Minutes of the 58th meeting of the Spongiform Encephalopathy Advisory Committee held on the 20th September 1999 at MAFF, Tolworth

Present:	Professor Peter Smith - Chairman Professor Adriano Aguzzi Professor Roy Anderson Mr Ray Bradley Professor Chris Bostock Professor John Collinge (Item 1 only) Professor Will Hueston Dr James Ironside Professor Harriet Kimbell Professor Ian McConnell Dr Mike Painter Mr David Pepper Mr John Wilesmith
Apologies:	Professor Peter Goodfellow Mr Chris Lawson
Secretariat:	Mr Tom Eddy MAFF Dr Ann Nolan MAFF Mr Alan Harvey DH
Technical Advisers:	Dr Danny Matthews MAFF Dr Ailsa Wight DH Mr Mike Dawson JFSSG
Observers:	Dr Peter Barrowman Joint Funders Group Dr Nich Wingfield " " " Ms Karen Finney MRC Ms Lesley Heppell BBSRC Dr Mark Bale HSE

Item 1. Preliminaries

1. Professor Smith welcomed members to the meeting and introduced Professor McConnell who was attending his first meeting of SEAC as a Member of the Committee following his recent appointment and Mr Alan Harvey as the new DH Secretary to the Committee.

2. The Chairman also welcomed Dr Elizabeth Smales, Dr Val Chishty, Mr André Hare, Dr Peter Bennett from DH, Mr Terry Donohoe from the Medical Devices Agency and Professor Geoffrey Woodward an optometrist from City University who were attending the meeting for the items on surgical instruments and ophthalmic procedures. The Chairman

added that Mr Charles Lister from DH and Dr Cliff Morgan from the National Blood Users Group would join the Committee for the item on blood.

Item 2. CJD Update - SEAC 58/1

2.1 Members had before them paper SEAC 58/1 that included the latest analysis of the vCJD epidemic carried out for the CJDSU by Nick Andrews from the PHLS. This analysis suggested that there was weak evidence of a trend of increasing incidence of vCJD. Members agreed that it was too soon to draw any firm conclusions about the future scale of the epidemic from this analysis. Dr Ironside commented that it appeared the increase in the number of cases observed in the last quarter of 1998 had not been sustained over the first two quarters of 1999.

2.2 Dr Ironside informed the Committee that DH had been notified of a total of 44 cases of vCJD and a further two very likely cases awaited confirmation. A number of other cases were under investigation including a patient aged 12 years old. If confirmed this would be the youngest patient to have contracted the disease so far. The Unit recognised the interest that this case could generate. Dr Ironside informed the Committee that the clinical and epidemiological team was hopeful that a full medical and dietary history for this patient would be available for this case.

2.3 SEAC 58/1 also included a map showing the location of 44 cases of vCJD. Dr Ironside informed the Committee that, together with colleagues from the London School of Hygiene and Tropical Medicine, the CJDSU had recently carried out an analysis of the geographical distribution of vCJD cases. As with previous analyses there was no evidence of clustering of cases.

Item 3. Surgical Instruments - SEAC 58/2/1 to 58/2/3 and SEAC 58/3 and 58/4/2

3.1 Dr Wight explained that, in preparing the response to the Committee's request for a full update of the situation with regard to surgical instruments, DH had identified a number of areas on which it would welcome the Committee's views.

3.2 SEAC 58/2/1 set out the action that the Department had taken, or was taking, in response both to the recommendations that SEAC had made in September 1998 and to the exchange of correspondence between the Chief Medical Officer and Professor Sir John Pattison earlier in 1999.

3.3 On the question of the possible use of disposable instruments, particularly for tonsillectomies, Dr Chishty explained that preliminary discussions had been held with surgeons and, as a consequence, a pilot study in which disposable instruments were used for tonsillectomies had been carried out. Although the full results were not yet available, it appeared that some of the disposable instrument sets had performed better than others. The study had also shown that with modification the performance of some of the instrument sets could be improved.

3.4 In response to questions from Members, Dr Chishty commented that if, following evaluation of the results of the pilot study, DH decided that the use of disposable instrument sets should be recommended for specific surgical interventions, the aim would be to produce guidance in collaboration with, and endorsed by, the relevant Royal Colleges. Dr Chishty acknowledged that what was normally issued was guidance, without statutory back up. Action to assess current levels of compliance with guidance was underway through an audit of

current practice. Once the results of that audit were available the Department would take any necessary steps to ensure that adequate quality control systems were introduced.

