have coped with recycled infection. A more informative sample in terms of the model will not be the younger cattle that we are going to look at later on, but the older cases, the 5 year old animals and over that are currently being surveyed will be of most interest. According to the Oxford

model, it will allow us to predict the number of positives we should find on the basis of the assumption of occurrence of disease. If there is great variance between what is seen in the survey and what the model predicts, this may offer support to this mode of transmission. At least that would be one of the possibilities.

396- **Mr Bradley:** I would still point out that the feed controls are not the same in all countries. Only the UK and Portugal have the feed controls that you are speaking of, and we continue to import massive amounts of pig and chicken meat which do not have these controls, and some of those countries have BSE. It is that area that I want to explore.

Prof Ironside: This study was using intra-cerebral inoculation. I was wondering if similar observations had been made in animals that have been infected orally. I guess you have not done that yet. I can't recall if it had been done.

Prof Bostock: One would have to go through the archive of Dickinson's work.

Prof Smith: Can I take this forward in part. I think the principle issue that we want to address concerns current control measures and whether these findings would lead the Committee to recommend any changes with respect to those controls. The words that I attempted to put into John's mouth, and I will now attempt to put into the Committees mouth, is that there is nothing in these finding that would immediately lead us to recommend any changes to the control measures that are currently in place. Is that the Committee's view?.

Peter Jinman: Just following on from Ray's point. If we move the age of the OTM rule, then the target group to look at is the age range that we might move the OTM -rule up to. We ought to be doing that now, rather than in 2001-2002 when we come back to revisit the subject. Now is the time to examine this target group. I know we will discuss this later.

Prof Masters: The only other control measures that we might want to think about is if there is another mechanism of natural tranmission, such as environmental contamination. For example placental contamination in high density housing conditions, like what has been seen in scrapie in Iceland. You might want to consider that if that turned out to be a significant factor for cases born after the ban.

Prof Smith: I am right in saying that you wouldn't want to go down treat route at this time.

Mr Bradley: Can I just mention that there are controls on parturition of suspect animals. Animals are isolated and all deposits, including placentas etc.

are disposed of under the supervision of the veterinary service. Furthermore, all farmers are advised, and may do, take good care of placental control in order to prevent may other disease that can be transmitted by the placenta in cattle. I think the situation is slightly different in sheep, where there is more communal lambing in comparison to cattle. Finally can I say that currently in the UK, there is no necessity for further controls. I am convinced of that, but for the rest of Europe it is a different matter, and if this Committee has a concern about public health from imports, bearing in mind that we are a trading nation, then we have got to get this message to the Commission and make our concerns known. If we were advising the Irish or French Government, where there is a rising epidemic, would we be advising something different than is currently happening?.

Prof Smith: I think as a Committee, we have previously expressed our concern about imported products, in terms of the controls that are in place, irrespective of the findings that John's group have described, and I think those concerns would remain.

453- **Mr Bradley:** I do know from discussions with vets that other countries are thinking about moving towards our feed ban. Whether they actually will or not is another point.

Deidre Hutton: Obviously, I'm interested in this as a public health problem. If this Committee has expressed its concerns, to who does it express them to? Presumably the government. But is there a public issue here in that there are two ways that people will stop eating things; one is when there are restrictions and regulations and the other is that the public know about it and actually make their own minds up. I was just wondering whether that was a route that the committee had considering following.

Harriet Kimbell: I support Deirdre. It's really important. For example, I do not allow my children to eat French beef, absolutely under no circumstances. Other people should be in the same position to advise their own children and to decide for their families whether they eat foreign beef. I think it's very dangerous.

Prof Smith: In a way the FSA is going down that route with the public consultation. Some of those issues are addressed in this document that they put out and are part of the discussion.

Harriet Kimbell: It's not specific enough to pick up those sorts of messages.

Adriano Aguzzi: The TSE ad-hoc group of the European union obviously has occupied itself extensively with this question and I think that the EU geographical risk assessment has very frankly spoken out on these issues and

has provoked all sorts of rabid reactions from governments of some European countries. So I think that the issue has been publicised fairly extensively in fact.

Prof Smith: OK. Can we turn now to if any further research might be put into place as a consequence of these findings, perhaps first looking initially at cattle. We'll be discussing under another agenda item with respect to the surveys that have been done in cattle. In humans we've no idea how much pre-clinical infection there is [...much of the ascertainment of sub-clinical human infection will depend on the development of sensitive diagnostic techniques].
That leaves us with pigs, chickens and sheep. Is the feeling that we should be doing more with, let's say pigs and chickens?, bearing in mind what's been said earlier and feed bans that are in place and bearing in mind the work that has been done which is summarised in the paper that is attached to John's paper on subsequent transmissions from chickens and pigs challenged with BSE. Or is the feeling that if anything is done, then the focus should be on cattle and sheep?.

Prof McConnell: It's a question of public health. If you've started a screening program and experimentally screened animals, you'd have to ask the question where is the infection now coming from? You'd either have to say that, if we are discussing chicken and pigs which are quite young animals when slaughtered, they are still being contaminated through the food chain, and I don't believe that can still happen, or there is some horizontal/vertical transmission which maintains infection in the pig population and we haven't seen it, and I think there is no evidence that this is the case. So I think to start a screening program on pigs, I'd think you'd have to answer that question.

Deidre Hutton: That could be a very important question to answer

Peter Soul: I am just really wondering what sort of tests we'd be doing. Presumably we'd be looking for PrP^{Sc} and if we find it I still wonder what that's actually going to tell us.

Harriet Kimbell: It's going to tell us that the bloody stuff shouldn't be in food products, that's what it's going to tell us

Peter Soul: I don't think that's true. I don't think PrP^{Sc} necessarily tells us if we're finding infectivity.

Harriet Kimbell: Well if you put that out in the press you will get a deluge of response. I suggest you try it and see what happens.

John Collinge: PrP^{Sc} has never been reported in any other context other than in a prion disease.

514- **Chris Bostock:** I think that the situation with chickens is difficult because as far as I am aware there is no reported case of spongiform encephalopathy in a bird, so we don't have any sort of baseline to judge it by. Chickens have the equivalent of PrP gene but it is substantially different and I guess we don't have the sorts of reagents that would reliably detect deposition of the abnormal form of PrP in chickens. The only thing that we have to go on is the work that has been done by the VLA where there was the primary transmission and then the chicken to chicken subpassage. Although there is the complication of the elevated incidences of neurological problems of male birds, this also happened in male birds in controls. It wasn't anything you could recognise as a TSE and perhaps that's something that could be pursued as a research objective to see what is that relationship or is that disease to try and satisfy oneself that this isn't a prion related disease. That my thought on chickens.
I think in pigs where we do have a demonstration that direct intra-cerebral inoculation can cause a TSE, then you do then have the opportunity of testing directly whether there is something which is transmissible within pigs. So one would envisage using pigs as a bioassay for potential sub-clinical disease in pigs. I don't know enough about those experiments to know whether sub-passage within pigs is part of that experiment.

Mike Dawson: From the oral challenge or from the parental challenge.

Prof Bostock: Well I suppose first of all you would want to do it from a positive so you would use the parental challenge.

Mike Dawson: There hasn't been pig-to-pig sub-passage in either of the challenge groups. There has just been a bioassay in mice.

Prof Bostock: So it might be then if that material still exists to at least pursue it in a limited way to see if there is any signs of low levels of infectivity in those animals that have been challenged orally.

Mike Dawson: The weren't detected by mice bioassay.

Prof Bostock: It might be detected by a pig to pig transmission and you will have a positive pig to pig transmission (as a control) if you sub-passage the parental primary challenge.

Prof Masters: You can also test just the levels of PrP in pigs and chickens by immunoassay and western blot.

Prof Bostock: There is a lack of reagents

Prof Masters: Then somebody should just start developing the reagents to do this.

Mike Dawson: Immunohistochemistry has been done on the pigs with negative results on the oral challenge.

Jiri Safar: Using antibodies against swine PrP?

Mike Dawson: No. not swine PrP isolates.

Prof Collinge: There are antibodies that detect pig PrP

Mike Dawson: Antibodies were positive in the parental challenge experiments so there were antibodies that picked up pig PrP.

Prof Collinge: Can I just ask a couple of questions about the oral challenge experiments in pigs with cattle BSE. Is there an issue with the breed of pigs used?. I don't know to what extent there different breeds pigs and what diversity is there, or what we know about the genotypes of the pigs that were inoculated and the range of genotypes amongst the pigs.

Mike Dawson: Can I answer that?. We tried to use a mix of common commercial hybrid types for the experiments. It was a single PrP genotypes. There was no variation in the coding region of the pigs that were challenged.

Prof Collinge: And the positive control for the experiment?

Mike Dawson: The positive control for the oral challenge experiment?. That inoculum is still being titrated in mice but that innoculum was not inoculated direct into pigs. It wasn't the same innoculum that was used in the parental challenge experiment.

Prof Collinge: Sorry, it has been transmitted at least to mice but it hasn't been intra-cerebally inoculated into pigs?

Mike Dawson: No, but it was derived from 29 clinically confirmed cases of BSE and in the past, confirmed clinical BSE has always transmitted into mice and we've always been able to demonstrate infectivity albeit there haven't been that many experiments of BSE transmission into mice, but there has never been a negative transmission so far from a confirmed case.

Prof Collinge: This particular experiment there isn't a positive control

Mike Dawson: There isn't a parental challenge with pigs with that innoculum.

572- **Prof Smith:** OK, so it sounds that there may be some scope for sub-passage into pigs if that material is still available.

Prof McConnell: On the issue of reagents in pigs, there are number of papers on this. Has Mike already got information on which antibodies were positive in these pigs that had TSE.

Mike Dawson: Well I haven't got it here but I can get that information. There are antibodies that will detect PrP.

Prof McConnell: So if one was to envisage some experimental screening developments that reagent at least exists. For chickens it is a different matter. That's why I come back to the point I made earlier that there is no neuro-pathology in chickens and therefore one is comforted by that.

Jiri Safar: I would really express my respect to John's paper, a well executed paper and the reason why that paper made such remarkable progress in our understanding is because he used the best possible reagents and western blot systems for the detection of PrP with very precisely defined antibodies to detect either mouse or hamster PrP. This is the highest possible sensitivity. The next step is to monitor infectivity in at least three different hosts and I would like to point to table 2, which is really important in the whole discussion which is going in a circle about the adequacy or inadequacy of the host for monitoring infectivity. In that table there is basically evidence for a shift in the pattern and biological characteristics of the original strain when you passage it once into mice and then titrate again in a mouse, transgenic mouse and in the hamsters. In all those cases there is very significantly extended incubation time of the original strain in hamster. Those incubation times, and this is another important part of the whole paper, are extended to the level which would indicate the titres in hamsters below 10^3-10^2 infectious units if you relied only on incubation time. But then, if you go to table 3, you see that the end point titre is 10^7-10^5 in hamsters. So what this is indicates is a whole story. If you monitor infectivity of the original strain coming from hamster and monitor in hamster....

End of Tape 2 Side A- Tape 2 Side B

Jiri Safar: ....the less infectivity that you accumulate in Sc237 which is the highest possible you can achieve. You may not see any disease in hamster, which is the original host, but you will see significant levels infectivity in mice. So again this is going to impact on the host used for monitoring the infectivity. Translating this story to BSE, for BSE monitoring in the chicken, the correct screening should incorporate chicken, mouse and cows, or transgenic animals carrying bovine PrP. Then you make correct judgements based on the fact that the strain may change biological characteristics and based on the fact that this pattern may be very unpredictable. Looking at the data

generated by passaging BSE to different species and then monitoring the infectivity in RIII mice is giving us an extremely limited picture, firstly of original titres and secondly, the susceptibility of the previous host.

John Collinge I mean, I agree there are major uncertainties and I think that this paper raises many more questions than it answers

Jiri Safar: Well essentially it goes back to the presumptions. The presumptions based on titrations in RIII mice and very limited titration done on the cow to cow experiments. Using the RIII mice titration, which are without any doubt about 500 less sensitive than the cow to cow titrations, we see only the tip of the iceberg. We don't see anything below the water, and that may be very significant in the questions we are asking with regards to public safety and safety of passages of the material through the original species.

P Smith: But in the chicken experiments, these were passaged into chickens and that should be a pretty sensitive test for sub-clinical infection in chickens and it hasn't been done in pigs and what we're suggesting is that it would be appropriate if possible to do that in pigs.

Jiri Safar: I mean the caveat in this case is that we don't know how the spongiform encephalopathy will look in chickens, either clinically , pathologically and otherwise. so there are certain caveats. There are immunoagents which we could use for immunocytochemistry in chickens . There are some antibodies against the n-terminus of chicken PrP generated by Harris in the USA, but they are not useful again PrP^{Sc}.

Prof Collinge: Just to reiterate in chickens we just don't know what we are looking for. There is no positive control. We don't know what the disease looks like in chickens and we have no antibodies, so how we can tell if there is a sub-clinical disease.

Prof Smith: Yes, but if it doesn't cause disease and it doesn't cause disease on passage then.....?

Prof Collinge: Well there was some neurological syndrome present on the first passage that wasn't present in the controls but then something was present in a lower frequency in the controls in a subsequent passage. It's all a bit …

Prof Smith: Chris is suggesting that this is something that should be continued to be investigated.

Prof Bostock/Collinge: Yes

Dr Bailey: One point we ought to make is that meat eating birds are only kept

until 49 days. These birds were egg laying birds which were kept on till they were 51 months P.I., which is way beyond the lifespan of broilers. We're actually dealing with a different type of bird really.

083- **Prof Smith:** Turning to sheep, this possibility (of sub-clinical infection) is being investigated in the program of sheep experiments that are underway and is obviously highly relevant, not only in respect of BSE but is also relevant to scrapie in terms of the scrapie elimination plan.

Chris Bostock: Can I just outlines the sorts of things that are ongoing at IAH. There are experiments as part of the validation of NZ sheep trying to transmit BSE to all genotypes of Suffolks and Poll Dorsets. You've got your own…..

Mike Dawson: VLA are doing Suffolks and Romneys and will being doing other breeds next year. Currently its underway in Suffolks and Romneys.

