HOUSE OF COMMONS

# Science and Technology Committee

## Oral evidence: Blood, tissue and organ screening, HC 990

## Wednesday 26 March 2014

Ordered by the House of Commons to be published on 26 March 2014.

Written evidence from witnesses:

- National CJD Research and Surveillance Unit (NCJDRSU)
- National CJD Research and Surveillance Unit (NCJDRSU) (supplementary)
- Serious Hazards of Transfusion Haemovigilance Scheme (SHOT)
- Professor Sheila Bird

Watch the meeting

Members present: Mr Andrew Miller (Chair); Jim Dowd; Mr David Heath; Stephen Metcalfe; David Morris; Stephen Mosley; Pamela Nash; Sarah Newton; Graham Stringer; David Tredinnick

Questions 145-200

Witnesses: **Professor Richard Knight**, Director, National CJD Research and Surveillance Unit, **Professor Sheila Bird**, Programme Leader, Medical Research Council Biostatistics Unit, **Dr Paula Bolton-Maggs**, Medical Director, Serious Hazards of Transfusion Haemovigilance Scheme, and **Dr Simon Mead**, Association of British Neurologists, gave evidence.

**Q145 Chair:** Good morning. Can I welcome our panel to this session? We have only a small number of questions, but, as there are four of you, it will probably take a fair amount of time to get through them. If you find that at the end there are additional pieces of evidence you would like to submit, please feel free to follow up in writing. For the record, I would be grateful if the four of you would introduce yourselves.

***Professor Knight***: I am Richard Knight. I am director of the National CJD Research and Surveillance Unit and a clinical neurologist.

***Professor Bird***: I am Sheila Bird, medical statistician from the Medical Research Council's biostatistics unit in Cambridge.

***Dr Bolton-Maggs***: I am Paula Bolton-Maggs. I am a consultant haematologist, and currently I am medical director of the Serious Hazards of Transfusion National Haemovigilance Scheme.

***Dr Mead***: I am Simon Mead, a neurologist from the National Hospital, Queen Square. I am an MRC employee; I work at the prion unit and I am the clinical lead at the National Prion Clinic.

**Q146 Chair:** I will start off by asking simply is the UK blood supply currently more or less safe than that of other developed countries—for example, the US or France?

***Dr Bolton-Maggs***: Certainly I would say yes. If you mean, as I think you do, infections in the blood supply—safety—the figures are very equivalent, if not better. I have the current figures for the UK, which show that the risk of hepatitis B being in donations is one in 1.3 million; for hepatitis C it is one in 28 million; and for HIV it is one in 7.1 million. There are not a lot of data from other countries. We have some from Canada, Australia and the Netherlands, and the figures are very similar. The rest of Europe, even though it is under the EU, does not have any up-to-date information that we can easily access. But infection is not the only risk with blood.

**Q147 Chair:** Do prions currently pose the most significant risk to the UK blood supply, or are there other pathogens, known or unknown, that we should be more worried about?

***Professor Bird***: Prions do pose a risk, but we do not know exactly the nature of the transmission from PRP positives in humans. We are concerned that there is not a blood test for positivity for abnormal prions, so we cannot protect the blood supply in the same way we protect it from hepatitis B, HIV and hepatitis C, which are based on testing.

***Professor Knight***: Although this is not my field I am looking from the outside as far as I understand it, as things currently stand there are many other negative incidents related to blood—many more than those related to prion disease—but you would be in a better position to comment on that.

***Dr Bolton-Maggs***: Yes, if I may. The biggest risk to people receiving blood transfusions is that somebody makes a mistake during the process. That accounts for by far the largest number of reports we have to the national haemovigilance scheme. I could pass round this chart, which shows at the top our reporting categories. Transfusion-transmitted infection is the little blip up here, and the bars down here are all the mistakes that are made in relation to transfusions.

**Q148 Chair:** These are different types of mistakes, are they?

***Dr Bolton-Maggs***: Yes. They are when people do not identify the patient properly at the start, or do not check identity at the time of transfusion. There is a whole raft of other mistakes. Our major concern is in that area, but there are several other categories. In terms of infections, we are very pleased that there are so few, but obviously for the individuals who get the infections you cannot talk in terms of statistics.

**Q149 Chair:** Leaving aside the mistakes, Professor Knight said that there are other potential risks. What are they?

***Dr Bolton-Maggs***: We know about hepatitis B, C and E and some bacterial infections. I am not an expert on the other fields, but I know that there is a very good screening or finding programme right across the world for emerging infections. A report is produced every month by Public Health — in the epidemiology unit — that scans for all the infections that might be a risk to the population. For example, when West Nile virus became an issue in the blood supply, countries very quickly developed testing for that. I do not think we do that as a routine, because it emerged as an infection in the US but not so much in England, but public health and epidemiology services are looking at migration of infections like that across Europe, and are very much keeping their eyes open all the time for emerging infections.