3.5 Some members expressed concern about the length of time the assessment of the use of disposable instruments was taking. Dr Wight explained that following SEAC's recommendations of September 1998 the Department had taken the issue forward with some urgency. She explained that the practical implications of using such instruments, including any hazards, needed to be evaluated before any decision was made to encourage the wider use of disposable instruments.

3.6 Dr Wight went on to explain that the Department had reissued advice via an Health Service Circular in August, with regard to the cleaning and decontamination of instruments. Both SEAC and the Joint Working Group recognised that effective cleaning played a key part in minimising the risk of transmitting disease. Discussions would need to continue with experts to see if instruments could be "coated" with a material that could be easily removed after use. Dr Wight confirmed that discussions about potential levels of infectivity had taken place with leading materials scientists. Further work was probably needed on instrument surfaces and protein adhesion, perhaps in conjunction with the industry. The Committee recommended that DH should follow this up and the Secretariat report back to the Committee.

3.7 The Chairman invited Dr Wingfield to speak to paper SEAC 58/2/2. This provided the Committee with a report on research into decontamination techniques that had been commissioned. A particular challenge had been how to identify and then measure small amounts of potentially infectious tissue that might adhere to surfaces. It was necessary to be able to do this so that the efficiency and effectiveness of cleaning and decontamination techniques could be assessed and the best ones identified. So far, few of the proposals received had adequately addressed this issue. The Department continued to seek research proposals in this area.

3.8 With regard to other research, Dr Wingfield remarked that the use of sodium hydroxide was showing some promising results although this was at an early stage and more work remained to be done.

3.9 The Chairman asked Members for their comments on the paper and, in particular, if they were able to suggest any areas where more research might be commissioned. In answer to questions Dr Wingfield confirmed that the research programme included the use of biological enzymes to remove infectivity.

3.10 The Committee welcomed the measures that the Department had taken to tighten up cleaning and decontamination processes. They also accepted that a wide-ranging research programme was underway and, although it would take a while before the results could be reported, Members expressed some concern about the time it took for research to be commissioned and the implementation of other practical measures that might be taken to reduce the risk of transmitting infection.

3.11 Mr Hare and Dr Bennett were then invited to present SEAC 58/2/3. In their presentation they set out the most recent results of the mathematical modelling that the Economic and Operational Research Division of DH had carried out into the possible risks of secondary transmission of vCJD via surgical instruments. It remained the case that large

number of uncertainties surrounded the level of infectivity, not least the future scale of any epidemic. This made it difficult to reach firm conclusions. They had sought to obtain the best available information about the levels of infectivity that might be left on instruments and expert advice on the types of surgical interventions that were likely to pose the greatest risk.

3.12 They had carried out a number of simulations using different scenarios that had not surprisingly, given the many uncertainties, produced a wide range of figures for possible secondary infection.

3.13 Members commented that this revised modelling represented an improvement on earlier work. A difficulty was, however, that huge uncertainties still remained, especially about the number of people who might be incubating vCJD. It was noted that under certain assumptions a self-sustaining epidemic could be possible. The Committee considered that it would be beneficial for the information and assumptions fed into the model to be carefully reviewed so that the key factors could be identified and the model refined as appropriate.

3.14 Some members questioned the assumptions about cleaning and decontamination leading to reduced levels of infectivity. There were some signs from experiments being carried out that the assumptions used were on the optimistic side and this was likely to be one of the key factors that would influence the model.

3.15 Mr Hare and Dr Bennett explained that they were aware of these issues. Whilst they were fairly confident about some of the factors that they had taken into account, they would welcome the opportunity to let other experts review their work. If they were to suggest ways in which the model might be improved, their recommendations could then be addressed. Members agreed that a group should be set up for this purpose.

Action: Secretariat

3.16 The Chairman then invited Dr Wight to speak to papers SEAC 58/3 and SEAC 58/4/2. Dr Wight explained that the purpose of tabling these papers was to seek the views of the Committee on those surgical interventions that were likely to pose the greatest risk. It had always been assumed that neurosurgery and operations on the eye were likely to carry most risk with respect to the transmission of vCJD. However, the emergence of vCJD might mean that this issue needed to be re-visited to see if the focus should change.