Chris Bostock: There is also some work to transmit BSE from primary passage in a sheep to all genotypes of sheep. We are thinking about how to design proper experiments to demonstrate horizontal transmission between sentinel infected animals and uninfected animals so that you can then test for the hypothesis that there is infectivity in sheep in flocks that is sub-clinical, perhaps in supposedly disease resistant genotypes, that is harboured in a way that could nevertheless be passed onto other sheep. These experiments aren't underway but they are being talked about. Proposals have been put to MAFF.

Prof Smith: One could hypothesise that there could be resistant animals which may be sub-clinical for their lifespan and that transmission experiment are planned in challenged animals to see if it is possible to transmit infection from those resistant animals to an animal of the same species.

Prof Bostock: Yes, and I think that once these experiments are all complete in their entirety that would cover experimental inoculation as well as co-housing as they would be in a flock. This would clarify whether that would be a mechanism of maintaining scrapie within flocks….

Prof Smith: Yes, and that's clearly important both for BSE and scrapie.

Ian McConnell: If we come back to the data which was presented to us some time ago by Van Keulen, who looked at the scrapie susceptible and scrapie resistance sheep. I think they are also testing PrP^{Sc}. I think with the resistant animals they never got any signal with PrP^{Sc}

Mike Dawson: Not quite Ian. In the ARR heterozygote (ARR/VRQ) animal they got staining in the mesenteric plexus and [..] very late in the incubation period. However the ARR homozygotes were clear.

Prof Bostock: It covers a whole range of the possibilities in sheep and it is quite an extensive experiment, because of the multiplicity of genotypes and the behaviour of different genotypes in different breeds.

Prof Smith: OK, I think we can probably pass on from this issue now. I think what we've ended up with is that we're not recommending any changes in control measures, we've indicated that some further work might be appropriate with respect to the neurological disease in chickens just to make sure that that is not TSE related. It would be worth looking at whether it is possible to do a second passage in the pig experiment between two pigs rather than between two mice. In sheep, there is an extensive program underway which will take account of the possibility to detect sub-clinical infection. And cattle we are going on to discuss. Humans, I think there is nothing more to do in the sense that we don't know about pre-clinical and sub-clinical infection.

Prof McConnell: Well there is the tonsil survey

Prof Smith: Yes. That will come up and I think we will be better addressed when we've got better diagnostic tests.

Prof Bostock: Can I just say Peter that we are also going to come onto the question of surveillance in sheep as well.

Mr Bradley: Could I just make two comments that perhaps the secretariat might consider to pass onto the press notice people from the MRC and from the FSA. In the MRC one, in the first paragraph it was talking about introducing the subject as BSE in mice when it was nothing to do with BSE, it was to do with scrapie. In the other one it says that in 1996 a ban was place on meat or bonemeal being fed to livestock. I think these are quite significant things which cause concern to people when they read them.

Mr Jinman: Can I just pick up on a procedural point and say a big thank you to the Department of Health for sending out this paper before it was launched on the press and everything else and all the sheets of information. And could it be a model for anything else that when we know the press are going to be interested, I think it is absolutely imperative that members of this Committee have got this information before the date it is launched into the public arena. And it was very nice to at least be able to put back some of the questions from the press on the morning when it happened. I would like to feel we were on the mailing list for 'press-type statements' so that we got the press releases. I certainly had to try and chase them up because local press were pushing for comment as much as national press. And I appreciate the point you made earlier on about directing it through yourselves but reality out there is that we're being asked every day once Journalists know you are a SEAC Member

and you've got to have some sort of answer, you can't be left high and dry. It's a procedural point.

208- **Peter Smith:** I should thank John for making that paper available in advance of publication so we could be notified, and obviously it is dependent on that. But yes, it certainly does help when you're being doorstepped. OK if we could then pass on to, I'm just looking at the clock we're a bit behind time.... The next item on the agenda is the letter that was published in the Lancet from Chris and colleagues about transmission by blood transfusion by sheep. Chris, if you would like to introduce that.

Item 4B- Transmission of BSE by blood transfusion in sheep

220- **Chris Bostock:** Well as the letter notes, this is really just a report of single animal going down with experimental BSE following blood transfusions of the experimentally BSE infected sheep. The aim of the experiment as a whole is to look at a range of times during the incubation period of BSE in sheep that has been orally dosed, take blood samples from them at various times in the incubation period and to transfuse those into recipient sheep that have been sourced from the MAFF New Zealand flock. The majority of the blood transfusions involve whole blood, some transfusions involve buffy coat. To date there is a single animal that has gone down. It was a donation of blood from an animal roughly half way through the 629 day incubation period. It resulted in disease in a recipient animal 610 days after receiving the blood transfusion. The other animals in the experiment are all clinically normal at the moment. Only one other animal received the blood transfusion and is alive beyond 610 days and that is an animal that received blood donated roughly a third of the way through the incubation period in the donor animal

Peter Smith: Thank you, Again I think the issues that we need to address here are; is there anything in these early results that would lead us to make any changes in infection control methods that we've recommended, and does this lead to any further research.

Adriano Aguzzi: I think that this is an extremely important result and I would like to bring to your attention the possibility of changing the experimental design in that I think it would be extremely important to take biopsies from the other sheep that have been transfused and then maybe during the incubation phase take lymph node biopsies, perhaps splenectomise them or take brain biopsies and western blot. I think this would perhaps give you the opportunity to provide an answer before waiting for the whole incubation period and seeing at the end whether the other transfused animals and the control animals contract disease. I hope you won't take offence but I think that if I had been the group leader, I would have done this type of biopsy experiment before publishing a paper with one single animal and no controls in it. It's just so important.

274- **Prof Bostock:** Well, fair enough. I mean this is the first time I think that scrapie has been transmitted intravenously and so we don't really know the pathogenesis anyway. I mean there are all kinds of uncertainties here. It's very much taking an opportunity to use animals that were part of a MAFF pathogenesis experiment. I think there are a lot of experimental details that we will now think about. I am slightly concerned about doing biopsies because I understand that there are indications that the act of taking biopsies can alter the progression of the disease. But if it just a 'yes' or 'no', then that is something that we could discuss with the Department of Health.

Ian McConnell: It wouldn't apply to blood. I mean you've got this very interesting cohort of 18 animals that are clinically normal.

Prof Bostock: You mean the other recipients.

Ian McConnell Yes, I mean if one were to do transmission experiments into transgenic mice using some of the buffy coat cells from those existing sheep, it might pre-empt or give you some information that would answer what might happen if you kept the animals longer.

Prof McConnell: So you are suggesting doing a bioassay in transgenic mice with buffy coat cells from these recipient sheep which may or may not be incubating disease.

Chris Bostock: I think the reason we chose sheep to do this was that it allowed us to transfuse large volumes of blood, which got over some of the problems of sensitivity with the relevant biopsies.

Adriano Aguzzi: Sorry for insisting, but I think the question that needs to be addressed with the utmost urgency now is, because you are reporting on one single animal, are you looking at a contamination, are you looking at some kind of weird accident, is it reproducible, is it something that you don't see in the control group?. I think this is extremely urgent at this point, because now this is in the public domain. In my view this would override your concerns about bioassays changing the pathogenesis, which I agree with you may be the case. I think you could minimise this by, for example, rather than splenectomising the sheep, taking some sort of superficial lymph. But I think that some kind of bio-chemical scrapie determination has a chance of giving you an answer. Of course if everything is negative then you are no wiser than you were before. But with all we know it is likely that you will get an answer.
I am suggesting lymphoid tissue rather than brain tissue, or at least as well as brain, because for all we know the accumulation of PrP^{Sc} is much more rapid in the lymphoid tissue than the brain. Eventually titres will be higher in the brain, but at a later point in the incubation period.

Peter Jinman: Three quick points. Firstly I have great admiration for our historical colleagues in the 19th Century. They did actually attempt an intravenous transfusion and my recollection is that he actually put in 1.56kg of blood from one sheep that had scrapie to another. Unfortunately, he wasn't aware of the incubation period following this technique so he didn't keep it long enough. But he did keep it over a year and it didn't show any signs. The second point is, are there plans to conclude that this is actually a transmission of BSE. At this point we do not know that the BSE agent is in this blood of the New Zealand sheep, we only know that is has come down with a spongiform encephalopathy. That seems to me quite important to know that if you put BSE into the original you get BSE out of the transfused animal. The other point is, are there any plans to do leuco-depleted transfusions from these sheep.

Prof Bostock: In answer to your second point, clearly we will be transmitting material from the recipient and the donor to mice. Initial looks using Western bloting indicate that the patterns were similar to each other and similar to a BSE pattern in sheep. But clearly we would be happier if that was confirmed by transmission to a mouse panel. In a formal sense, picking up on Adriano's point, it won't prove in a formal sense that the recipient was in some way infected by another route completely unknown at Compton. I mean all the donor sheep are at Edinburgh so there is complete separation and as far as we can see there is no possible way that that animal and the recipients came in contact with any BSE unless they did so at the [??]. We recognise all the limitations of a single animal, in terms of lack of controls etc., but it was reported for what it is.

Ray Bradley: and leucodepletion?

Prof Bostock: Not in this experiment no, but clearly the demonstration that you can transmit BSE experimentally from the blood of infected sheep does provide the opportunity to formulate experiments to test leucodepletion.

364- **Prof Smith:** To some extent, this result has been anticipated by the control measures that SEAC recommended previously in respect to human blood. Charles Lister is here from DH. Charles is there anything you want to say at this stage.

Charles Lister: At the moment all red cells and other blood components are leucodepleted. The only issue we are still looking at is in relation to plasma. The majority is imported from the US, but there are circumstances where UK plasma is used as fresh-frozen plasma which has been highlighted in the media this week. The reason why we use this is because it has not so far been possible to find another source, or a substitute product that is suitable. However we are currently working with the National blood authority on a risk assessment to

clarify some of these issues and hope to have some feedback by the end of the year.

Prof Smith: That is not pooled, is that correct?.

Mr Lister: That is correct. Each unit is from a single donor.

Prof Collinge: I have just a point. A question of whether this is BSE or not is important. NZ sheep were used, but there is this issue of pasture contamination and animals getting scrapie for reasons we don't understand at all. As you say, it is quite important to strain type the agent. I am well aware of the difficulties of publishing western blots and publishing them in journals, but certainly my issue of Lancet, it wasn't very clear at all. From the studies we did together some time ago, the differentiation of sheep BSE and scrapie seems to be most efficient by looking at the fragment size of the unglycosylated band. Some isolates of sheep scrapie seem to have a similar glycosolation profile to BSE and I wondered whether that fragment size really was the same. In my issue of the Lancet, I could really see the lower fragment at all.

Prof Bostock: No we couldn't see it. So we would require full deglycosolation to do that properly.

Prof Collinge: Right

Prof Masters: You gave us data on mouse blood BSE infectivity earlier this year. Are you going to publish that data. That will impact on the publicity surrounding the sheep.

Prof Bostock: That has been published. It wasn't taken by Lancet, but I will need to check where. It was submitted and accepted in one of the blood journals.

Prof Aguzzi: Maybe I can address your question about whether there is anything we should do with respect to transfusion medicine in the light of this new data. Some three years ago, I was advocating that measures be taken, including leucodepletion, for which I got of flak. I believe that the current situation has not changed since that time. We still do not know whether leucodepletion and other things are necessary, and we actually don't even know if they are sufficient. We still don't know the precise distribution of the infectious agent in blood, although I believe that this is not the first time that infectivity has been demonstrated in blood. Everyone who has really been looking hard in the hamster and mouse models has found infectivity, all be it at very low levels. On the minus side, just as the hamster is not a human in terms of pathogenesis, one could use the same argument for sheep. The bottom line is that the possibility that something like this coming through had been

contemplated in the measures that have been taken. I think the measures were drastic, but I still believe it was the right thing to do. I think that one can not go much further. Any further step would probably cost lives in terms of shortage of blood products.

Prof Smith: Is that the view of the Committee?.

Members: Yes.

Prof Smith: And in terms of further experimentation, as Chris has indicated, this is a single case in an ongoing study, and clearly Chris has been uncomfortable about it being one case, which has put him in a very difficult position in terms of publication. However, because of the nature of the finding, it is of some significance, all be it only in one animal.
It does open up the possibility of studying leucodepletion, which is a critical issue in terms of the human blood supply, and it would be interesting to address that in the sheep model. Now we have a model that potentially might be quite close to the human situation, I guess the Committee feels that this should be done as a matter of high priority. Is that a fair summary?.

435- **Harriet Kimbell:** It is one thing to say that there isn't enough blood elsewhere, and therefore we can't increase control measures, and that is one stance to take. However, I think the public would want to know what our view is about the safety of blood. They then might want to take steps to transfuse within a family or to transfuse by another means. I don't think we can just leave it and say that there is nothing else we can do, so we have to lump it.

Diedre Hutton: I completely agree with the point you have made, but I think it is very important to make that point in public. For example, the lead item in the BMJ this week is 'is our blood safe'?, and they talk about the control measures taken elsewhere, where people residence in the UK in the 1980's and 1990's are prevented from donating blood. We need to be quite clear about the basis on which we make our decisions, and if the risks to life are greater from not having plasma and blood products, we ought to make that clear as well.

Prof Smith: We don't make decisions, only recommendations. My response when asked to comment on measures taken in US, Canada and Australia was that it seemed a sensible precaution, and were we able to do it, it would be something we would consider. I assume the nation blood service has considered this option.

Charles Lister??: We have certainly looked at the possibility of simply importing all our blood from elsewhere. We use something like 2.5 million units of red blood each year, and there is no way we could get that quantity of blood from anywhere. We also need to be confident that we can supply a safe

supply in terms of viral contamination.

Prof Smith: I don't think we are in a position to stay what the risk is from blood that is transfused now. We certainly can't say that there is no risk, and there may be a substantial risk, and that unknown risk has to be balanced against alternatives.

Prof Kimbell: So the answer to the question 'is blood safe'?. is 'probably not'.

Prof Smith: Well, we don't know is the correct answer. We can't say.

Diedre Hutton: But you are not well if you receive a blood transfusion.

Prof Smith: Exactly, and I think that this has to be balanced against the risk. Given the choice I suspect that you take the blood in most circumstances.

Prof Kimbell: But you might give your child your blood rather than allowing it to have it from the pool. If the corollary is that blood might not be safe, then that is a decision that someone might want to take.