***Professor Knight***: You asked whether prion infection was the biggest risk, so you are asking about magnitude. I do not know that that is true. The difficulty, as has been suggested, is that for a lot of these other concerns there appear to be very good tests for them. We understand about bacteria, viruses and so on, whereas at the moment we do not necessarily have very good tests for prion disease, so the difficulty is about being able to protect the blood supply in the same way as is undertaken for these other agents; and there are ways of treating and managing blood that reduce infectivity and that do not apply to prion disease.

In relation to things like the misidentification of patients, it is still important, because when you are given blood the risk to you as a blood recipient is the risk of that action, whether it is infection or otherwise.

***Dr Mead***: The main difference with prion disease is that there is no test. The scientific evidence as I view it points to a concern that maybe one in 2,000 people is silently infected. We know from animal research that, if there is an infection in the body, it includes the blood. We have had hard evidence that variant CJD has been transmitted on blood transfusion. The concern is that, without a test, infections now ongoing might build up a problem in the future, because we know that the incubation times for these disorders can be so long — even over 50 years. You could be building up problems with infection that we have no way of picking up that may lead to clinical problems down the line. That is what I am concerned about.

The priority is to move forward with studies to show whether blood tests can pick up those silent infections, and look to ways to try to prevent their spread, if they are there. As to whether there is a real risk of things happening now, we can have a certain confidence about clinical cases, but we cannot be confident about whether infections are being transmitted.

**Q150 Chair:** You are categorising things in three areas: human mistakes; the risks for which there are good tests; and the risks—prions or other unknown pathogens—for which there are no tests. That is basically where you draw the lines.

***Professor Knight***: Although I think the uncertainty is a bit wider than that. West Nile has been mentioned. If you want to know whether a human being is infected with West Nile, there are methods of doing that. You can determine in many ways for HIV or other things the base population prevalence of those infections. The trouble with prion disease is that we are working on uncertain assumptions. As Simon said, for very good public health reasons we work on the assumption that about one in 2,000 people is infected, but that is based on the appendix data. We do not know for sure whether the appendix data really mean that these people are infected. Even if they do, we do not know whether these people are infectious. If they are infectious, we do not know for what period of time they are infectious, so there is another uncertainty—the uncertainty of knowing how big the base population risk is.

**Q151 David Tredinnick:** I want to ask you a few questions about tracking transfusion-transmitted infections. My understanding is that the European Union published a series of blood safety directives between 2002 and 2005, and we have the UK Blood Safety and Quality Regulations, which require serious adverse events and reactions related to blood and blood components to be reported to the MHRA. In that case, why do we also have to have the serious hazards of transfusion—SHOT—scheme working collaboratively with other bodies? Can we not roll the two together? Would it not make more sense? Would it not be more cost-effective and efficient and mean that they have less chance of dropping catches?

***Dr Bolton-Maggs***: The SHOT scheme has been in existence since 1996, and the MHRA became a competent authority in 2005 because of the EU regulations. They are mainly concerned with the quality of blood from donation through to the laboratory. What they are interested in does not stop at the laboratory door, because if anything happens to the patient as a consequence of that, such as infection, it becomes reportable. Those things have always been reportable to SHOT. When SHOT originally started, it did so with public health surveillance, to get the infections, so there is overlap in that area between what the two organisations do. We are currently working together to get a joined-up system, because we agree it makes a nonsense.

However, there is a large body of work that SHOT does in terms of clinical events and teaching and training which the MHRA does not do. We link very much with patient blood management in putting the patient at the centre of everything we do. If you like, it looks like this diagram. There are things the MHRA collects to do with quality that we do not necessarily do, but there is a large area of things that happen to patients linked with good patient management that SHOT has always done, and continues to do, in terms of teaching and training. We want a collaborative system that would satisfy both those sections.

**Q152 David Tredinnick:** You have just told us that we haven't got a fully collaborative system right now.

***Dr Bolton-Maggs***: We haven't got one.

**Q153 David Tredinnick:** You are working towards it.

***Dr Bolton-Maggs***: We are meeting regularly with the MHRA to try to get a unified system.

**Q154 David Tredinnick:** Following on from that, given that the incubation period for some infections can be several months, or even years, how can you be sure that all transfusion-transmitted infections are recorded?

***Dr Bolton-Maggs***: You are quite right. Quite often patients with an infection turn up much later after transfusion; they may develop symptoms or they are found to have a marker infection, say hepatitis B. If they have been transfused in the past, a great deal of work is done to see whether or not the infection they have now links back to that transfusion. That work is undertaken by the specialist department within the NHSBT or the blood services. Some of those patients may present now, but they acquired their infection two, three or four years ago. Because there are very careful vein-to-vein records—if you have had a blood transfusion we should be able to track it back to the donor—that research is done to demonstrate whether the infection came from the blood donation or whether it is something the person acquired by a different route. Sometimes patients reported to our system this year will have been infected a few years ago.

**Q155 David Tredinnick:** Do you think the SHOT scheme should be a mandatory requirement for all hospitals and blood establishments? If not, why not?