3.17 The Chairman commented that the Committee had in the past discussed the issue of tonsillectomy and ap~~pendectomy~~. Members indicated that operations involving central nervous tissue would be likely to pose the greatest risk, followed by operations involving lymphoid tissue. The present state of knowledge meant that they were not in a position to assess accurately the relative risks but nonetheless drew attention to the action the Government had taken, on a precautionary basis, in relation to blood when faced with a similar potential threat to public health.

3.18 Members pointed out that the Committee had been made aware of certain lymphoid tissues having been found to be infected. They considered that it was possible for certain practical steps to be taken to minimise or eliminate the risk of transmitting disease, in particular over tonsillectomies, and DH should be encouraged to take the necessary action.

3.19 In summing up the Committee's conclusions the Chairman agreed that effective

cleaning and decontamination of instruments was a key measure, in reducing risk. The Committee welcomed the action that DH had taken so far and that an audit to evaluate compliance with guidance issued on decontamination techniques was underway. However, it was possible that such techniques would not completely remove infectivity and, given the uncertainties, the Committee considered that if it was possible to introduce practical steps to reduce the risks of transmission then such steps should be taken. The Committee had concluded that, although operations involving the central nervous system were likely to carry the highest risk, it was not possible to say whether operations that involved lymphoreticular tissue carried significantly less risk. The Committee had identified tonsillectomy as a discrete operation where action might readily be taken and had noted that DH were carrying out a pilot study into the use of disposable instruments for that purpose. The Committee welcomed the extensive research programme that was underway but considered that the key gap remained the development of an effective and easily performed diagnostic blood test to detect infected individuals. The Committee recommended that efforts to develop such a test should be pursued with urgency and recognised that industry could have an important role in helping to take this research forward.

Action: Secretariat

Item 4. Ophthalmic Procedures – SEAC 58/4/1

4.1 The Chairman asked Mr Donohoe from the Medical Devices Agency (MDA) to present paper SEAC 58/4/1. Mr Donohoe explained that, following SEAC's earlier advice on contact lenses, a number of issues had arisen in relation to the use of other types of diagnostic contact lenses fitting sets and ophthalmic devices that came into contact with the eye.

4.2 Paper SEAC 58/4/1 provided information about the use of diagnostic contact lens fitting sets. The Committee noted that these sets were available as either "hard" or "soft" lenses. It appeared that "soft" lenses used in both high street practices and hospitals could be easily replaced with single use lenses without undue difficulty. The main problem identified was over the use of "hard" lenses. Those used in high street practices could be replaced with single use alternatives without too much difficulty. However, a move to the single use of "hard" lenses within hospitals was likely to be more problematical. Professor Woodward explained that, for patients referred to hospital clinics because of the nature of the visual impairment suffered, often the use of a large number of fitting sets was required before the correct lenses could be prescribed and then manufactured. He went on to explain that any immediate move towards the single use of hard lenses could lead to a delay in patients receiving treatment. Mr Donohoe informed the Committee that the MDA had met with the contact lens manufacturers' association who had advised that all contact lenses could be supplied on a single use basis if so required

4.3 SEAC 58/4/1 provided information about the range and use of a number of ophthalmic devices. Single-use components were available for a number of devices and their use could be introduced without too much difficulty in both high street practices and hospitals. There were, however, other devices, used mainly in the hospital settings, where single use components were not available.

4.4 In their deliberations the Committee noted that any risk of transmission remained theoretical. In confirming its earlier advice with regard to the single patient use of trial contact lenses the Committee agreed that this advice should be extended to cover diagnostic lens

fitting sets. With regard to ophthalmic devices the Committee agreed to recommend that:

a) as a precautionary step to limit any possible transfer of infectivity, those components of ophthalmic devices that touch the cornea should be for single patient use, wherever practicable;

b) the use of protective coatings or films that could be removed after each use should be explored;

c) research into the binding of abnormal prion protein to glass and plastic surfaces be undertaken.