473- **Prof Smith:** You assuming that your blood is safe!

Prof Kimbell: Absolutely, but people will make that decision, or they will want to keep there own blood for themselves.

Prof Smith: That is a possibility.

Charles Lister???: The department is trying to encourage more autonomous blood transfusions for reasons other than CJD.

Prof Smith: I assume that is not possible in emergency situations, but where there is a situation where transfusion is possible, storing up blood in advance to have to transfused back is being encouraged.

Prof Masters: Could we just consider what the next step would be if you felt it was necessary. I would suggest that if you are interested in risk reduction, you would be trying to identify donors that are at increased risk in the general pool. Those would include people that ate school lunches for example. It will all depend on what risk factors have shown up in epidemiology.

Dr Ironside: In terms of risk, presumably the greatest risk was eating meat products in the past. Unknown people have been exposed to BSE, and you may want to donate one's own blood to relatives, but how do you know they you don't have it.

Prof Smith: Until earlier today, one might have plumbed for old people!

Prof Aguzzi: Perhaps this falls into oblivion, I would just like to remind this group that DNV have been commissioned to do a Risk assessment. Of course one could argue that this is a pretty unrealistic exercise, because the input values are unknown. However, for me the most important message from the study was to derive a value that would predict whether there would be enough transfusion-induced cases of vCJD to maintain the epidemic within the population, or whether the few sporadic cases of iatrogenic vCJD would die out by themselves. Just like 3 years ago, what must be done is to find out what the incidence of pre-clinical/sub-clinical disease is within the population. If we had a value, then using modelling etc. like DNV, we would be able to say what might happen in the transfusion medical sector. I hope we will hear later about the tonsil study, but I think primate studies would also give additional input.

Ray Bradley: In the information papers, there was a short article on thrombocytes, or platelets. I just wondered if we had any research to investigate if there is any infectivity in the platelets, or if it is likely or plausible?, bearing in mind that these cells are derived from bone marrow, and in cattle at least, they can be generated in the mininges of young animals.

519- **Prof McConnell:** Someone raised the question of the cell transmission in BSE. The lack of any cell transmission or any association between BSE and cattle white cells I presume that does not alter. The reason why I ask this question is because I was asked for a response on the safety of milk after this story broke. There is a large number of white cells in milk. I gave the standard answer about the pathogenesis in cattle is quite different to sheep and humans, and this result has no implication. However I though that the Committee should be aware of the sort of questions we are getting asked by more informed journalists, and may be we should rehearse what the position is.

Prof Smith: yes, and I guess that is also true of blood in meat.

Chris Lawson: Can I just follow that up. The paper does raise the question of whether there is any food safety implications. I would be grateful for a view from the Committee about whether they see any particular issues arising from this in relation to food safety.

Chris Bostock: Could I just respond to Ray's point on platelets. If one is going to look at leucodepletion, and leucodepletion if shown to be effective at reducing the titre, then that would indicate that infectivity is associated with leukocytes rather than platelets.

Prof Masters: I think leucodepletion also takes out most of the platelets as well.

Prof Aguzzi: From what I have learnt leucodepletion has a efficiency of 2-4 logs at most. If anything it is a modest effect. If you think that using the bioassay, we can hardly detect a difference of 1 log in infectivity titres.

Prof Smith: My understanding is that leucodepletion does not remove all the leukocytes.

Prof Aguzzi: That is right. There is also fragmentation of lymphocytes during the leucodepletion process.

Prof Masters: It would also fragment platelets.

Prof Smith: I think we have always emphasised that this is a risk reduction rather than a risk elimination strategy. In terms of food safety, clearly if we found BSE in sheep, clearly this would be an issue.

Prof Bostock: If BSE were found in sheep, then this would simply compound the problems that we already recognise in terms of widespread dissemination throughout a sheep carcase. Personally, I don't think this changes my views on the safety of cow derived products, because what we do know about the pathogenesis in cattle is rather different from what we know about the pathogenesis in sheep. I don't think there is anything to suggest that there are significant levels of infectivity in cow blood, but one could test that by doing a direct cow to cow transfusion. However, on the basis of what we know at the moment, my caution would be in relation to the eventuality that BSE is found in sheep, rather than what we now know about BSE in cattle.

Prof Kimbell: Are we proposing to do the same experiment in sheep using cows. i.e. transfuse cows.?

Prof Masters: I was going to make the same point. What you have done is to show intra-species transmission by blood and what has not been done in cattle so far has no investigated that.

Ray Bradley: Blood and buffy coat was assayed in the pathogenesis experiment.

Prof Smith: I think that has not been done

Prof Aguzzi: But what was done in the pathogenesis study was to transmit blood intracerebrally.

Mike Dawson: There has been no transfusion study. Spleen has a high red blood content, and that is being assayed in the cattle to cattle pathogenesis

experiment, although that doesn't contain the same amount of blood as a transfusion.

570- **Prof Smith:** Has the experiment where you put BSE infected sheep blood intracerebrally into sheep been done?.

Prof Bostock: No

Prof Smith: So there is no read across there

Prof Bostock: The original objective of the experiment of BSE in sheep was as a model for vCJD in humans. The primary objective was not to study the infectivity in sheep blood. If we did the experiment in cattle, the primary objective would be to ask if there is a risk of infectivity in cow blood per sa.

Diedre Hutton: Can I just ask a question about para 14, about those 13 people who received blood from a donor who subsequently developed vCJD. It says that is not a good thing to identify these patients, but have these patients been 'tagged' so that when they die, will obtain the information.

Prof Ironside: There is a comprehensive system of identifying patients who received this blood.

Prof Kimbell: So hat happen if they turn up wanting to give blood?. Do they say no?

Prof Smith: Yes, they do say no, but there is a debate going on about what to tell the potential donor.

Charles Lister: Can I comment here. Three are three people out of the 13 in the age range that is eligible to give blood. At the moment, none of them are blood donors. The blood service have pre-registered them, so if they do turn up to donate, they can be easily identified. We have had a discussion with ethicists etc. around the question of what these people are told when they are informed that their blood is unacceptable. Currently the guidelines are that people are not informed because there is no way of detecting if these people are infected and no treatment, and there is little advice that can be given. However, from a blood service point of view, they clearly have a duty of care.

End of Tape 2 Side B- Tape 3 Side A

Charles Lister: They will be told that because they have previously received a blood transfusion, there are various reasons why your blood may not be acceptable, one of which is connected with this particularly risk around vCJD. Once they had given blood, they would receive a letter explaining that their

blood was not accepted and they would then be given the opportunity to find out more if they choose to. If they choose to find out more, they would be given information and we would have to make sure that proper counselling was available. At the moment, the blood service is preparing a protocol to formalise that process.

Prof Kimbell: Do you take the blood and destroy it?.

Charles Lister: We could do, but the individual might then return again to donate blood, and that might create a problem for the blood service if they continue to take blood, which does involve an invasive procedure, knowing that they are not going to use it.

Chris Bostock: How many blood donors have received a blood transfusion. What would be the consequence for the blood service if a blanket ban was made on blood recipients giving blood.

Charles Lister: It has been estimated that this would lead to a 10% drop in blood stocks, which has always been considered to be risky. It would deplete the blood supply too much to be considered. However this is something that has been introduced in France, and I think this is something that we do need to keep considering as a possible way forward.

048- **Prof Bostock:** That would be one way of avoiding the issue

Charles Lister: It would.

Prof Kimbell: What would prompt you to take that step?.

Charles Lister: I think that would be something that we would be looking to the blood advisory Committee to give a view on. I think at the moment it is thought that such action would have such an effect on the blood supply in the UK that it would put lives at risk for that reason, and the balance is currently in favour of not doing it. Presumably if we received further information that suggested that there was more than a theoretical risk of transmission through this route, then that might be prudent to do that.

100- **Prof Smith:** I would like to press onto the agenda item before lunch.

4c- Implications for the feed ban- blood products

Peter Nash: The paper for this item is 63/15, which asks the Committee to consider the implications of this research for the feed ban. Dried blood products are currently exempt from the ban under a Commission decision in 1995. Hence this is a European-wide exemption. The UK Government

translated the exemption into UK legislation after consulting with SEAC in 1998. In practise there is very little, if any, dried blood products used in animal feed in the UK. Two renderers are currently processing animal blood and producing about 3-4,000 tonnes of dried blood products for a variety of purposes, including animals feed, although we are told that all of the feed, or nearly all, is exported. The reason that it is not used is retail pressure, which insists that dried blood is not used and I understand that it would have to be declared in the ingredients if it was used. The Commission decision which introduced the exemption referred to the advice of the SSC and paragraph 8 outlines some of SEAC's previous concerns when they were asked to consider this matter in advance of the UK implementing legislation. There was some concern about the possibility of recycling infection, but it was noted that all source material would be from animals under 30 months of age, and there was reference to the dilemma which would allow humans to consume bovine blood, but not bovines. The Committee was influenced by the fact that blood meal was not knowingly included in UK meal, and I have just indicated, that remains the case today. There was also a reference to the ELIZA test, although I am not sure if that is relevant.
So the question is are there any factors which lead you to alter your earlier opinion on the use of blood in the feed for farmed livestock?, and if there are, would you draw any distinction between ruminants and non-ruminants, and are there any scientific arguments that you would wish to draw to the attention of the Commission in favour of a revised view. I imagine that if there was a change in SEAC advice, the UK government would wish to draw this to the attention of the EC in Brussels.

145- **Prof Bostock:** I don't think that I was party to the original discussion. I have always though of this in terms of bovine blood, but it was interesting to read here that 20,000 tonnes of sheep blood goes into the system. The relevance of the experiment in this one animal, if anything, would related to sheep. Recycling of scrapie, irrespective of experimental BSE, especially at a time when MAFF are embarking on a scrapie irradiation program is a risk.

Prof Smith: That is a point that is made in para 14.

Mr Bradley: Firstly, I need to declare an interest, because I have a client that manufactures blood, although not the blood that is referred to here but spray dried blood products, particularly plasma. This is not collected from UK cattle, only from pigs, but it is collected from cattle form other countries, some of which have BSE.
I concur with Chris that the problem here is sheep blood.
Just so people are aware of these two different processes, dried blood is, I believe, only steam treated. I do not advise any industry on this particular aspect at all, but it is relatively low quality material, which could theoretically be contaminated with stomach contents and that sort of thing. So it is 'sterilised' and then feed as a course meal. It may also be used for fertiliser for

example
Spray dried blood is quite different. It is collected in a much more hygienic manner from animals that are passed fit for human consumption. Although the temperature would not destroy the TSE agent, there is a separation procedure at the start of the heat process which separates it into plasma and red cells. The red cells are usually fed to fish for fish farming, and the although the spray dried plasma can be fed to any species, it is particularly important to fed back to pigs because it contains antibodies which protect pigs from post-weaning scours and this type of thing. It has a protective disease component. Personally I don't have concern about pig blood or cattle blood, because it is not collected as this type of value added product from British cattle. Importantly, this industry does not use pithing. At least in the company that I advise, no pithing is used because that could allow brain material to enter the blood. However pithing is done in a number of British cattle, although I understand that this will be stopped from 1 January 2001 by Commission decision. Therefore there could be brain material but only from animals under thirty months of age. The funny thing that I do see and hear is that we collect 50,000 tons of blood from clean cattle, presumably under thirty months of age, but overall most of this is imported. However, I thought we had an export ban which prohibited the export of anything of this kind. Can someone confirm that this is the case, because if it is not being exported, it must be used domestically?.

214- **Peter Soul:** I think the point is made that it is incorporated into livestock feed and the livestock feed is exported.

Peter Nash: In para 4, you note the total amount of blood. Most of that is not rendered. the amount of blood that is dried is referred to in para5, which is 25,000 tons, of which 20,000 tons is pig blood. If you apply an approximate yield of 10% dry matter, that gives rise to 3-4,000 tons of blood product. I would guess that the dried blood products would be of non-bovine origin if they are being exported.

Mr Bradley: That covers that point, but since we collect 50,00 tons of bovine blood, what happens to it. It is not rendered?.

Peter Nash: It is spread and injected onto the land.

Prof Bostock: So {..,ooo's] of blood is used as fertiliser?.

Peter Nash: That is my deduction and I would need to double check that, but it is the main outlet for the blood.

Mr Bradley: SEAC have discussed that previously and I don't want to open up that discussion again. Personally I am content with our previous advice on that. The implication of Chris's results in terms of sheep is what concerns me. There

is no BSE I sheep as far as we are aware, but it would appear that some of this is incorporated into feed that we are exporting?. Would you agree with that?.

Peter Nash: Yes. A small quantity, but nevertheless.

Prof Kimbell: I think Chris's point about trying to eradicate scrapie when we may be recycling the agent in our country is also valid.

Mr Bradley: We do not know about blood from scrapie infected animals, but it is an inference that we could draw. I flag up the issue of sheep blood rather than the other two at the present moment.

250- **Deirdre Hutton:** Can I ask a naive question. I suppose fish aren't a risk. I thought that was the only thing I could eat. Have SEAC considered fish

Mike Dawson: There is a EU project which is investigating fish susceptible to BSE.

Diedre Hutton: If we don't know, is it right to feed them possibly infected material

Peter Nash: The feed ban in the UK covers all farmed livestock, which includes fish.

Prof Smith: Leaving aside the sheep issue for the moment and just looking at the cattle, it looks as though some cattle blood from animals under thirty months could be incorporated into feed and fed back to cattle. Previously when we looked at this issue, we were content for that to happen for the reasons laid out in para8. Does our position remain the same in light of information that has a accumulated since then. I guess that Chris's groups work is only indirectly relevant to cattle.

Prof Bostock: That would be my interpretation.

Prof Smith: So is the Committee be content for this to continue, given that only a small amount of blood gets back to cattle in feed, and this blood is fit for human consumption.

Prof Kimbell: I'm not happy, but is very difficult. the public will say that they eat the blood in normal cuts of meat.

Peter Soul: I think the Committee should be asking itself, is what you have already said, which is that you have concerns about intra-species recycling. There is a difference between feeding the blood of cattle back to cattle and humans eating meat containing cattle blood.