***Dr Bolton-Maggs***: I absolutely do. When we began in 1996 participation was quite low; it was 26% of hospitals. At that time, the culture of reporting when things go wrong was not very strong, but now SHOT has 99.5% of NHS hospitals and trusts across the UK signed up to report, so it is very robust in those terms. What we do not know is whether people have incidents that they are not reporting because they do not think they need reporting, or for the very basic reason that they do not have the time to put in the reports, but I think the level of reporting we have is very encouraging.

**Q156 Chair:** Is there any reason for that tiny fraction not joining?

***Dr Bolton-Maggs***: It is one or two hospitals. We write to them and say, "Why aren't you signed up to report?"

**Q157 Chair:** What answers do you get?

***Dr Bolton-Maggs***: Sometimes it is that they are linked to another hospital that does the reporting. For example, where there have been mergers of trusts and you have big hospitals that are entire unto themselves but are linked in a single trust, they say that their teaching hospital colleague is responsible for reporting. I am not sure how reliable that is, because what you need on the ground in the hospital are people who will do the reporting. Usually, they are called transfusion practitioners, or they are laboratory or nursing staff. With the current increase in pressure in terms of workload and everything else, I am sure that not everything gets reported because people do not have the time to do it, but I think that infections absolutely would be reported.

**Q158 Stephen Metcalfe:** I want to look at the tracking of potential transmission of vCJD. The TMER is looking at this. Dr Mead, I think you said there was hard evidence that it could be transmitted through blood transfusion.

***Dr Mead***: Absolutely.

**Q159 Stephen Metcalfe:** On the back of that, are the Government doing enough to prevent transmission? Should they be doing more—for example, leucodepletion?

***Dr Bolton-Maggs***: Leucodepletion has been in place for a long time. It was introduced by the blood services as one part of the methodology that they hoped would reduce the risk of transmission.

***Professor Knight***: It was introduced in 1999, I think.

***Dr Bolton-Maggs***: Yes.

**Q160 Stephen Metcalfe:** Okay, and it is still used.

***Dr Bolton-Maggs***: Absolutely, because it has all sorts of other benefits to transfusion, quite apart from possibly being able to reduce the risk.

**Q161 Stephen Metcalfe:** Are there any other processes we could introduce that would assist?

***Dr Mead***: The introduction of leucodepletion is quite an interesting one. It was rather prescient, in that it was done before there was hard evidence of transmission of variant CJD. The evidence developed between 2004 and 2006. I sit on the ACDP and some other CJD committees. It strikes me now that there is scientific consensus that the key thing to move forward with is a prevalence study to try to develop a blood test. That would be the biggest thing to make further improvements. I have to qualify it though by saying that the point is that we need to deal with the uncertainty. We do not know for sure that one in 2,000 people is infected in blood and is therefore posing a risk by blood transfusion, but the only way to find out is to run tests on that tissue itself and understand those tests better, and even get multiple tests. The only way we can do that is by a scientific study that uses these tests in practice and starts to take it one step further. That is the key thing to decide.

***Professor Knight***: If I may respond to the question retrospectively, a lot of measures were put in place; it was not just universal leucodepletion. As Simon has hinted, a lot of these things were done well before there was any evidence that blood was infectious. There was a prevailing body of expert opinion when a lot of these things were done that blood would not transmit prion disease, so a lot of precautionary measures were taken quite early on in a very admirable way.

**Q162 Stephen Metcalfe:** Now that we know that blood can transmit prion disease, is it possible that other prion diseases could be transmitted?

***Professor Knight***: It is possible. There is no good evidence for that at the moment. Indeed, the TMER study looks specifically at sporadic CJD as well as variant CJD.

**Q163 Stephen Metcalfe:** When you say there is not any evidence of that at the moment, is anyone looking for it?

***Professor Knight***: For example, in the TMER study sporadic CJD is analysed in the same way, and at the moment there is no identified case where it is reasonable to say that sporadic CJD has been transmitted by blood. There are theoretical reasons for thinking it is less likely, but even despite that it is being studied.

**Q164 Stephen Metcalfe:** Obviously, the TMER looks at transmission via blood. Are there any equivalent studies about transmission through, say, surgical interventions?

***Professor Knight***: There are various things that are done about surgery, and there are parallel sets of what you might call enhanced surveillance. There is a Public Health England occupational exposure study of needle stick injuries and things like that. On surgery, in the CJD unit we take detailed histories of all surgical operations. We get the hospital and GP notes where we can; we look through all the records; and we have a database of surgical operations. Clearly, we try to see if there is any connection between patients through surgical operations. We have done case control studies, which obviously involve cases and controls, and looked at surgical transmission, and we have done this in big studies with European colleagues.

At the moment we have not discovered any good evidence that surgery has transmitted variant CJD. For sporadic CJD, there is a handful of cases that appear to have been transmitted by surgery, and not for quite some time. The case control studies and other studies that have been done are varied. Some of them produce evidence that surgery may be a risk and some do not, but they are very difficult studies to do. On surgical incidents that may occur, Public Health England has records of people who are supposedly at risk from this, and there are of course efforts then to follow up those people and, if possible, to do post-mortems on them in the event of death.

**Q165 Stephen Metcalfe:** Could you expand a little on the scale of that study of the surgical side of things? Is it every operation that takes place?