4.5 The Committee agreed to provide advice to Ministers along these lines.

Action: Secretariat

Item 5. Blood - SEAC 58/5

5.1 The Chairman explained that the Committee had been asked to review its earlier advice in view of the decision of the USA and Canadian authorities to defer donations from people who had lived in the UK cumulatively for six months or more between the 1st January 1990 and the 31st December 1996. The Committee welcomed the progress that had been made towards the implementation of the policy on leucodepletion and noted the comments from Dr Morgan that clinicians were increasingly considering how they could reduce the use of donated blood without prejudicing patient heath. The Committee concluded that it had nothing to add to its earlier advice with regard to blood destined for transfusion.

5.2 The Committee also considered the results of published research. The Committee were particularly interested in the work published by Dr Mary Jo Schmerr and colleagues in which they had been able to detect the presence of the abnormal prion protein in infected sheep and elk showing clinical symptoms of disease but not in apparently normal uninfected healthy animals.

5.3 The Committee was informed that this research had been reported at various conferences and that the researchers involved had been in contact with the CJDSU about carrying out tests on [illegible] material from [illegible] vCJD patients. Dr Schmerr was also in discussion with MAFF about obtaining material from cattle infected with BSE.

5.4 The Committee considered that although there were some shortcomings in this research it potentially marked a step towards the development of a diagnostic blood test.

Item 6. BSE epidemiology and R&D Update

6.1 The Committee had before it paper SEAC 58/6 summarising results from the key cattle experiments. Dr Matthews drew Members' attention to two long term cattle experiments SE1821, the comparative bioassay in mice and cattle, and SE1918, the attack rate experiment. There were cattle in these experiments which were still alive some 79 and 92 months post inoculation in SE1821 and SE1918 respectively. A few had shown intermittent mild clinical signs which had not progressed to full clinical disease. The programme management group at VLA had agreed it would be sensible to terminate the experiment and examine [illegible] ni[illegible]

~~the cattle for pathological changes in order not to miss, or be unable to interpret, mild pathological lesions due to BSE in old animals.~~

6.2 The Committee noted that there was a further case of spongiform encephalopathy in a lion and briefly discussed the availability of data from cases of spongiform encephalopathy in wild cats. Dr Matthews explained that there were limitations to MAFF's legal powers to gather data in this area and MAFF had no control over autopsies in zoos so most of the information was provided on a voluntary basis. Members noted that London Zoo scientists had proposed to conduct a full epidemiological study of exotic species including the history of feeding practices in zoos and components of foods provided for ruminants and exotic species. Members also noted that none of the exotic species were currently being strain typed in mice. [illegible] the Nyala, kudu and a domestic cats had ~~previously~~ been [illegible] successfully biologically strain type the [illegible] ~~tested~~ that ~~It~~ here was very little frozen, unfixed material available which could be used for this purpose.

6.3 The Committee noted that there had not been any cases of FSE reported in domestic cats during the course of the year and agreed this was consistent with an apparent decline in the epidemic.

6.4 Members noted that the cases of BSE diagnosed as a result of post mortem examination of brains of cattle from the OTMS were being recorded as official cases and that the offspring cull had been invoked where appropriate. The figures were not included in the epidemic curve which was drawn up on the basis of date of clinical onset as there was no such date available for these cases. The problems concurrent with the interpretation of such data, only available late in the epidemic, were discussed. The Committee agreed that it was important to make comparisons of like with like and that it must be made clear that these were not new clinical cases. A similar presentational problem had been encountered by the Swiss. Members noted that Portugal had now reported 312 cases compared to 307 in total in Switzerland.

6.5 Members noted that the reduction in the number of BSE cases in the UK in 1999, compared to 1998, was likely to be of the order of 27%. Currently between 40 and 50 cases were reported each week.

Item 7. Sheep

7.1 The Committee had before it paper SEAC 58/7 which contained a summary of interim results from the experiments on BSE in sheep and a short report on three scrapie projects looking at the distribution of PrP^{sc} in sheep of various breeds. Dr Matthews cautioned that the interim results needed to be interpreted with care. The results suggested that the clinical phase of the disease in the Romney sheep was more protracted than that in Cheviot sheep but this may be a reflection of a more intensive clinical study in the former experiment. In the Cheviot experiment immunostaining of PrP was evident in some lymphoreticular tissue at 6 months but not at 12 months. Results from the 3 month post challenge [illegible] were expected shortly.