Mr Jinman: But practically, if we are talking about 1.2 infected animals (range 0-4) entering the food chain in a year, and assuming we don't consider sub-clinical disease in cattle, and we have no evidence of infectivity in cattle blood, if we are doing a risk assessment, the risk is so incredibly small.
If we stay away from the feeding of animals back to animals in an emotional sense, and focus on the science, the risk factor must be minute in animals under thirty months of age.

Prof Smith: I think that is right.

Mr Bradley: We feed milk back to cattle. It is a question of where you draw the line. I think it is drawn in the right place at the moment.

Mr Jinman: I think that is the way it should be presented. There is an a emotional argument which is nothing to do with this Committee about whether feeding things back to other things is right. There is also a futuristic concept about the dangers of other diseases. I think we are all a little uncomfortable about feeding species back to themselves, but in a practical sense, the risk factor is minute on the evidence we have today.

Prof Smith: Is everyone happy with that.

Prof Collinge: I think the ideal is to avoid cannibalistic recycling, but I agree that the risks here is very small. However the principle of recycling, particularly while BSE is continuing, is not one to encourage.

Prof Smith: What would happen if we advised to stop it.

Peter Nash: The first thing I imagine we would do is present your advice to the Commission. The Commission would then ask the SSC for it's view, and if they agreed with you, then there would be a Community wide ban. If they didn't reach a similar conclusion, we would have to take a decisions about whether to introduce a UK ban on not.

330- **Prof Aguzzi:** I wish to make a strong point here. We are talking about intra-species recycling. we have witnessed so many bad surprises with this disease. Just two hours ago we were discussing the fact that we may only be seeing the tip of the iceberg in terms of infectivity because of the accuracy of the assays. I think the point could be made that even if the risk is small, it should not be taken.

Mr Jinman: But if you use that argument, they we should certainly not import food from some of these other countries where they are using blood meal at a far greater rate, often from UK derived sources. It is a question of where you

put this risk. I do take your point, but if that is the case, I will certainly not buy food from a whole series of countries where I know this product is exported to and used in far greater levels that it is here.

Prof Collinge: I think we should certainly maintain the principle that intra-species recycling is to be encouraged.

Prof Smith: I think we can say that, but that we also say that the risk that we are considering here is likely to be extremely small, and it is essentially an animal health issue rather than a human health issue, in terms of perpetuating the BSE epidemic in the first instance.

351- **Prof Collinge:** While we are on this, can I just make a point of information. Some of you may have ready an article in the Sunday Times, by Jonathan Leake, which I was somewhat surprised by. He was calling my office on several occasions last week and I had not returned any of his calls having taken the decision some time ago not to give him any further interviews. Unfortunately, I picked up the phone on Friday evening and it was him. He asked for a comment on Chris's paper, and I truthfully told him that I had not read it. He asked if I would read it on Saturday and give him a ring , and I said that if I had time I would, but didn't have much intention of doing so. Hence I was somewhat taken back by his article, which gives the impression that I gave an extensive interview which is not the case.

Prof Bostock: I spoke to him after he had tracked me down at home

Prof Collinge: He did say that he had minutes of relevant SEAC meeting and he would go ahead and writing something anyway if I refused to talk to him. I don't know if that was true or not.

Prof Kimbell: He told me that, and I asked him where he got them from and he wouldn't tell me. He knew exactly which meetings we had previously discussed these issues before, because I went and got my own minutes and checked back.

Prof Smith: Thank you for sharing hat experience with us!.

Prof Kimbell: Would it be possible to tell the Committee if there are journalists that you think that we shouldn't talk to. I had know idea who this bloody man was, and I also shall never speak to him again. It would be nice if you have a black list to tell us about it so we don't make the same mistake.

Prof Smith: An informal warning would be appropriate.

Prof Collinge: It hard to know what to do, I asked the MRC press office and

they advised me ignore it. I did feel tempted to write to the editor, but it is difficult.

Prof Smith: I had told a number of other journalists not to place much credence in what Mr Leake writes, but that is not the audience he is addressing.

386- **Mr Bradley:** Can I just make one point on this general issue. In regard to the company that I work for, I am very familiar of their proposals. They collect pig blood separately from cattle blood, and their advise is that it can be used across species, not withstanding the fact that pig antibodies present in the spray dried plasma have particular value for pigs. The big issue to me is still the sheep, even in the absence of BSE in sheep.

Mr Jinman: Just as a point of information, the OTMS cattle that go down the line, the blood is sealed separately. It is a different blood bank which is sealed by MHS and the seals are recorded. I know this discussion arose in relation to the press and it is a separate entity, and it is rendered as part of all OTM cattle.

Prof Smith: Can we express the general point that intra-species recycling is undesirable, but in this particular instance in respect to cattle, we think the risk is low. In regard to sheep, the issue particularly impinges on the NSP, and maybe it would be most appropriate for us to refer this to the people in charge of running the eradication plan as a potential impediment ot that program, and they would want to make some sort of assessment of how that might impact on that program.

420- **Prof Bostock:** At the moment, the eradication scheme proposals is based on genetic selection, recognising that there is a potentially high infectious load of scrapie out there. It does seem to me that at some point, the scheme does need to incorporate husbandry practises, including feed, to speed up the eradication process, and I would have thought that this is where potential infectivity thorough this route may become an issue.

Mr Dawson: Phase three of the NSP is how to address the question of disease on infected farms. Phase 3 consultation will hopefully be launched in the new year.

Prof Smith: Can we briefly consider the issues of tallow and gelatin, which although they are not in the paper, can still be legally fed back to cattle.

Peter Nash: yes. These are two big subjects which SEAC have addressed, most recently in October 1997. In regard to gelatin, there is a EU export ban on gelatin made from UK bovine material. For enforcement reasons, the UK over-implements that ban in the sense that we also have a domestic ban on gelatin made from UK bovine materials. Hence there isn't any gelatin made from UK

bovine material in food, cosmetics, pharmaceuticals etc. In relation to feed, gelatin does appear in very small quantities in relation to imported gelatine. It is mainly used in veterinary medicines, although that would be made from foreign gelatine or gelatin made in the UK from foreign material.
One must also remember that some human food might also contain imported gelatin. The SSC and SEAC have looked at the use of gelatin. Earlier in the year the SSC effectively said that that gelatin was safe providing the SRM's were removed and you avoided making gelatin from high risk countries. They also made reference to the very tough processing involved in the manufacture of gelatin.
Tallow is allowed in animal feed, although very little is used in the UK. About 2,000 tons of mammalian derived tallow is used in poultry feed in the UK. When SEAC looked at this issue in October 1997, its main concern was the removal of SRM. Most UK tallow is used for soap manufacture, although there is one manufacturer that is producing tallow that may end up in animal feed, all be it exclusively poultry feed. The SSC has looked at the issue and has approved the conditions that are currently used as far as I am aware.

472- **Prof Smith:** It doesn't look as though there is any areas of significant concern. That being the case, I think we can stop for lunch.

LUNCH

Surgical Instruments

475- **Prof Smith:** Welcome Andre Hare and Peter Bennet for our discussion on surgical instruments. The revised parts of their assessment have been circulated to us. I apologies to new Members who have not seen the whole report, which is very thick, but I think we have got enough substance here to discuss. You will recall at the last meeting that we did discuss this at some length , and there was some concern that the input values that were going into the modelling were not agree by the committee. We had a sub-group meeting subsequent to the last meeting at which this was extensively discussed, and I think input values were agreed by the sub-group, which included those members, including John (Collinge) who unfortunately can't be with us now, who had expressed concern at the last meeting. I think he is now happy with the input values that we have used in the revised draft. Perhaps I could ask Andre to take us through where you have got to as a consequence of that exercise.

Dr Hare: I hope you have all got a copy of the papers. I don't think we need to go through the process. What you have got in the papers is an outline of the final report, most of which has been written. You should also have a summary of the report, which includes the conclusions, and a revised Chapter 8 which summarises the results of the model runs and extensions of the model to cope with revised estimates for the anterior of the eye.

Just to put this into context, we would be happy to go away with your endorsement of the risk assessment and the structure of the report that you have got before you. The core conclusions are very similar to the conclusions in the earlier report. The likelihood of a self-sustaining epidemic is reduced because of the reduced infectivity estimated for the anterior eye. This has quite an impact because of the large number of operations involving anterior eye. Hence reducing the estimate of infectivity has had quite an effect. However there is still a possibility of a self-sustaining epidemic. there is also a possibility that a sub-group of patients undergoing repeated neurosurgery could also produce a contained self-sustaining epidemic under worse case scenarios, using the most pessimistic assumptions for decontamination and tissue infectivity.
In short, the CNS and posterior eye is still the main threat, and decontamination is still the key variable for reducing the risk. I am quite happy to answer any questions.

Prof Smith: Thank you. I think the key bit is the two diagrams, which summarise the risk assessment. I am referring to the section on RA on surgical instrument on page 8-9, which summaries the risk for an individual operation and the collective risk of operation form a single type.

Prof Kimbell: It is clear if you understand it, but these figures don't mean anything to me. It would be really helpful to have this in figures in terms of how many cases, rather than 10^{-3}, because I am not sure many people other than you lot round this table will understand what that is all about. I am not sure where this is going, but it is unintelligible in terms of numbers. Page 8 means nothing to me.

Dr Hare: The scale on the left hand side refers to the number of surgical cases relative to the number of primary infections. What the 10^{-3} implies is that there is only a small number...

Prof Smith: By surgical cases, you mean transmission of vCJD through surgery. So for every naturally occurring case of vCJD acquired from consumption of contaminated beef, that is the number of infections that would follow as a consequence of surgery, which is one in thousand.

Dr Hare: Yes. For ever case transmitted by surgery, you have a 1000 cases that contracted vCJD by contaminated beef.

Prof Kimbell: If this is going to be circulated widely, it would be exceptionally helpful if you included that as a footnote.

Prof Smith: I think there is the issue of the publication of this.

Dr Hare: So far, the audience has primarily been yourselves. and is written as

a scientific report.

Prof Kimbell: I am sorry to let the side down.

Prof Smith: As the consumer representative, Harriet has made her point.

Mr Jinman: I know when this subject was raised last time, I raised the question of obstetrics operations. That has not been addressed. I know the last time you said that it was not included in your figures. Obviously in view of the recent report of possible maternal transmission in vCJD, and information from the original scrapie models, I still think this is quite important to include these aspects in the risk assessment because the amount of intervention in the maternal side is critical because long term, the disease could be going a different way.

Dr Hare: The basis for this RA is to look at the potential effects of surgical practise. Are you suggesting that there should be another RA to look at maternal transmission?.

Mr Jinman: It raises the question of how you define surgical intervention. But if you consider a caesarean section on a person who is subsequently diagnosed with vCJD. Then you are taking about generational transmission. I just feel that we have got to start to look at that assessment because it is such an important part. We then also look at all surface transmission and so on. I know John Collinge picked up on this last time.

Prof Smith: What is included in this RA is the re-use of obstetric procedures in terms of the reuse of instruments used for such procedures.

Mr Jinman: That doesn't include standard forceps etc. That should be included .

Prof Ironside: We did discuss these at the group meeting. I guess it is a question of what is considered to be normal forceps use in human delivery, although what I saw personally it wouldn't be considered normal. But certainly things like [opesiotomy?] were included in the RA.

Diedre Hutton: And epidurals?

Prof Ironside: Yes. That would fall into the same category as things like lumbar punctures. That whole issue was flagged up at the last Committee meeting by John (Collinge) and were included.

Prof Aguzzi: I was not here at the last meeting, so I am not sure if this was discussed, but were Dr Weissman's results with the wire-bound infectivity

taken into account?. this is extremely important and relevant because he demonstrated that a small piece of metal exposed to infected brain homogenate will transmit infectivity even after extensive washing, at the equivalent to 30µl of 10% brain homogenate, or 5-6 logs increase in infectivty when looked at in terms of weight.

Prof Ironside: Charles Weissman was a member of the group who revisited this and we did discuss this.

Prof Smith: I think that was included in some of your modelling, although not in this section here.

Dr Hare: I think there was a question mark about the cleaning process involved if I remember rightly.

Diedre Hutton: Can I ask how pessimistic your most pessimistic assumptions are in terms of decontamination. I have a real worry about decontamination. Anecdotally, where I come from people are apparently re-using disposable instruments, they are not decontaminating things on a routine basis and they are not necessarily implementing the Government's recent directive about possible infection control. I would have quite pessimistic assumptions about decontamination, and hence I was wondered how pessimistic yours were?

Dr Hare: The most pessimistic one we have got is a 5 log reduction, which is 100,000 fold decrease in infectivity. Hence if there is 100,000 ID50's on the original instrument, decontamination would remove all of it. That is the most pessimistic assumption.

Dr Bennet: That includes both the effects of cleaning and autoclaving. Now that is pretty pessimistic in comparison to what a decent process ought to a achieve. irrespective of new technology.

Prof Aguzzi: Even in light of the Weissman results?.

Dr Hare: In terms of the decontamination, the autoclaving results we have suggest that the first autoclaving step should remove at least 6 logs if properly carried out, and sometimes as much again. This is at 134°C, if it is done properly. We have taken a lot of advice from decontamination experts and sterile service people.

Prof Masters: A 6 log reduction seems very optimistic rather than pessimistic given what we know about the heat stability of BSE.

Prof Aguzzi: Especially when you immobilise it onto solid surfaces.

Dr Hare: Our most pessimistic assumption is 5 logs at the moment, and that is for the first autoclaving process after it has been contaminated. For the second autoclaving cycle, the most pessimistic assumption is that there is no additional benefit and no additional decontamination.

Dr Bennet: It is worth stressing again that those figures include cleaning, washing and autoclaving. In other words, you would expect any decent washing procedure to remove 1-2 logs, in which case you are talking of a only removing 3 logs of infectivty by autoclaving. However there is big range there. We would not be surprised if current decontamination processes erred towards the most pessimistic assumptions.

Deidre Hutton: I would not be either.

Prof Smith: I guess at some point in the future we will see the survey that has been conducted on present practise. the rumours are that present practise leaves something to be desired. Any timing on when that report is due Ailsa?