***Professor Knight***: For people with all forms of prion disease that we see, we get a lifelong history of every surgical procedure, including dental procedures and the suturing of wounds and things like that. We collect that information and then we get hold of hospital and general practice notes and try to see if there are any records of operations that we have missed.

**Q166 Stephen Metcalfe:** You look back through the medical history.

***Professor Knight***: Yes. We have big databases with all of these in them. You want to know whether two people who have been diagnosed with prion disease were, for example, on the same surgical list, or had an operation in a hospital at the same time. That sort of thing is extremely complex. When you are looking for spatio-temporal clustering—Sheila is much more expert in this than I am—it is very difficult to do, because the plain fact is that events do cluster. Three buses do come along at the same time, and that can sometimes be just chance.

**Q167 Stephen Metcalfe:** What number of investigations back through medical histories are you conducting on an annual basis?

***Professor Knight***: We would do it in every case of prion disease that we know about, so it would be of the order of 50 or 60 to 80 cases a year. We also have data on people who were referred to us initially as suspect cases who turn out not to have disease.

**Q168 Stephen Metcalfe:** Are 50 to 80 cases statistically significant? Can you work with that as a number?

***Professor Knight***: We are accumulating these things over time. We now have quite significant numbers, having run the unit since 1990 and having pre-existing data going back to 1970, at least in England and Wales. Because we are part of European collaborative organisations sometimes we have been able to do very big studies, although for variant CJD the studies will always remain small because, fortunately, relatively few people have been affected.

***Professor Bird***: Perhaps I could come in on vCJD patients. Sixty-seven patients received blood or blood products from those who had become vCJD cases. Of those, only 18 have died, having been at least five years out from that exposure, but we have post-mortems on only eight of the 18. As Richard says, in each of these instances it is crucially important to gather information about what is still a new disease. Of those eight, half were positive for the abnormal prion, but fully to understand that we also need to know the age of the individual, the genotype and so on. Gender, birth cohort and genotype are critical descriptions for each of these. We do not know necessarily even the genotypes of those who died, and that has an impact on whether, if infected, that individual might have presented in life.

***Professor Knight***: I was addressing the surgical aspect.

***Professor Bird***: There is another network. If, for example, the Chair had been a vCJD case and Mr Metcalfe and I had both donated a unit of blood, then either the Chair ate his BSE, or you or I did, so you and I are now at high vCJD risk and have to take precautions for the rest of our lives. I now die without having given permission in life for people to find out whether I am PRP positive, but actually I am, let us say. You have to continue throughout your life taking precautions, whereas if I had given permission for vCJD informative testing to be done in the event of my death, hopefully, because we are just a very small network, you would have been let off taking those lifelong precautions.

The implications of giving permission in life are different for the different sorts of network, and can have real implications for surviving individuals. It will not always be the case. If I were the vCJD case and had given blood to both the Chair and to you, the fact that you were negative still would not let the Chair off lifelong precautions. The implications of permission for informative testing are different according to the sort of network you are caught up in, which is quite a complicated thing to have to explain, but very important.

**Q169 Stephen Metcalfe:** I apologise if this is touching on someone else's area, but who should be gaining that permission, and at what point? Is it at the point at which you donate blood?

***Professor Bird***: Again, it depends on how the network becomes identified. Some networks will have been identified to the CJD incidence panel, and at that time might have had responsibility. The enhanced surveillance study, as I understand it, tries to get that sort of permission, but has not to date — so I am told — been very successful in getting those permissions. I do not know how the case is put and by whom it is put, and I do not see a public accounting of the numbers who have been asked, those who have declined and those who have given permission. I do not know whether the CJD surveillance unit knows.

***Professor Knight***: I think it depends. The follow-up of people who are, as it were, at risk in some sort of way, and who may or may not have infection from prion disease is very complex. Some of them when they are notified that they are at risk have the opportunity of joining Simon's national monitoring study. He can talk about that. The people who are deemed to be at significant risk are informed of that risk. They are given a standard letter that explains ways in which they can involve themselves in research: how, if they have an operation, tissue may be used for research; they could voluntarily donate blood; they could give consent for autopsy, or whatever. My understanding is that all of that is given to people. It depends largely on how they are notified, but for some of those people it will come through their GP.

If people do not wish to take part they do not take part, but they, and also the people who are thought to be at risk but not informed because their level of risk is thought to be very uncertain or low, are flagged. In the event of their death, my understanding is that local information services flag that death on the electronic health system. Then the Health and Social Care Information Centre—I think it is called—and something called the Personal Demographics Service identify those deaths. They notify Public Health England and, depending on the category they are in, they will be notified to us in the CJD unit, or Simon at the National Prion Clinic, and things follow that course.