7.2 Members noted that the apparently intermittent presence of PrP immunostaining

might simply be one of sensitivity and that, as yet, western blotting was not part of the routine protocol. In comparisons at VLA, immunocytochemistry for PrP had proved as sensitive as western blotting. Samples were being archived so that as more sensitive technology is developed it could be applied retrospectively.

7.3 Members noted that nearly 90 sheep brains from cases of scrapie were currently being strain-typed in mice. In addition to brains being tested on the basis of cases of each genotype and breed from each infected farm (as recommended by the subgroup to screen for BSE) these tests included multiple (up to 10) brains from the same farm. This was in order to build up a picture of phenotype of different agents based on strain-type in mice together with the clinical profile of the disease and the genetics (breed and genotype) of the sheep. Members noted that transmissions to mice of scrapie were sometimes unsuccessful; of nine contemporary isolates only six transmitted to mice. The consensus was that if BSE was present it should transmit to mice.

7.4 The Committee also had before it a paper summarising progress on surveillance for TSEs in sheep (SEAC58/8). At the June meeting the Committee had asked for a progress report on surveillance for BSE in sheep. The paper set out the theoretical aspects of the use of western blotting [illegible] immunobl [illegible] ~~both for detection of TSEs which did not distinguish between the BSE and scrapie agents (referred to as immunoblotting) and also for~~ PrP^{sc} typing where comparisons between agents based on differences in [illegible] glyc [illegible] and th [illegible] after prote [illegible] ~~between the three dimensional structure~~ might be possible. The paper also set out some of the constraints involved in applying the PrP^{sc} typing technology. Progress on testing sheep brains using conventional strain typing in mice was summarised, and annexed to the paper was a draft summary of results of immunoblotting of both sheep and cattle samples at VLA. Much work had been carried out in collaboration with Prionics in Switzerland showing the western blot technique to be a possible alternative to histopathology or EM detection of SAF. VLA had not had any material from BSE infected sheep made available to them and it had been impossible to carry out detailed PrP^{sc} typing studies in the absence of such control material. Such material was now becoming available in limited quantities from the pathogenesis experiments in the Romney sheep at VLA and Cheviot sheep at NPU. A further annex summarised progress on all of the recommendations made by the SEAC subgroup.

7.5 Members noted that the comparison between VLA and Prionics of results of immunoblotting different regions of sheep brain were unusual. They noted that the key difference in the two laboratories methodology was that VLA included a centrifugation step. The differences gave rise to some concern about the performance of the test using the same reagents in different laboratories.

7.5 The Committee agreed that the development and application of diagnostic tests for BSE and scrapie was a very complex area but that progress appeared to be slow. It was essential that criteria for diagnostic tests were agreed by experts prior to commencement of further surveys. While such criteria might change as time went on it was essential to eliminate differences of opinion about test performance in order to interpret surveys. Members noted the potential confusion about the application of tests to detect TSEs (BSE or scrapie) and tests to differentiate between BSE and scrapie. Members also noted that the only test that the Committee had accepted (in the July 1998 meeting) as definitive evidence

of BSE was strain typing in mice and this had been endorsed in the subgroup report earlier this year.

7.6 The programme of strain typing in mice recommended by the subgroup was in place. Further development and validation of PrP^{sc} typing or related technology was needed before it could be applied to screening sheep for BSE with any confidence. The complexity of the sheep PrP genetics and the concern about the possibility of phenotype change on subpassage within sheep meant that a range of control material from appropriate sheep would need to be built up. At present the only material which was becoming available was from the pathogenesis experiments and further material would be needed. Members noted that although MAFF had put out calls for proposals to develop differential diagnostic tests the response had been poor with few new players or novel ideas being put forward.

7.7 The Committee agreed that a subgroup should consider what the next steps should be with regard to further survey work. They would need to look at the objectives of surveys to ensure that it was possible to achieve the objectives with the tools available. Objectives should be geared toward the overall aims of determining the distribution and abundance of scrapie in UK sheep flocks and whether there is any BSE present.

Action: Secretariat

7.8 Members noted that it had been roughly estimated that taking forward the recommendations from the subgroup and extending the surveillance in cattle could cost in the region of £60 million over the next 5 years. They noted that there were many constraints on progressing the work and that a paper was to be discussed by the High Level Committee chaired by Sir Richard Wilson.