Ailsa Wight: Perhaps in the next month or so, although it has not been decided. However the intention is clearly to publish it because we need to get on and get regional offices to do whatever they need to do

John Stevenson: I just wanted to put the important issue that Colin Masters raised in context. Results from the decontamination research steering group indicate that simple washing removes 5 logs of infectivity. That is without any autoclaving whatsoever. I think we must always remember that prions are not totally heat resistant. Autoclaving reduces infectivity by several orders of magnitude, but doesn't remove the infectivity entirely as it does with a conventional virus or bacteria. Hence what Andre is really saying is that washing is estimated to remove 4 logs of infectivity, and hence autoclaving only reduces infectivity by a single order of magnitude. I think that this is pretty pessimistic actually.

Prof Aguzzi: I am sorry, but I have to take exception to that. The wire experiment showed that putting wire into an infected brain homogenate, washing extensively such that you might expect only a few fentograms of protein attached to the wire, and then implanting it into a secondary recipient animals gives you infectivity titres that are equivalent to 30µl of 10% brain homogenate. Arithmetically, the washing has increased the infectivity.

Dr Stevenson: What you have said is exactly right. My comments are to do with infectivity in solution. Charles' (Weissman) experiments in terms of solid phase infectivity have really been taken out of this particular risk assessment because that is a very peculiar issue. The think that what we must realise about those experiments at the moment is that the time of contact which is necessary

for the transmission of infectivity is, as yet, unknown. Those experiments have not been completed by Charles. That is crucial to these risk assessments. At the moment we are just talking abbot infectivity in solution, and obviously solid phase infectivity is a very important bit as yet it is an unknown quantity.

Prof Smith: I think that in terms of assessing the absolute level of risk, we know we can't do that because of the enormous uncertainties. However we know that the risk could be substantial. Using the pessimistic model, you say that for every 10 cases of vCJD that are occurring through consumption of contaminated beef products, there is going to be another case that is due to surgical procedures. That is a pretty substantial risk, and it may be an underestimate. Under a pessimistic scenario, and even under some of the less pessimistic scenarios, there is a potential important public health risk here. It is quite clear looking at the scales on the left hand side (of page 8), there is an order of magnitude change in those scales associated with how effective you assume the sterilisation process to be. I think that illustrates the point you make about this being a critical factor. It appears to be an area where there are some deficiencies in terms of what is currently done, both in terms of anecdotal reports and initial reports on a more widespread survey.
What we are asked to do is endorse this report, and I think we did that to some extent at the last meeting in that I think that we acknowledged around the table that many of us were not in a position to endorse the technical aspects of the report, but a SEAC sub-group containing technical experts had endorsed those technical aspects. Hence as a Committee I think we were content to accept their endorsement. There was concern about the input values, which again were not endorsed at the last meeting, but those that had problems with the input values were convened, including Charles Weissman and John Collinge and I as far as I am aware they have now endorsed that sub-group report.
Hence what we are asked to do is endorse these revised sections, perhaps with some attention to their comprehensibility, and consider whether we would wish to alter the statement that we made this time last year in light of the RA. The relevant paragraphs in the statement from 20/9/99 are 6-8, if I could just take you through those.
The Committee confirmed its earlier view that rigorous implementation of washing, decontamination and general hygiene procedures
were key measures in minimising the risk of infection. We noted that an audit was planned and I guess we should be expecting to see the results of that audit soon. We looked at the mathematical risk assessment and noted
the huge uncertainty about many aspects of the model, which still remain, including critically, the possible number of people who might be incubating vCJD, which is clearly going to be an major determinant of risk. The group of experts have convened and reported back to us.
The final line is that the theoretical risk of iatrogenic transmission could depend
on a number of factors and it was likely to be greatest from operations involving central nervous system and ophthalmic tissue. I guess we would

modify that to say posterior ophthalmic tissue, followed by lymphoid tissue. I think that remains the case from the revised analysis. Then the statement reads that the Committee considered that, wherever
practicable, the use of disposable instruments for such surgery was to be encouraged.

Diedre Hutton: And then thrown away.

Prof Smith: We could add that.

Prof Ironside: I have been to a number of meetings about this and I think the preferred term is 'single use' instruments.

Prof Smith: Single use, which are only used once!.

Diedre Hutton: It is terribly ironic. These things that we are recommending will only work if the instruments are disposed of. How can we be assured that this will happen?

Mr Jinman: It is the BSE story again. It is the policing aspect.

Prof Kimbell: How can we be sure?. If it is not going to happen, then we might decide to change our advice and make it more draconian.

Prof Smith: Well. I think we can add that proviso that they must be disposed of. However it is not our job to police it. It is DH's job to make sure that it happens.

Prof Bostock: You could include that the advice is conditional on the correct disposal of instruments.

Prof Smith: Yes, we could word the statement appropriately. We word it in the knowledge of what is coming along, which is a report that suggests that techniques are not alright.

Prof Ironside: If I could comment on that. There is a document circulated by the DH which states quite clearly that single use instruments must only be used once. How one polices that is however another matter.

Dr Wight: There are emerging mechanisms [within the clinical?? assurance] that will put the onus on chief executives and trusts to address the decontamination issues across the board, and not just in relation to vCJD, although that is an emerging part of it, which is a start.

Diedre Hutton: That was an excellent circular that DH sent out, which states

that the chief executives have got to take personal responsibility for this issue. I chair our local communicable disease advisory Committee, which has representation from all our local NHS trusts, and chief executives have been sent lots of circulars to say that they are responsible for just about everything, and they don't feel they have enough resources to do everything. I still feel that hospital infection control is not given a high enough priority, whatever there is in a national plan. If DH could find some way of giving this issue a higher priority than some of the other 144 things that chief executives are also responsible for would be really helpful.

Prof Kimbell: This is about protecting people from death.

Deidre Hutton: Well, some of the other areas of responsibility do that too!.

Prof Smith: This is not only going to be a concern in respect to vCJD, which is probable a minor issues in comparison to some of the other diseases that might be transmitted.
We then said that tonsillectomies was a discreet operation where specific and practical steps might be taken to reduce the risk of transmission). I think that remains true and DH has been looking into the feasibility of using single use disposable instruments for tonsillectomies. I suppose we just have to caution that by looking at Andre's figures. If one looks at the total risk, where you have actually drawn out tonsil as a specific set of operations, it is actually rather a small component of the total lymphatic tissue risk. I think if John (Collinge) was here, I think he would maintain his stance that tonsils have high levels of infectivity in his experience, and it may nit be uniformily distributed across the lymphatic tissue. In particular, he rather alarmingly said that he had looked at 2 appendix from vCJD cases, and both of which were negative, which is rather alarming for many reasons in terms of surveys etc.

Prof Ironside: I can comment on this. The appendix is not primarily a lymphoid organ but the tonsil is entirely a lump of lymphoid tissue, so you would expect to find more in there. In many appendixes, there isn't any lymphoid tissue present, so it is not a great surprise that in some cases, no infectivity can be detected.

Prof Smith: What about these surveys we are doing?.

Prof Ironside: I don't really want to start a debate on that, but we exclude from analysis the cases in which there is no lymphoid tissue because you can't analyse the sample unless there is lymphoid tissue present.

Prof Smith: But that was a relatively small proportion?.

Prof Ironside: It was between a quarter and a third of appendix samples were

not suitable for analysis. To go back to the tonsil, although as John says, one can detect abnormal PrP quite easily, that is not the same as infectivity, and Moira Bruce presented some preliminary data on infectivity in terms of transmissions at the last SEAC sub-group meeting.

End of Tape 3 Side A-Tape 3- Side B

Prof Ironside: .....and indeed brain, and I felt that new data was particularly helpful in informing the risk analysis. Although the data is preliminary, it didn't really seem to indicate that there was a huge level of infectivity present in tonsil in comparison to spleen for example. I think that re-enforced the feeling that we should be looking at lymphoid tissue generically rather than focusing on tonsil. I think that is the position. I think there may be operational reasons for looking at tonsillectomies as a discrete and relatively minor procedure in comparison to something like splenectomy.

Prof Bostock: Could we not rephrase the statement to note that discreet operations such as tonsillectomies were identified as procedures where practical steps could be taken. Hence we use tonsillectomy as an example rather than as an explicit case.

Prof Smith: It seems to me that, other than some rewording, there is nothing in the new assessment that has been done that would lead us to change the conclusions that we came to last time. Is that the view of the Committee?.

Members: Yes

Prof Kimbell: What happens to this RA now Peter?.

Prof Smith: It is presented to the Department of Health.

Alan Harvey: It has always been our intention ot put the results of the RA into the public domain, and has already been pointed out, the whole document, which is specialist, is not in a form that would be readily understood by the lay-person. Hence what we would be aiming to do to is produce a summary of the conclusions in a form that people could understand for publication. Hence it is our intention to publish the outcome of the risk assessment in the form I have have just described.

Prof Kimbell: What will happen at the business end of this. What is it going to be used for?.

Alan Harvey: It will inform the policy making process in the department and what should be done next in terms of handling the outcome of the review of decontamination practise that Ailsa has already mentioned, and taking forward

the key conclusions on single use instruments and encouraging their use. There are decisions to be made by Ministers, and this RA report, which has now been endorsed by SEAC, will now inform that policy making process.

Ailsa Wight: That is why I think it is important that if the Committee has got anything to say that was different from the advice that was given in the past, or if there are conclusions that arise from this that differ from what we are might want to do, then please say so, because we are seriously considering what needs to be done.

Prof Smith: We don't mention it here, but highly relevant to this is the research program that is underway in terms of the sort of metal that is used in surgical instruments, including coating of instruments, as a possible way of minimising contamination.

032- **Dr Stevenson:** Maybe I could say a few words about that. I have previously reported to SEAC on the last meeting of the steering group. We will be holding another meeting in December, where I hope a substantial body of research data will be presented which will give information about the efficiency of decontamination and maybe provide some new ideas about how that can be improved. I will present a report of that meeting to the SEAC Committee in the new year subsequent to that meeting.

Prof Smith: We have expressed our concern and endorsed the RA. I think we are now putting it firmly into the hands of the department for whatever action is deemed appropriate, and we will watch with great interest.

Mr Jinman: Can I ask if similar data is produced in any other country. Have we any information from anywhere else on similar RA , or even levels of decontamination occurring in other countries for comparison.

Dr Wight: Not that I am aware, but there may be. We haven't spent a lot of time looking at that.

Dr Safar: I am not aware of anything in the US.

Dr Stevenson: The only thing that I am aware of is data that the washing equipment manufacturers give. I have already mentioned the 4 logs reduction in total contamination. That is data generated by the industry itself. I don't know of any other independent assessment.

Prof Ironside: There was a meeting between, I think, Members of the ACDP/SEAC JWG and their French counterparts so time ago. I wasn't at that meeting, but Don Jefferies was. They did discuss issues related to this and what to do about difficult instruments such as [gaskets?] which can't be autoclaved.

I haven't seen a report of that meeting, but my understanding is that the basic premises that the French were operating from were very similar to this. There main concerns were around issues of decontamination of instruments.

Dr Bennet: From the Steering group for decontamination, I am fairly sure that we had looked, and there was no systematic attempt in any other country to actually go outside and look at what was happening on the ground, to the extent that this study had. I think this is a first. Other countries can not necessarily assume that they are any better or worse than we are.

Prof Ironside: Just as a corollary to that, I wondered if, in addition to publishing a public statement on this, it might be appropriate to also publish the full paper as a scientific paper, particularly if this is the first study of it's type. I think that would a good outcome.

061- **Prof Smith:** I think it would be excellent to put it in the public domain in that way. I think there is quite a strong case for putting the full report I the public domain,, all be it that only a few of the public will probably read it. However the likes of Philip Comer could read. I think it would be worth having the whole thing in the public domain at some point, but in different forms for different audiences.
OK. I would like to thank both you and your colleagues very much for the enormous amount of work that you put into this. You have clearly been on a hiding to nothing when doing this, and no-one is ever going to be completely satisfied with the assumptions that you made. However, I think it has been extremely helpful in enabling us to come to some sort of conclusion. I guess your task may not be finished because dental procedures came up at our last meeting, I think that is not currently incorporated into you present work. However, you do indicate in your text that it would be very easy to incorporate these in, so that maybe something that you will be asked to do. Unless there are any other questions, thank you very much.

Risk assessment on small incinerators

080- **Prof Smith:** I would like to skip to item 10 on the agenda, as Philip Comer and Peter Cleasby are here on time. Philip is well known to us. He is from DNV and has dome a number of RA for us. Peter Cleasby is head of MAFF's rural, marine and environment division. They are here to present what is planned with respect to a risk assessment of small incinerators. I hope they can give us some background about why this is being done. I think you are then essentially asking us to endorse the terms of reference that will be given to DNV for this RA.

Peter Cleasby:

DH R&D update

320- **Prof Smith:** I think we can go back to our original agenda now. Can we have the R&D update.

Dr Stevenson: I have presented a brief summary of the research projects that are underway at the department and the ones that have been completed. In the attached paper, I have really highlighted four issues. Just taking 1 and 4 together, this really highlights some of the problems that we face in terms of collecting samples from patients and to highlight the problem that PHS have had in collecting samples of CSF, urine and blood from a controllable cohort which we wanted to set up in order to validate some of the diagnostic tests which we are hoping will come along in the near future. This is really to highlight that these problems exist, although I think there will be a positive outcome in the sense that we will be able to get a significant amount of samples from elsewhere. While we are talking about diagnostic development, as we all know, we have been very concerned about the lack of progress in being able to commission research in this area. To that end, the founders, led by DH and MRC, particularly Mark Pitman, will be holding a meeting early in the new year between potential industrial partners and interested academic groups to try and accelerate this and bring together the people who might generate novel diagnostic kits with the commercial companies who will be able to make and distribute them. We hope that will be a success, and there there has already been quite a lot of interest from a number of commercial companies and also from academic groups.

We have already heard about the RA analysis, and as we have discussed, one of the main parameters going into that risk assessment analysis is the infectivity of tissue, primarily from vCJD patients. This is really to update you on how we are progressing with that. We hope that we will be able to commission a piece of research that will give us some hard data to feed into some of the key parameters in the RA that Andre Hare has just outlined. In particularly, at our last meeting we were discussing the problem of dental tissues, and James (Ironside) does not have any dental tissues at the moment, but probably some of the trigeminal ganglia and Dorsal ganglia that feed that part of the face will give us a reasonable assessment of what that risk might be.