It is quite correct that trying to get autopsies on people who are thought to be potentially at risk is very difficult. It is my understanding from the interim report of that system that in 2013 there were 11 deaths in the enhanced surveillance cohort and, as far as we know, no post-mortems were done. Speaking personally, very recently I was informed that somebody in a category we would be interested in had died. It was a Friday lunchtime, which is in any system the worst time you can be told anything. I rang the GP, who was not working that week. None of the GP's colleagues was able to deal with the problem. I was able to find the local hospital so I rang the local hospital and spoke to one of the doctors. Needless to say, it was not a doctor who knew anything about that patient, but

they gave me details of the bereavement service. I went there and found out that a death certificate had been issued two days before and no post-mortem consent had been given. There was no way of contacting anybody further until Monday or Tuesday, when it would have been too late. It is a very inefficient system in that way.

On the other hand, personally speaking—this is now my personal view—I would be very opposed to mandatory autopsy, which is true in some countries in the European Union. Although there are very clear public health benefits from this information, there are lines where personal choice does count.

**Q170 Mr Heath:** Perhaps Dr Mead can help me with this. You have a cohort of at-risk patients, or not necessarily patients – individuals. To what extent is there surveillance on a neurological basis of that cohort? Are they invited for regular neurological checks?

***Dr Mead***: First, I should make it clear that the at-risk group I am involved in following up is a very small proportion of the total number of individuals at risk because of variant CJD in blood products. The small group I am involved with are those who have been exposed through transfusion of a whole unit of blood, or more. Given the small numbers, this means that I and my team have the capacity to go and visit people in their own homes and have a full discussion with them about the science behind it and why we are interested in working with them, and trying to engage them to find solutions to the problems and uncertainties we face.

Many of these people are really annoyed about what has happened to them and the risks they have been put under, and that makes it difficult to engage, but the majority wish to participate, and we build a relationship. Therefore, we hope that we will learn of any symptoms of any illness that develops, and that people will be more willing to volunteer blood samples and tissue should the worst happen and they were to die of another illness.

**Q171 Mr Heath:** You do not do genotyping or anything like that.

***Dr Mead***: Yes, we do. We have genotyped every patient who has offered, so we can extract DNA from a blood sample. We have taken blood samples from all those who have been willing. In case in future anyone develops prion disease, we can look back and see if there was a blood test and whether it was positive at that time. It is a very valuable resource, but thankfully that has not happened yet. Through this work we have a relatively high autopsy rate from this group when individuals have passed away.

**Q172 Mr Heath:** Even when they died of other causes.

***Dr Mead***: That is right.

**Q173 Mr Heath:** I am misunderstanding something. I thought I heard earlier that no autopsies had taken place.

***Dr Mead***: I think that is a different group.

***Professor Knight***: That was a separate group. The enhanced surveillance groups are complex. There are many different groups. Simon is talking about very specific groups.

***Dr Mead***: There are eight autopsies from this group of 18 or so. Three of those were individuals who developed variant CJD. The remainder were individuals who died of other things, but the point I wish to make is that the reason we obtained in life consent to an autopsy was the fact there was a high level of personal engagement with a small group of individuals. The much wider group, including haemophilia and people at surgical risk, involves several hundred individuals.

It is worth making the point on surgical risk that the concrete harm going on at the moment, when there is a look-back exercise after a diagnosis of variant CJD, is that all the contacts of that patient are notified that they are at risk, with no opportunity for a blood test to confirm or not whether that risk is real, and with an indefinite prospect of a potentially incurable disease. It is a great shame that we have not moved faster towards ways adequately to sterilise surgical instruments to avoid the need to write these letters. I agree with Richard about the difficulties of scientific epidemiological study in this area about surgical instruments—but there have been several manuscripts that suggested there is an increased risk of CJD in surgery, although there is no scientific consensus on it at the moment.

**Q174 Mr Heath:** Professor Bird, as I understand it, you are keen on mandatory post-mortem of the at-risk group.

***Professor Bird***: I have suggested—this suggestion was made about 10 years ago—that because this is such an important and difficult disease, and the consequences of BSE are something we visited upon the world, we need to try to understand variant CJD. I think it is regrettable that much valuable evidence is buried or cremated. I appreciate how difficult these conversations are with patients. When there is a specialist group having those conversations, as Dr Mead said, there is the potential for a higher consent rate, but the practice is that overall we have very little post-mortem evidence from the set of highly at-risk individuals. I would like there to be an almost annual accounting of the types of vCJD at-risk network, how many people within those networks survived for at least five years from putative exposure, how many died at least five years out and how many post-mortems there have been, so that we can see for each of these groups what the information accrual and the loss of information is.

**Q175 Mr Heath:** You are looking at this from an epidemiological position in terms of population prevalence—in which case, if we had a satisfactory blood test we would not need that, would we?

***Professor Bird***: Exactly. If we had a satisfactory blood test, reliance on post-mortem evidence would not be as great as it currently is. A research priority undoubtedly is a validated blood test. In the first instance, its performance need be sufficient only for surveillance. Instead of having done the prevalence study in appendices, that study could in essence be repeated in the anonymised testing of blood samples from blood donations, or whatever, to find out the prion positivity in blood, if we had a validated test.

**Q176 Mr Heath:** But a post-mortem would tell us whether the carrying of prions had resulted in lesions.

***Professor Bird***: Absolutely.

**Q177 Mr Heath:** So there is a further step.

***Professor Bird***: There is a further step, as Dr Mead said, about positivity in tissues or blood in life, and then what the pathology is at post-mortem gives a more complete understanding. Each of those instances is extremely precious.