7.9 Committee asked for a position paper which summarised the situation with regard to BSE and scrapie in sheep setting out progress to date, the complexities and problems of looking for BSE in sheep, and the costs of addressing the recommendations of the subgroup. If possible the paper should also set out a timetable for the research and surveillance programme to indicate when results might be anticipated. It should also cover the dynamics of working with the sheep industry, the social impact on farmers and the legal constraints on what can and cannot be done under the Animal Health Act and relevant Community legislation.

Action: Secretariat

Item 8. Offspring Study

8.1 The Committee considered paper SEAC 58/9 setting out the proposed experimental design and costs of a study of offspring from BSE affected dams. Given the long period of time before results would be forthcoming (possibly 7 years) members debated the value of the study but could not reach a conclusion. Discussion was deferred to the November meeting, when further epidemiological analysis of the BSE epidemic was expected to be complete, so that the debate could take the latest conclusions about the significance of maternal transmission and the likely progression of the epidemic into account.

Item 9. OTMS Survey

9.1 Members had received a letter in July outlining interim results from the OTMS

survey. Dr Matthews updated the Committee on progress: 4163 heads were collected of which 3951 were suitable for examination. 18 (0.454%) were positive on histopathological examination of the obex. Samples of rostral and cordal medulla were sent to Prionics for testing by western blot and a further sample had been retained for testing using DELPHIA. Results from Prionics had been slow in coming forward but so far at least one of the two medulla samples from 2055 animals had been tested by western blot. Of the 18 animals with positive histopathology at least nine were also positive by western blot but conclusions about correlation could not be drawn at this point as tests were carried out blind by Prionics and the full set was not complete. There were no animals so far which were positive on western blot but negative on histopathology.

9.2 To interpret the findings, knowledge of the age structure of the animals sampled was considered critical. The Intervention Board had been approached for data but so far there had been problems in obtaining reliable information about dates of birth and dates of processing under the OTMS. Many of the animals were aged purely on dentition and without documentation to prove their age. As a result only 1871 of the 4163 cases have a good match so far with 91% of them being 5 years or over. Much of the data may be available but simply entered in such a way on the database that a manual check may resolve the matching problem. It was expected that possibly 50% of the records might provide sufficient information to set out the age structure of the animals slaughtered during the relevant period. The ages of 17 of the 18 histopathology positive animals were known. One was close to its 5th birthday, 2 were 5, 7 were 6 , 2 were 7, 1 was 8 and 4 were 11. The age of the last case was currently being investigated.

9.3 Members noted that, irrespective of how the prevalence was distributed across the age classes, the results did not suggest a much higher level of disease prevalence than previously anticipated - it was roughly in accord with the predictions for the number of cases. Mr Wilesmith explained that the pathologists carrying out the histopathology examination believed these cases to be within 3 months of onset of clinical disease on the basis of experience from the pathogenesis study, cohort study and general observation. If this was correct it suggested an unusual bias in the stage of disease which was being detected which might need further investigation. Professor Anderson agreed that the Oxford group would take account of the findings in their modelling of the epidemic.

Action: Secretariat

Item 10. Matters Arising

10.1 Members had received a correspondence item (SEAC/Corr/58/01) about a prepublication paper about the results of studies investigating the potential for contamination of beef carcases with brain tissue at slaughter. Members confirmed that they were happy with the conclusion which had been drawn by the previous Chairman Professor Sir John Pattison from such comments as members had made.

Action: Secretariat

10.2 At the previous meeting the Committee had endorsed the EU SCC advice that dicalcium phosphate produced from UK cattle bones should not be incorporated into ruminant feed. Members noted that the request for the Secretariat to follow up sources of material being imported had met with a slight delay due to confusion because dicalcium phosphate was used as a source of phosphate not calcium as previously thought. A further

update was expected to be available for the November meeting.

Action: Secretariat

10.3 Members agreed that the OTM rule review should form the major element of the November meeting. Discussion could only take place in the light of revised epidemiological analyses which were currently underway. Members noted that the November meeting was scheduled to be a two day meeting but preferred a long single day meeting if possible.

Minutes

11.1 Members agreed that any final comments on the minutes of the 57th meeting should be presented to the JFSSG Secretary within 3 weeks of the meeting. Minutes were agreed, subject to such amendments.

Action: Members/ Secretariat