Finally, people have already mentioned the analysis of the tonsil and appendix studies. The ones that have been set up are continuing, and we will be reporting on the next batch of retrospective samples early in the new year. As some of you may be aware, as these studies have got underway, the importance of trying to set up a much broader study to look at a larger tranche of the population has been discussed for some time. There are quite substantial logistical and ethical issues surrounding such a large study. The ethical issues surrounding the smaller studies have been bad enough, but to try and expand this by an order of magnitude is really quite problematic. The MRC have now

set up two sub-groups to look at these issues. One is chaired by John Saunders and will look at the ethical and legal issues surrounding sampling a large tranche of population for a disease which is fatal, and where we don't have any cure or any diagnostic tests for. The other sub-Committee, chaired by Professor Borasavic, will look at the protocols for sample gathering and tissue processing to make sure that it is done optimally and ensure that all the centres that are involved in this study will work together in a co-ordinated way.

Prof Kimbell: Have you thought about widening the debate of the ethical issues to the public generally to get some form of public endorsement for testing?

Dr Stevenson: Yes we have. There are a number of mechanisms available to the department for assessing public interest. I think if we were to do this, we might want to address the whole problem that is plaguing surveillance of infectious diseases throughout the whole country, which concerns obtaining informed patient consent for samples for research purposes. Those instruments are available. However they are not simple to set up, and we would have to be very careful about the questions we ask.

Prof Kimbell: This issue is not just confined to this particularly disease. It is something that needs wide public debate, and you might save yourselves hassle and time in the long run by opening it up to some form of consensus conference or something like that in order to get it into the wider public arena. That might lead to the production of protocols that do have public approval, which would make your life much easier. Whatever you decide in a small Committee is not necessarily going to get you there in the long run.

Dr Wight: I think that is absolutely right.

Prof Kimbell: Talk to the BBSRC and other people who have held consensus conferences, to see how they would set it up and whether it would be appropriate. Personally I think it might save a lot of problems in the long run.

Prof Smith: Yes, I think the experience to date has been that even with small committees, it has been quite difficult to get agreement within the Committees, depending of course who sits on them.

Dr Wight: I think just the process of telling the public that you are not frightened to discuss it would help enormously. I think we have to try and get some understanding of the issues. With all the current topics about consent in terms of what you actually do with the tissues is another area, as James is only too aware.

Prof Smith: I think it is important that these results that John mentioned about

negative appendix samples in vCJD patients is feed into this group, because the choice of tissues in such surveys becomes critical, and it would be a pity to use less sensitive tissues.

Prof Ironside: If I can just comment. I think this issue of the negative appendix is potentially very confusing. I would expect an appendix to be negative if the area you sampled had no lymphoid tissue, and that may well explain John's results. We had similar findings in some of the material that we have looked at at autopsy, but we have obviously also found some positives.

Prof Smith: That is a problem with using that tissue for bioassay.

Prof Ironside: Yes. It is particularly a problem associated with gut associated lymphoid tissue. If I can just add to the comment on dental tissue, we did have a presentation from dentists at the last SEAC meeting, and I have since taken advice from a number of sources about how to address this problem of obtaining dental tissue, which is largely a technical problem and not one of consent. I have been advised by a colleague in Glasgow that there is a method devised in Japan which can be used to sample dental pulp and teeth without disfiguring the face. I am going to take lessons on that.

Prof McConnell: John, you mentioned the need to stimulate research into diagnostic development. What do you consider are the impediments to that?. If this was the diagnosis of AIDS for example, there would be no end of people generating ideas. Is it the unwillingness to work with TSEs, or the lack of secure facilities or what?.

Dr Stevenson: It is all of those reasons. The lack of facilities will hopefully begin to be addressed by some of the new money that has been injected into the field. A lot of the larger diagnostic companies feel there is not a lot of money to be made out of this. BSE will go away in a few years, and vCJD may not be the Armageddon that we may think it is. Hence the diagnostic companies are not prepared to put resources into this area. Hence that is why in the meeting in the new year, we are going to be concentrating on the smaller diagnostic companies where there may be a commercial case to be made. As you know, developing diagnostic tests for this particularly disease is quite difficult. There is no gene, there is no immune response etc. You all know what the problems are. hence we might need some genuine innovative, ground breaking thought to do this properly. Having said that, there are several groups, some of which are represented around this table, who are putting in significant efforts into developing diagnostic assays, and the work that they are doing ids very important. However, the overall effort is really quite small and the more people we can get involved in this field, the better. Money is not the problem. We have money to spend on good proposals.

Prof McConnell: I think the containment facilities, particularly in academic institutes, are a big problem. This involves installing dedicated facilities.

Dr Stevenson: In addition, most academics don't see the development of a diagnostic test to be an intellectually attractive problem.

Prof Smith: OK. Thanks John. I will pass on to Mandy for the MAFF R&D update.

MAFF R&D update

460- **Mandy Bailey:** Thank you. What I would like to do is draw the Committee's attention to three specific points in the paper that has already been circulated. I would then like to provide the Committee with the result that I mentioned this morning in the context of the OTMS1 survey and the DELFIA test results.

Firstly in the paper, the first item I want to mention is in relation to the BSE in cattle pathogenesis experiment. The first table in the paper provides information on the repeat assays in RIII mice. If you recall, the initial assays in C57-blacks were anomalous. these bioassays are not yet complete, but we do have positive results from the frontal cortex at 36 month PI and cervical DRG at 38 months PI. You will see in the little table these are shaded in light grey. Turning to table 1, I think this table is slightly misleading and we will rectify it in the report next time round. This table gives you the inoculation dates fro these various tissues, and only 2 of these cells are shaded, which relate to the 2 tissues that I have just mentioned, which were positive this time around, but were negative in the different strain of mice. However that is not to say that we are not getting other positives in the repeat assays. Everything to date, other than the 2 results I have just mentioned, have also been positive in RIII mice. Hence the lack of shading in the table does not mean that we have not been getting similar results in the RIII mice than we had previously seen in the other strain of mice.

Secondly, the last page of the paper was missing, and the rest has been tabled today. What I really want to draw your attention to are the ongoing results obtained on the work on BSE in sheep with different genotypes. Previously we have presented results from the Romney sheep, but we have begun to get the results through from the Suffolk sheep. This shows some positive ICC results at an earlier age in some tissues in the suffolks, notably tonsil and peyers patches. Also looking at the table of results, you will note that some of the cells have a bold outline around them . This represents that we have had some results from mice bioassays which indicate infectivty in those tissues which were not being picked up as positive by ICC. This is ongoing work and is not complete, but to date, the other encouraging aspect from this experiment is that none of the ARR homozygotes or heterozygote are showing positive by either bioassay and ICC. That is obviously good news in terms of the scrapie eradication plans, although this is of course is BSE.

The final point I would like to make is that for the first time, we have got some results from work at IAH which actually is complementary to the other sheep work in that this time we are looking at cheviot sheep. It is our intention to include further IAH experimental work which is complementary to other experiments that you receive routine reports on. Most what you normally receive concerns experiments at VLA, so we are now going to include IAH work as well, because a lot of the experimental work is complementary. That is all I want to say on the results that have been tabled, unless there are any questions?.

Mr Bradley: In regard to the first table, we have got RIII positivity for two new tissues, and C57 negativity, Is that correct?.

Dr Bailey: Yes. What we are getting previously was not total C57 negativity, but we detected infectivity earlier in this second bioassay using RIII mice.

Mr Bradley: In other words, it came up positive later, but not on this one. Hence the interpretation could be that C57 might not be as sensitive at detecting a low level of infectivity. Is that a fair judgement?.

Mr Dawson: That is one interpretation.

Mr Bradley: Are there any other interpretations?. So, other than this group of experiments, are we using C57's for important detection's of infectivity, or are they all now RIII detections?.

Mr Dawson: I need to check that, but I think they are RIII detections elsewhere. If you remember, this particular experiment was switched to C57's because of concerns about the longevity of the RIIIs.

Mr Bradley: I think historically, before these two results have come forward, although incubation periods have been longer in C57s in comparison to RIII's, the sensitivity of detection was regarded as equivalent, and the titres of infectivity were regarded as equivalent. So, if we interpret this in the way that I have suggested, then that is quite a change. In other words, we have two different types of s7 mice which respond differently to the same challenge.

Prof Bostock: I need to go and check the details, but my understanding is that the RIII and the C57's at IAH, if you do a titration curve, you get the same titre of infectivity.

Mr Dawson: That was the basis of the original switch.

Prof Bostock: that is right. You get a longer incubation period, but the same titre of infectivty. However, in situations where you are having problems of

natural suvivablility of RIIIs then the decision was made to go with the C57s. What wasn't realised in that experiment was that different sources of C57 vary in their original incubation period and it may well be that the particular line of C57s used in the pathogenesis exp., also varies in terms of there susceptibility.

Prof Smith: They were challenged with the same material?.

Mr Dawson: Yes. Well, they were not neassarily infected with the same inoculum, but it would have been derived from the same tissue. Hence there could be some fluctuation in the original sample.

Mr Bradley: Just a comment on table 6. It says that 'tissues are positive by RIII mice bioassay, but not necessarily confirmed by histopath'. Do you mean ICC?.

Mr Bradley: No. This is just on clinical scoring at the moment.

Prof Smith: OK. Mandy can you move on.

Dr Bailey: I now want to present the DELFIA results from the OTMS survey. In the first of the OTMS survey, we had a target population of over 4,000 animals aged over five years. the brain samples from these animals were examined by histopathology and prionics western blot. there was good correlation between both these methods, with 18 positive samples. This was mentioned earlier. 3,356 samples have also been tested by DELFIA. These samples were taken from the caudal medulla. The VLA have tested some of the sample in two of their regional laboratories to validate the results. Certainly the 12 histopathologically positive samples which were tested in the two labs gave very good agreement. (Overhead). I am going to show you the DELFIA results. The VLA got 443 samples which tested negative for histopath and Western blot, but gave an elevated response in the DELFIA test. I think the difficulty the VLA are faced with is knowing how to interpret these results. They decided that they would send some of the samples to France to use the CEA. A total of 63 samples were sent blind, which included 1 clinically affected BSE suspect and 7 of the OTMS samples that were positive by both histopathology and Prionics. The CEA test failed to detect any of the 7 positive OTMS cattle. That may give us some concern in terms of the European survey, but it has not helped us interpret the DELFIA OTMS result. They are planning to further test some of the samples that were giving the elevated DELFIA response by ICC, and this further study will include both confirmed BSE cases as positive controls and NZ cattle as negative controls. Although it would be good to bioassay, we can't because the samples were not collected in a suitable aseptic form for subsequent bioassay. Obviously there are a number of possible explanations that people have offered, but I am not sure that any one of them gives us a definite conclusion. Clearly there are issues related to sampling

methods and things, but these are from the VLA archive and there is no particular reason to think that the sampling or the storage was a problem. The reason that we didn't test the full number in the first instance was because some of the samples were discarded if they were thought to be unsuitable for analysis. There was a fairly rigorous selection process. Perhaps, the only point I would make, and I am afraid I am not an expert in this type of test, so maybe Chris Bostock or Mike can add comments. I know IAH was involved in the development of DELFIA . The DELFIA assay is different from the DELFIA test that was evaluated in the EU. They are measuring protease K resistant PrP whereas this one is looking at insoluble PrP as a percentage of total. GuHCl is used to measure solubility. It may be that these animals are genuinely pre-clinical and this test is picking up something earlier, or it may be that it is picking something different. The arguments have been put forward and there is al these possibilities, but we are not yet in a position to know what these results mean.

End of Tape 3 Side B- Tape 4 Side A

Mr Dawson: Perhaps I could add that the original DELFIA was evaluated last year in the first round of EU trial and performed quite badly. The format has since been changed and now included this measurement of the insoluble PrP as a percentage of the total as determined by differential guanidine extraction. Before testing of OTMS samples began, a mini rerun of the EU trail was performed in house, and the results obtained were such that the assay would have probably passed the EU trial last year, with 100% sensitivity and 100% specificity measuring clinical BSE cases and normal NZ cases. The assay will be going through the next phase of the EU evaluation which is probably going to begin next month. It might be interesting to wait to see how it performs next time around, but other people have indicated that the NZ cattle are not the ideal controls to use for that particular evaluation, although it is difficult to get UK or European cattle which are known not to have been exposed to infection.

Prof Smith: I assume there are degrees of positivity. Are the 17 positives distinguishable from the 400 positives for DELFIA?.

Mike Dawson: There is quite a spread. (overhead). The line is draw at 10% insoluble PrP as a proportion of the total. That is the bottom axis is. The cut off was based on the NZ negatives.

Prof Smith: One of the histopath positives just scrapes in as a positive in DELFIA. So if you lowered the sensitivity, you do wonders for the specificity.

Dr Safar: Is the test still using 3F4 antibody?.

Mike Dawson: That is a good question.

Prof Bostock: I think they are using FH11 as the capture antibody and 3F4 as the detector antibody.

Dr Safar: In our experience, the 3F4 antibody does not recognise bovine PrP on a western blot. When we compare the affinity to the 3F4 antibody to existing anti-bovine PrP antibodies, it is at least 1000-10,000 times lower than existing 6H1 antibody that is used by prionics. I think that antibody was developed again hamster PrP I think. It is a monoclonal antibody and it recognises hamster PrP quite well. The epitope is between residues 108-112 of the human and hamster PrP and there is a single amino-acid difference between bovine and human PrP, which is essentially diminishing this affinity, and explaining the affinity results. hence it is amazing to me that the DELFIA is performing as it does with 3F4 as the monitoring antibody. We can not use 3F4 for the detection of bovine PrP in our lab.

Prof Bostock: In this test, 3F4 is as good on bovine as it is on hamster.

044- **Prof Masters:** Can I ask what the age distribution is of the 443 positives, compared to the 3356 negatives.

Mike Dawson: The whole population was five years old or more.

Prof Masters: Yes, but did you see a difference in the mean age of animals that were positive in comparison to the negatives?.
The second question is how many NZ controls have you tested?.

Dr Bailey: Basically, in terms of the numbers, there are 13 that were at the 30 months. But there is a range as you would expect. Most of the animals are around 5-6 years old.