***Professor Knight***: One of the difficulties you may have in understanding this is that the people who are designated as being at risk fall into multiple categories. There are those who have been notified and know they are at risk, but there are lots of people who are designated at risk but are not notified, so they are in an entirely different group. The comments Simon made relate very much to people who are notified and known as a specific sub-group, and the comments I was making referred largely to the people who do not necessarily know and have not been notified.

**Q178 Mr Heath:** But it is almost infinitely extendable, isn't it? Everyone eats a beef burger over 50 years.

***Professor Knight***: Yes, although there is another comment I would make. I agree that the blood test is extraordinarily important. If you had a blood test that really worked, it would be a great boon in all sorts of ways, but the surveillance system should pick up people who develop CJD, so if there are people at risk who develop variant CJD the standard surveillance system will, I hope, pick those up. The difficulty is about the people who are infected and have sub-clinical disease — that's who we want to identify.

The real difficulty is that, if you have a blood test that is validated in detecting an abnormal result in somebody who is clinically ill, will that work in someone who is sub-clinically infected? That of course is difficult. It is also difficult to validate. If somebody is sub-clinically infected, will the blood test be positive throughout the whole period of sub-clinical infection, or become positive only at a particular point? That is a very difficult thing to validate.

We have tried other approaches to this. For example, one approach was to go through accidental deaths in the coroners system — where I come from, it would be under the procurator fiscal system, but in England it is the coroners system—to suggest that material at those kinds of autopsies could be examined for infection in the population. Unfortunately, that proved impossible, because coroners in general did not wish to take part.

**Q179 Mr Heath:** Might there be a case for at least looking at post-mortem material from those who are certified as having dementia at the time of death?

***Professor Knight***: That is quite a difficult business, because many people have dementia.

**Mr Heath:** They do.

***Professor Knight***: And I do not know how you would go about doing that on a global scale. Our unit is very well aware that the age-related incidence of sporadic CJD drops off sharply with age, which does not make sense for a supposed neurodegenerative disease. It could be that there is under-ascertainment in the elderly. Two out of three of the blood-transmitted cases were, in terms, elderly, and it is the case from the appendix study that one cohort, which would now be entering the mid-50s to mid-70s age range, had a significant set of positive results, so there is a question as to whether disease is being missed in the elderly. I think the only way you could go about doing that would be to try to define a manageable area, identify dementia in it, look at atypical dementia and try to investigate that in more detail.

There are dementia studies going on in various parts of the country. We have had a fairly detailed collaboration in Cambridgeshire, for example. We recently decided that we would like to do one in Lothian and perhaps collaborate with the Cambridgeshire set-up, whereby we would offer detailed investigations in life and try to get a high autopsy rate in atypical dementing illnesses. We submitted a proposal to the Department of Health and we are waiting to see what will happen. I do not see how it can be done on a national scale at the moment.

**Q180 Graham Stringer:** Following on from that, you stated you are confident that there is little under-reporting of variant CJD, yet the answer you have just given seems to indicate that it is difficult to distinguish variant CJD from certain forms of dementia, so how can you be so confident?

***Professor Knight***: The answer is that, if you ask any honest surveillance system whether there are any missing cases, there is only one answer: yes. The question is the magnitude of it. What we try to do is to have overlapping methods, so we get clinicians to refer us suspect cases and we deliberately leave it very open. We do not have any set criteria. If somebody thinks it might be prion disease, they can refer a case. We ask pathologists to refer any cases to us that they come across. We get death certificates with certain rubrics on them sent to us in batches, and if there is anything that we think needs to be followed up we try to go through the medical records. We have an embedded spinal fluid laboratory which does tests for these diseases; that is a national laboratory funded by the Department of Health. We know when clinicians suspect a case because they ask for the CSF test as part of the routine diagnostic procedures. Of course, we are sometimes notified of cases through families who approach the CJD Support Network—a charity. We have done various things to try to ascertain that we have not missed cases. We did a big retrospective study of death certificates in England, to see whether we might have missed cases before 1996.

All I can say is that, in general, with the neurological community being very aware of this situation, we think we are probably not missing many cases. The disease itself is a fairly striking one. Most neurologists, if they see it, will recognise it as something unusual, or they will recognise it as a prion disease and let us know.

If you look at what has happened in the UK, the number of people who have been diagnosed as having any form of CJD in total has risen gradually. The annual mortality rate, which is rather more important, has gradually risen over time, suggesting that people are identifying cases more often. If you look at the ratio of referrals of suspect cases to proven cases, that ratio has dropped at the same time as the number of cases has gone up, which indicates that clinicians in general are getting a bit better at this. Alongside that, there has been the introduction of much better diagnostic facilities and diagnostic tests, like MRI and CSR proteins. We cannot be absolutely confident, but we have as good a surveillance system as is practically possible.

If you look at what happens in other countries, the only real comparison we have is with sporadic CJD. We have annual mortality rates that are broadly similar to most other countries. The countries that are now embedded in collaborative networks are very extensive, including Canada, Australia, Japan, Israel and virtually the whole of the European Union. It is very widespread. If you look at those countries, the annual mortality rates of sporadic CJD have risen in almost exactly the same way as they have in the United Kingdom, again suggesting that it is all to do with improved surveillance rather than cases of variant CJD being mistaken for sporadic CJD, especially if you compare us with Australia. In Australia there is said to be a very, very low risk of any kind of animal prion disease. The way in which annual mortality rates have changed in Australia has very much mirrored our own, suggesting that the figures for sporadic CJD do not hide any variant CJD that we have not discovered.

The reason for being interested in the elderly—this is an average statement about the health service—is that, if you are, say, 45 and you develop a serious dementing, disabling neurological illness, in the United Kingdom you are almost certainly going to see a neurologist. If you are 90, you might not see a neurologist. Therefore, neurological expertise may not be good in that particular set of clinicians. Therefore, we are interested in whether we are missing cases in the elderly, but particularly cases of sporadic CJD. That is what we are most interested in, but along the way we could ascertain whether we have missed cases of variant CJD.

**Q181 Graham Stringer:** Thank you for that very comprehensive answer.

***Professor Bird***: I think there is a very specific reason to be concerned about variant CJD in the older birth cohort, and that is because of the work my group did on dietary BSE exposure. That showed that the 1940 to 1969 birth cohort was more exposed than the younger birth cohort, and that prior expectation, if you like, is borne out in the prevalence data in appendices that have just come to the fore. We do not have enough testing as yet in the older birth cohort in the appendix study. We have tested fewer than 9,000 in the 1941 to 1965 birth cohort. When we had tested only about 9,000 to 10,000 in the younger birth cohort, it was the prompt for the second surveillance study in order to make the information more precise. That prompt has not been followed up in the older birth cohort, so we have particular reason to be on the lookout for whether some form of vCJD might present in the elderly.

The other consequence of the dietary data was that the implication of the mismatch between the birth cohorts that consumed and the birth cohorts that became clinical cases is that there is age-dependence susceptibility to a dietary exposure progressing to clinical

disease. It was the dietary data that allowed that separation and that inference to happen, and that is also why we are fairly confident that we will not have variant CJD cases in those born in 1990 and later. We cannot be sure yet; we have not had any as yet. We will be a bit more confident if we get to 2015 and still do not have a 1990-born vCJD, and I will be very confident if we get to 2020 without having had one. It would be a vindication of the prediction from the dietary data. That is why I am concerned that the figure of one in 2,000 is accepted as the general summary of the surveillance data. It is premature to conclude that there is not a higher PrPSc prevalence in the older age group. In my view, we need further testing in that age group.

**Q182 Graham Stringer:** You have partly covered this, Professor Knight. Professor Ironside said that your unit had methods for improving the surveillance of variant CJD in the elderly. Can you tell the Committee a little more about what methods of surveillance you have got?

***Professor Knight***: I am sorry. Professor Ironside said that we—

**Q183 Graham Stringer:** He said that your unit had recently proposed a new approach to CJD surveillance. What has been the Department of Health's response to that?

***Professor Knight***: The Department of Health response was that they were intrinsically interested in such an idea and they invited us to submit a proposal, which is what we have done. That was fairly recent. My understanding is that that proposal is being considered. My understanding of the consideration of it, although I am not in the Department of Health, is that they are interested in such a study, but obviously it costs money and therefore it has to be considered in terms of its benefit and cost.

**Q184 Graham Stringer:** Can you tell us a little bit about how it would vary from current surveillance?

***Professor Knight***: At the moment it is a passive surveillance system, in the sense that we ask people to refer. They refer through a national system to us and the National Prion Clinic, but it is up to clinicians to refer the case. As I said, we have various checks in place, like death certificates. If we get death certificates that suggest something a bit unusual, or, even if they have CJD on them and we do not know about them, it might be an elderly person and we would investigate that by getting hold of their medical records and finding out more about it.

In Lothian, which is the region where I work, and its associated satellite units, there is now quite a nice set-up of memory/dementia clinics and services that are interested in investigating memory and cognitive impairment in the elderly. We want to form a collaborative network so that when they see people they try to categorise them as clearly as possible. To be fair, a lot of these people are going to have classical things like Alzheimer's disease, which are usually very easily clinically distinguished from prion disease. If they see people who they think have unusual dementia, or in some way it is a bit atypical, we will visit those people and take detailed clinical information from them and examine them; we will offer things like MRI, which might not always be done in elderly dementia patients; and we will try to get a high autopsy rate, because the autopsy

rate in elderly dementia is very low indeed. In doing that, we will try to link up with maybe one or two other systems. One I have mentioned is in Cambridgeshire where there is a dementia project of a similar sort going on  a dementia register. It is trying to identify all people contacting health services within a region who have dementia, trying to select a reasonably defined subset, trying to investigate them in more detail than would normally happen, and trying to get a much higher autopsy rate than would otherwise be the case.