Prof Master: It was simply to see if the positive animals were a bit older than the negatives, which is what you would expect if you were seeing a sub-clinical infection.

Peter Soul: I believe VLA did perform some profiling to examine that question, and they didn't find any significant correlation between ages.

Mike Dawson: There were just under 250 negative NZ cattle used in the mini-trial.

Prof Ironside: Just for my own clarification, the 17 cases that were positive by histopath., they have been western blotted and there is good correlation between those results.

Mike Dawson: Yes, they were done blind in Switzerland by prionics.

Prof Ironside: So the 443 that are positive by DELFIA are all negative on western blot.

Dr Bailey: DELFIA picked up the 18 positives by western blot/histopath, but also picked up 443 others.

Prof Ironside: No, I am interested in the DELFIA positive, histopathology negative samples.

Mike Dawson: They are negative by prionics western blot.

Prof Ironside: If those were sub-clinical infections, I guess you would expect the western blot to be positive and you may also see something on ICC.

Mike Dawson: Unless it is looking at a different form of PrP.

Prof Ironside: Yes. The two techniques are not necessarily comparable. I realise that.

Prof Smith: I am not sure we should spend too much more time on this. It is worrying result, hopefully for the test, but otherwise for the cattle population.

Prof Bostock: This is a classic problem in diagnostics where you are trying to distinguish between true negatives and true positives. Very often you get a tail where you run into problems, and essentially you have to decide whether it is better to have false positives or false negatives. Either that or improve the technology to tighten up the distinction.

Prof Smith: Yes. The issue though is are these false positives.

Prof McConnell: In light or that, shouldn't you risk testing some animals under thirty months by DELFIA.

Mike Dawson: It is an option that has been considered.

Prof Bostock: It would be an interesting control.

Prof Masters: The fact that none of the 250 NZ cattle came into the positive range should help you to come to an opinion on the validity of your test.

Prof Bostock: I would agree, but it depends if there is difference in the PrP in cattle raised in Europe.

Prof Masters: Impossible. I can not think of a biological reason why NZ cattle's PrP would be different to a UK cows PrP.

Prof Bostock: They have different genetic stock for a start.

Prof Masters: Were they of different genetic stock?.

Mike Dawson: They were essentially the same breed, but almost certainly from different blood lines.

Prof Safar: I think the easiest explanation in this case is sampling technique, and the way the samples were taken and processed. We know that in the brain stem, the PrP levels vary massively from the grey matter and the white matter, and hence it makes a major difference where you take the brain sample from. The complexity of the anatomy of the brain stem ultimately shows that drifting a few millimetres away from one area, you will have a totally different ratio of white matter to grey matter which will massively influence the final PrP^C concentration. We have recently tested a large number of American cows and we see this variation as a standard result.

Prof Bostock: I think how the sample is stored is also vital.

Dr Safar: Absolutely. PrP^C is extremely sensitive to proteolytic degradation, so if the tissue was left at 5^0C for a few hours, the PrP^C concentration definitely drops dramatically. After 24 hours at 5^0C there is not too much PrP^C left in most of the structures. It is still detectable , but there is much less than in immediately frozen tissue like in experimental animals in the lab.

Mike Dawson: I don't know for certain, but I believe that the samples for NZ cattle were taken from the same brain area than the UK cattle. As far as I know, there were handled and stored in the same way.

Prof Ironside: And it is the case that you think that none of the 4443 samples that were positive by DELFIA are suitable to perform bioassays on?.

Mike Dawson: They have been handled in such a way that it would be very difficult.

Dr Safar: I think this is extremely important, because as Chris has already pointed out, with the increase in sensitivity of assays, there will be an increasing need to correlate information. I think there is a general agreement that the bioassay is the most sensitive assay that we have available. Hence in the next round, can I suggest that the samples should be taken in a way that would allow correlation's with bioassays. At least in some proportion of the samples. that is the only way to distinguish between the true and false

positives.

Mike Dawson: That is already happening. The decision has already been taken as a result of the analysis of these samples. This is for the OTMS2 survey. We are about half way through the samples and we will put in some provision for the remainder of the collections.

Prof McConnell: What will these be inoculated into. Are they going into rIII mice or transgenic mice?.

Mike Dawson: They are going to be held pending the outcome of the diagnostics.

Prof McConnell: It would make sense to put them into transgenic mice.

Mike Dawson: If there is a validated transgenic mouse model.

Dr Safar: One very simple way to evaluate the analytic sensitivity of the assay is to do the positive sample into the negative control. The end point and the cut off value in such an experiment will tell you exactly where the sensitivity of the assay and how it translates to the sensitivity in the group of blind samples. Have you done the dilution experiment?.

130- **Mike Dawson:** I am not sure if the VLA have done the dilution experiment with this assay on these samples. The dilution experiment was done last year with DELFIA 1, but I am not sure if it has been done with DELFIA 2.

Prof Smith: I don't think we are going to solve this, but it is a problem one way or another. It is something that we will obviously want to come back to. Can I ask Mandy to press on with sheep surveillance

Sheep Surveillance

133- **Dr Bailey:**

Proposed BSE survey

420- **Dr Nash:** SEAC looked at cattle surveys in February 2000 and concluded that the top priority was to repeat last years survey of OTMS over five year cattle brains. As you have heard, that survey is now underway. We are sampling 10,000 cattle brains in a repeat of the survey last year. The other Development since February is that there is now an EU decision requiring community wide testing of casualty and fallen stock beginning in January 2001,

and being repeated every year. That will require the UK to sample 7,000 brain samples. that leaves the third proposed survey on which we are seeking SEAC's views. This concerns a survey if animals born after 1/8/96. SEAC views are firstly requested on how important such a survey is, secondly, should it start in January or August next year, and thirdly, SEAC views are requested on any of the technical aspects which are listed in the annex of the paper. On the question of when we should start the survey, there are some practical considerations, but SEACs views are requested on the scientific aspects. The argument for starting in January is that firstly , becasue it is an important survey, it is better to press ahead with it. Secondly, if there is going to be a review of the OTMS, and whether we should change it in the second half of next year, it would be useful to have the results before a change is considered. the arguments for delaying the survey until August are that firstly, there is the practical argument that VLA are starting the casualty and fallen stock survey in January, and hence it might not be a good idea to begin another survey at the same time. The second, possibley more relevant concern as far as SEAC is concerned, is that the animal will be on average 5 years old in August 2001, and there is potential criticism if we carry out the survey when the animals are too young. So there are arguments in both directions.

Prof Smith: So we are firstly asked to consider the importance that we attach to this survey. I would think that we attach considerable importance to it.

Members: Yes

Prof Smith: Secondly, we are asked for a view on the start date. January or August

Prof Kimbell: When ever they can manage it.

Prof Bostock: It seem to me that the only reason that Peter raised that was actually scientific was related to the age of the animals, and coinciding the survey with maximising the changes of finding infected animals. I would have thought that that was an overriding concern from our point of view. I think there is another issue. If the survey is going to formally look at the effectiveness of the enforcement of the feed ban, what is the control. What is it going to be compared with?. hence you get a figure for the number of infected animal, what is the direct comparitor that will enable a judgement to be made on the effectiveness of the feed ban.

Prof Smith: I guess all we have got is the Oxford model predictions.

Prof Bostock: Yes.

Prof Smith: Based on a certain amount of maternal transmission.

Prof Bostock: But if one is setting out to test effectiveness, then it ought to be quite clear that it is against a theoretical model rather than a real figure derived from analysis of a previous cohort.

Dr Nash: You said that the over ridding Scientific concern is to maximise the changes of finding a positive. Would that lead you to conclude that the survey should begin in August?.

Prof Bostock/ Members: Yes. August 2001.

Prof Smith: Yes, although the point is made that there is almost as much BSE in 4 year old cattle as there is in 5 year old cattle.

Prof Bostock: If you look at the tables, the mode age is getting later and later and moving towards 5 years.

Prof McConnell: What assays would be used in this survey?.

Mike Dawson: it will be an immunoassay. I am not saying that it will be DELFIA, because I think we have to resolve these difficulties that we have got at the moment.

Prof McConnell: Because you have not resolved that issue, it might make it difficult to begin the survey in January.

Mike Dawson: There is the option of using the other EU-evaluated assays.

Prof Smith: January is quite close. If we ask for a start in January, it is pretty unlikely that the survey will actually begin then. Correspondingly, if we ask for the survey to begin August, there might also be delays.

Mr Bradley: We should say that the start date should not be later than August.

Prof Smith: An August start date does complicate thing in terms of consideration of revisions to the OTM rule. This data may be highly relevant to that review.

Dr Safar: In August, the EU should have finished evaluation of the second round of diagnostic tests. Hence it will be apparent which test is optimal and which should be used as part of this surveillance program.

Prof Smith: That is a good point. Beginning in August will give more time to sort out these assays.
OK it seems to be that for various reasons, the August start date seems to be the

most appropriate.
In terms of the technical details of the survey, I guess the main technical detail is what test is used, and we have discussed that. The proposal is to take 7,000 animals born in the last half of 1996, which will be the ones of the relevant age and conduct some sort of systematic sample.

Prof Smith: OK. if there is no more comment. Can we pass onto the BSE epidemiology update. I think we can also take the item on the post-1996 case as read. Essentially the bottom line is that we don't know the cause, and we are not likely to find out.
I think we can also take the revised figures from the Oxford Group on BSE predictions. this is predicting the number of cases that would be expected to be born after August 1996 on the basis of 10% maternal transmission. There was some confusion between the figures that were presented at the meeting and the figures that were presented in the table. The figures that were published in the table did not take account of the selective and offspring cull, and they have now submitted revised prediction which take those into account. Unless anyone has any specific comments on those two items, I will ask Peter Soul to add anything on BSE epidemiology if he wishes.

Peter Soul: No, I am quite content with that.

Timing of the BSE-Inquiry report

577- **Peter Nash:** This will be a larger item at the next meeting. The meeting will be passed to Ministers on Monday and will be published as soon as possible after the House of Commons reassemble on 23 /10/00. that is much as I know. the only point I would make is that although we don't know what the report is going to say, and it is all hypothetical, the Secretariat would expect any discussion at the November meeting to focus on the management and operation of SEAC as a whole, should there be any such advice in the report, rather than commenting on the Committee as it operated before 1996. However we will have a better idea when the report is published.

Prof Smith: Can I just check how many Members have been offered a copy of the report when it is published.

Dr Harbron: Everyone should be. We passed on all Members names to the BSE inquiry unit, and they have informed us that they will pass a copy out to each Member.

Prof Smith: I think Members who were witnesses at the inquiry have already been contacted, but that is not all Members. Hence if you want it, on the day of publication, you will receive a summary report and a CD-ROM which has the other volumes on it.

Dr Stevenson: Is the publication timetable in the public domain?

Dr Nash: That form of words has been approved. Nothing I have said is confidential.

Mr Bradley: Is the report on US Sheep from the EU in the public domain.

618- **Mike Dawson:** I was told that it could be discussed by SEAC, but I don't think it is in the public domain yet.

(other discussion on date of publication of the Inquiry)

Openness- Publishing SEAC agendas

635- **Dr Harbron:** I have tabled a short paper that was in response to the consultation document that was sent round by Robert May on the code of practise for scientific advisory Committees. The Secretariat is proposing that we now adopt that some of the openness practise that are proposed in the code of practise.
Specifically, we are proposing that we start to publish the agenda of each meeting in advance. We are not proposing to publish minutes, and we are proposing to hold an open meeting, hopefully in the first half of next year.

Prof Smith: Any comments on that. Specifically, it is proposed that we make the agenda publicly available just before the meeting so everyone will know what we have discussed, and hold an open meeting some time in the new year. This will not be a meeting of this kind, but perhaps a two day meeting when the first day is an open scientific meeting, which the public can attend, and we will have a normal SEAC meeting the next day. Firstly, is everyone happy for the agenda to go into the public domain?

Dr Stevenson: The agenda as it stands includes both the time and the place of this meeting. Bearing in mind the concerns raised by Members of the Committee about approaches by Journalists, should that information be omitted, or are we quite happy for the tie and the place to be included in the agenda.

Prof Smith: I think the decision has been made that this meeting is the public domain unfortunately.

Prof Kimbell: When the MAFF bulletin comes out which includes the agenda of other committee's, does that include the place where the meeting has been held?. Are we proposing to put our agenda in that?.

Dr Harbron: What I think we are proposing is to put it onto the MAFF web-site. I think the timing will be such that it will be difficult for us to put it in with other agendas. We only fix the agenda a couple of weeks before the meeting.

Dr Nash: I think on the question of the location of meetings, if you felt very strongly about it, we could leave that off. However I have to say that when our press offices are asked when and where the meetings are, they disclose that information. Hence I don't really see much point in trying to keep it secret.

Chris Lawson: The public summary does include the date of the next meeting anyway.

704-**Prof Bostock:** What is the primary objective of publishing the agenda ahead of the public summary of the meeting?. I think it is fair enough to publish the agenda so that people are aware of the issues and put that in the context of the results of the discussions. However all one is doing by publishing the agenda prior to the meeting is to create a two week period in which people will get hassled, and we are not formally to discuss anything ahead of the public statement. It seems to me rather strange that we are proposing to advertise the fact that we have talked about these issues, and yet somehow we have got to wait for two weeks.

End of Tape3-SideA - Tape 4- side B

000- **Prof Bostock:** ..but it is the disassociation between the agenda and actually dealing with the results of what those discussions were.

Prof Smith: - I guess there are two purposes of publishing the agenda. One would be to make it available in advance, so that people feel they got specific information that might be relevant to a particular agenda item, they can then make known to the Committee in advance of the meeting so that material could be considered. However, the way in which its been proposed to publishing shortly before the meeting it is unlikely that this use will be made of the agenda. The other is in the interest of openness. However, I agree that all it is going to do is to cause us problems. I wonder if an alternative would be to publish the agenda after the meeting?.

Prof Kimbell - Then I think we should publish the minutes instead. I think we should publish them.

Peter Nash- An alternative of publishing the agenda after the meeting is to publish in advance of the press conference, which would mean that it would give the journalists an idea of what we will be publishing in the press

conference. At the moment they don't know in advance. That will be an alternative.

030- **Mr Harvey-** The other thing we mentioned when were discussing this is that whenever we publicise the date of next meeting, at the same time we can publicise the date of the news conference which follows that meeting at which the public summary would be made available. The subtext would be to publicise the second date which the journalists could focus on to find out what happened rather than 'doorstepping' people at the meeting.

Prof. Bostock: I think that would be much more helpful to all.

Prof Smith: Can we agree that we publish the agenda in advance of the press briefing, but not in advance of the actual meeting.

Prof Kimbell: - Are we really against publishing the minutes?.

Prof Smith: This is an issue we have discussed before.

Prof Kimbell: We have different members of the committee now

Prof Smith: Yeah! I was going to say that we should obviously discuss that again. Previously, the feeling was that there are quite often things which are discussed which are confidential, so there would have to be a confidential section of the minutes anyway and experience of other committees has been to end up with minutes that would be like our public summary.

Dr Harbron:- I think the likelihood is that the minutes would be watered down. I have looked at the Food Advisory committee's minutes that they publish, and they actually look very like our public summary. That tends to be the trend for food committees that publish their minutes. Their minutes look like our public summary. So what we will probably end up doing is publishing something that is very like the public summary, but calling it minutes. It depends on whether the Members feel the minutes themselves are a useful document for them, or whether they would be content with something which looks more like a summary. The likely trend is that if we publish the minutes, that is what they are going to look like.

Prof Smith: Other views?

Prof McConnell: I think it can constrain discussion. In a lot of things we discuss, we consider fairly grizzly scenarios, just to see to what extent we are covering issues. The other think is that we sometimes consider pre-publication material, and I think that would not be submitted so readily.

075- **Peter Jinman:** Two things. Firstly, my understanding is that this is an advisory committee to the Minister. It is not an advisory committee to the public, and therefore it is for the Minister to decide what he wishes to with the information that is given to him. If he decides to publish it, that's up to him. Our responsibility is to give him that information. Secondly, we have got people around here who are at the forefront of some of the research and we want them to be able to feel free to offer some of the information - there is nothing more annoying going away from a meeting like this and tomorrow have something published, which we should have been in possession at the meeting and be able to discuss it, knowing there is going to be another month before we have the next chance to discuss it. I think any constraint on that sort of information would be a terrible constraint on this committee to try and draw any sensible conclusions and really give good advice.

Prof Kimbell: How does the freedom of information act affect us, or the human rights judicial view?.

Prof Smith: Well that maybe a bridge we might have to cross, but for the moment, there seems to be at least a majority in favour of not putting minutes into the public domain. But circumstances may change.

Mr Bradley: I agree with what we have said, but a lot of it is relating to timing. If we publish the minutes two or three years later, it would have little relevance and I therefore go back to the Inquiry - has not the Inquiry actually published the minutes of the SEAC meetings that we had all over that period. I think that they may be actually on the internet, so if that is a natural fact, we just have to be cautious about it. But publishing them some time after the meeting when the material in them is no longer a hot -potato?

Prof Smith: Use a 30 year rule!. I thinks that's good, A lot of SEAC material has gone into the public domain I didn't know if the minutes has such have gone into the Inquiry, but certainly material in the minutes has gone into public Inquiry. That is certainly worth considering.

Mr Bradley: One place you could consider publishing is in the annual report. The last one might be a little bit close, and minutes may not have been agreed by then actually!

Prof Smith: Well lets give it some thought. We probably need to meditate on this a bit. I think that there is a consensus that we don't want rush into publishing minutes now, but there is an agreement that we should put out the agenda. Is there agreement that we should have an open meeting in the first half of 2001, as it were to show people what we do?.

133- **Dr Stevenson:** Can you clarify what you mean by open meeting Peter.

Will this be in an auditorium like the FSA hold?..

Prof Smith: The first 400 in get seats!. It would have to be something like that I think.

Prof Kimbell: You asked about possible topics for discussion at an opening meeting. One of the things that could do with a public airing is the disposal of rendered MBM which is floating around. We have been agonising about landfill versus incineration versus whatever. I would be interested to hear what people have to say about that.

Peter Jinman: One question that might arise if we hold a public meeting is that we may well need legal advice, because flowing from the Phillips enquiry is likely to be a lot of litigation. If there is going to be discussion in public, I think the meeting has to be taken with a degree of caution.

Mr Bradley: I was thinking the same thing. It is not so much of having it, its when you have it and I think the early part of next year might be premature. I would very much like to see what this Inquiry says and hear the Government's response which is going to be at least 3 months afterwards before committing to an open meeting. If we are already committed to holding a meeting we might be confounded by all this fall out from the Inquiry. I would much prefer to delay it rather than have it that quick. I can't see any reason for the speed.

Ailsa Wight: It seem to me that one of the thing that might need to begin a dialogue on is sheep and all the issues surrounding that I would have thought would be topic that could be very usefully addressed

Prof Bostock: Its not just BSE, but scrapie in sheep

Ailsa Wight: The whole issue really. It is just trying to understand some of the uncertainties so people are aware of the issues and the complexities, and try and get across the message of some of the difficulties we are facing. I think that would be useful and there is a need to start that dialogue

Peter Jinman: Surgical instruments could be usefully discussed.

Ailsa Wight: I thought someone might suggest that! like this [??]

Peter Nash: We had thought that over a one day public meeting, half the day would be given over to agricultural issues.

Prof Smith: Well, perhaps people could feed ideas into the Secretariat then at the next meeting we could begin to think about how that could be organised, or we can have some proposals for the next meetings I will be surprised if the

Phillips Inquiry doesn't actually come up as recommended much more openness in these sort of committees, so irrespective of what Robert May's group has recommended, I think the pressure to open up the Committee is going to be there from the time that Phillips is published. But obviously we can review things as they go along. OK.

Dicalcium Phosphate

192- **Peter Smith:** Dicalcium Phosphate again - I thought this was finally killed last time.

Lucy Harbron: I did put this paper together a long time ago and I am not sure if I can remember , but I can remember the gist of it. Basically what happened last time was that Danny had asked whether vertebral column was including in the material that was used to make the MBM that was suggested would be used for poultry feed. He said no, and he was wrong, it is
The decision at the last meeting was that there was limited circumstances where it was OK to use dicalcium phosphate. These were when it was solely used for poultry feed, assuming that it could be appropriately policed to make sure that it was only used for that purpose, setting aside the practicality of whether that could be done or not. The question is does the error that Danny made in respect to vertebral column effect the decision that was made at the last meeting.

Prof Smith: So the error is really on the second sheet in the papers after the cover sheet . Would we still standby the statement that we made last time, which is that although we are opposed on principal to intra-species recycling, because of the particular circumstances of the manufacturer concerned and the end product is only used for poultry feed etc. and this could be safety policed, and imported bovine bones from the USA and the Netherlands were used or UK derive bones under thirty months were are content. The last bit of the statement would have to be deleted which refers to vertebral columns . Are we still happy to have this used for poultry feed even though under thirty months vertebral columns are included in processing.

Prof Kimbell: Not really no

Diedre Cunningham: Can it be adequately policed?.

Prof Smith: Well that was not up to us to judge and that's why we put that in there.

Diedre Cunningham: Do we wish to say what we though 'adequately' meant?.

Prof Smith: Well that is was not fed to anything other than poultry.

Diedre Cunningham: Yes, but there got to be some indication in there and I was wondering whether SEAC would make a recommendation about how we would interpret 'adequately' because it seems to be a rather important issue.

Prof Smith: We could say that it was policed to be sure that it was only fed to poultry or something more definite.

Deidre Cunningham: I am just a bit suspicious that it might not be.

Prof Smith: I think we all were, but we have been told our job is not policing.

Prof Bostock: It does seem to me that this new information increases the inheritance risks and if it was to find its way into [susceptible livestock then it would present a real risk. The issue of whether it presents a risk to poultry probably remains the same.

Prof Smith: Can we put in a proviso of that nature.

Prof Bostock: Providing that it can be guaranteed that it is only fed to poultry , then the advice remains the same.

Prof Smith: And we perhaps we could add that [?]if there were any danger that it might be fed to other livestock, we would be very concerned.

Prof Bostock/Members: yes

Mr Bradley: Could I comment on the imported bones from Netherlands, a country with BSE. This does not specify whether these are Dutch cattle or any kind of cattle, in fact it doesn't tell you the species and the same for the United States, so I think that one needs tightening up. On the basis of what is written there, I would be much more content with under thirty months old cattle with the vertebral column in , than I would from these imported bones with the possibility of even having skulls in.

264- **Prof Smith:** Well the USA is probably all right, it is the Netherlands that we are worried about.

Ray Bradley: Chronic wasting disease?. we certainly don't want that over here.

Prof Smith: True, true.

Mr Bradley: Nobody has ever challenged chicken with it. Why do we even put ourselves in this noose. If it is US cattle bones, then I might have a little bit more confidence.

Deidre Cunningham: Why are we doing this. Is this because of commercial pressure?

Members: Yes

Mr Bradley: I completely agree with what Chris said before, but I think this is a very open statement. It does not even say they are from United States. They might have been imported from France or Ireland for all we know.

Prof Kimbell: We have been bullied on this. We have been presented with this paper so many times wanting us to change our opinion.

Prof Smith: No, no. I don't think that is fair. The information has changed and we have been misinformed on a number of occasions. We have had it a few times before, but I think its more because we have been misinformed rather than there is pressure to put this through.

Prof Kimbell: If we said no, would it be a catastrophic decision?.

Prof Masters: No. It effects one manufacturer employing 74 people.

Prof Bostock: As I understand it the last time, the inconsistency was having taken out vertebral columns, then the only source of infectivity was bone marrow, (in inverted commas).If we thought that was a risk then we are lead down the route of asking why we are not taking it out of beef on the bone.? It seems to me that if one is accepting vertebral columns with DRG with all sorts of things, then the possibility of infected material getting into the material is much greater. I think that significantly changes the basis on which the decision has been made. So I think it does significantly increase the risk if it got to susceptible livestock.].

Prof Smith: So I am hearing that you would be more comfortable if we actually didn't allow this?

Prof Bostock: Yes, unless guarantees can be made.

Prof Smith: - Yes, so if you put in those provisos that this does significantly increase the risk to other livestock if it isn't solely feed to poultry and that should be taken into account in any decisions made about this.

Peter Nash: Yeah, it should be worded as strongly as possible. The views around the table are that you only think it is acceptable if it can be guaranteed that feeding to animals other than poultry should be avoided. We can put it as strongly as we can.

Peter Jinman: and vertebral columns are excluded?.

Prof Smith: Currently they are included, we have said that this enhances the risk.

Prof Smith: I think we are been asked to make a judgement with vertebral columns included.

Prof McConnell: There is a difficulty with squaring this with our position on blood.. I agree with sticking to our previous position, but it is slightly illogical. We stop short of saying that blood should not be fed, but how do we respond to question 2 in annex three?.

Prof Bostock: In a formal sense there has been no demonstrable infectivity in blood although there has been infectivity in tissue attached to vertebral columns.

Prof Smith: I think that would of a distinct difference One would be more worried about this than blood OK. I hope we have finally putt this one to bed?.

Agreement of Minutes

Prof Smith: We have got the minutes of the 61st meeting which we are not asked to agree today, but this is the final draft for agreement. So if you have got any changes you want to make to those, if you don't make them before the end of October, it will be assumed that you agree them. So if you could write in with any further changes to those. Is there anything to say on sheep genotyping?

Peter Nash: No. The consultation document was launched on the 28th July. Comments are requested by 30th October . You should all have seen the consultation document. If anyone has any comments can we have them before 31st October.

Prof Smith: The sheep risk assessment Chris?

Chris Lawson: Proposal has been invited from approximately 6 organisations, including DNV, and- they are due in very shortly.

Prof Smith: and dentistry?

345- **Alan Harvey:** Just briefly. Members will recall that we had discussion in July about dentistry. The committee concluded by reiterating the need of

thorough cleaning and sterilisation practices to be observed in respect of used instruments. We have been in discussions with the British Dental Association who have since updated their fact file, which they make available to their members on request about CJD precautions and they have built into that the advice that was given. The committee also talked about the need for further research to be undertaken to analyse oral tissues from vCJD patients. John has covered that and that is being looked at in conjunction with the Edinburgh unit. As far as the risk assessment is concerned , that is something that Andre's group will considered once they finish their current work they were describing earlier on.

Prof Smith: OK any questions from any of those 3 areas?. OK

Any other business

353- **Prof Smith:** The only other item I think, apart from telling you that November 28th is the date of the next meeting, is that the members fees have changed.

Peter Nash: I won't attempt to explain this and I think the secretariat will circulate a paper explaining. In brief , up to now there has not been clear arrangements for paying fees for other meetings, other than SEAC meetings, i.e. the press conference, sub-committees and that sort of thing. We have reached agreement with DH and the finance department about the arrangements for claims fees for these other meetings, which will be back dated from the beginning of the year. There is one thing that I need to sort out, but once that is done, we will circulate a document to all Members summarising precisely what the arrangements are.

Prof Smith: Thank you. Any other business?.

Chris Bostock: Just arising out of this morning's discussions on blood, it would be helpful if one could have information on the extend to which blood is distributed across agricultural land and what short of land is it permitted to be used on. For example, I didn't realise that whole untreated blood was distributed this way.

Prof Smith: I assume you want separate information for bovine, sheep and pigs?.

Prof Bostock: Yes indeed, if it is separated

Peter Jinman: It is collected from one point usually. I don't think is divided up, but it depends on the abattoir- If the abattoir only deals with pigs, then that is true, but in mixed abattoirs there is a tank that is fed into a hopper and

sprayed on the land.

Prof Smith: Can we request that information is assembled on blood that is almost the end...

Mr Bradley: Quickly, pithing. The fact that the SRM ban from the EEC becomes operative from 1st January and since our joint committee with ACDP also has an interest in this issue, can we get an update on whether that will succeed as from 1st January or not?

Chris Lawson: We will be consulting shortly on proposals to implement that element of Commission's decision and we of course will be consulting openly. I think we have a pretty good idea what the responses will contain, but the fact is that decision has been made in Brussels and we will have to implement it.

405- **Prof Smith:** OK Thank you very much. There is a programme that they have in MAFF which takes whatever agenda there is, and squashes it all between 10.30 and 5.00!. It has been a heavy agenda today and thank you for going an hour over.

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