**Q185 Graham Stringer:** There has been a study in France where healthy monkeys have been exposed to variant CJD and they have developed symptoms that are atypical of prion diseases. Are there any implications in that study?

***Professor Knight***: This study in France was?

**Graham Stringer:** I am not sure I have the name.

***Professor Knight***: Were they people who were exposed?

**Graham Stringer:** No, they were monkeys.

***Professor Knight***: That is the macaques study. It is difficult for me to comment on the macaques study because, as far as I know, it has not been published.

**Q186 Graham Stringer:** So we are in advance.

***Professor Knight***: It is terribly difficult. People are aware of this study because, for example, at least some of it has been presented at scientific meetings; I think there is an abstract from a scientific meeting that describes it. Many people are not quite clear what to make of this result, and there is uncertainty as to whether or not it represents an unusual form of prion disease. Without more detailed examination of the material it is very difficult. My understanding is that the illness in the macaques is more like motor neurone disease than prion disease, but I do not know the details. The implications of the study are known. For example, the Haemophilia Centre Doctors' Organisation knows about it, because they would obviously be a group who could be potentially at risk. If you were to extrapolate what has been said about the study, without knowing the details of it, and it was the same for humans, presumably you would look to see in humans if they had some form of motor neurone disease-like illness, and that would require a rather different methodology. Without having the published details, it is extremely difficult to comment. I know that people who have heard this discussed have some uncertainty as to what the study actually means.

**Q187 Stephen Mosley:** Professor Knight, I am afraid that my questions are mainly to you again. We had some powerful evidence from Ms Christine Lord, GRO-A GRO-A. We have had both written and oral evidence. She suggested that the NCJDRSU may have misclassified some cases after death. She named seven examples. They will be redacted in the evidence. I know you cannot talk about the specifics of the individual cases, but she claimed these seven cases had not been diagnosed as vCJD. Had they been?

***Professor Knight***: Obviously I do not know about the specific ones in that particular submitted evidence. I have been to her website and looked at the list of all the names on it. There are lots of people named on that website who indeed have definite or probable variant CJD. There is certainly one name on the website that has what we call possible variant CJD, although we thought it was very likely that the person had variant CJD. There were lots of names on that list who had proven genetic CJD, and lots of names on that list who had proven human growth hormone-related CJD. There are certainly names on that list who, as far as I know, have never been thought to have variant CJD, and therefore would not be included in our statistics.

There were also names duplicated on the lists. For example, in one version of the list someone was listed as having variant CJD and they were listed again, once under their married name and once under their maiden name. That may explain some of the confusion and duplication. There were also people who were simply listed as, for example, a 37-year-old housewife in Cambridgeshire. Of course, I have no idea what that means, so it is impossible for me to comment on it.

I suppose that the question you are asking is, in relation to what I have read on the website and in her book, have we deliberately misclassified cases? The answer is no. On the other hand, if I had deliberately misclassified cases, that is what I would say, but we haven't.

**Q188 Stephen Mosley:** You are in front of a Select Committee, so you are taking quite a risk if you are deliberately misleading us.

***Professor Knight***: I cannot think of any motive that I personally would have for doing that, to be honest with you. Our real aim along the way, by all of our overlapping methods and investigations, has been to make sure that we identify all the cases as far as possible. We would not want to do that.

If the question is whether we have misclassified cases accidentally, that is a bit difficult. It depends on what you mean. All I can say is that we have a case classification system and, like every disease, you have to make judgments. If I see somebody in a clinic and I decide they probably have multiple sclerosis, there will be a certain amount of doubt; if I say they probably have epilepsy, there is a certain amount of doubt. When we say that somebody probably has variant CJD, we think it is extremely likely that they have variant CJD, but, no, we are not 100% sure. If we say that somebody, on the balance of everything, is very unlikely to have variant CJD, it is very unlikely, but without actual final proof it is impossible to say. We think that the diagnosis of probable variant CJD is a very probable diagnosis  I wish my diagnoses of probable epilepsy or probable MS were as good as that. It is a very high degree of probability. We do our best to classify cases in a fair way. If we see somebody and we do not think it is variant CJD, but there is a possibility that it might be, we have a separate classification system for that, and we keep records of those people. There are not many people in that category.

If one makes the statement that there are 177 definite or probable cases of variant CJD, we have classified four people in the whole of this time as having possible variant CJD, and there have been one or two other people about whom we have had a great deal of uncertainty but, on balance, we think it is very unlikely that they have got variant CJD, but we cannot prove it without autopsy material, and not everyone has an autopsy. I do not

think we have missed huge numbers of cases; maybe one or two here or there—it's possible. If the cases have been misclassified accidentally, and inevitably, because of poor information, it is a very small percentage indeed.

**Q189 Stephen Mosley:** I want to ask you about the processes you follow to make sure you get that right. Before I do that, I have a couple of specific points that Ms Lord raised. Have there been any cases of genotype MV who have had vCJD?

***Professor Knight***: The answer to that is very simple. All definite and probable cases, as they are currently defined, who have been tested have been MM. Not everybody has been tested. The vast majority have been tested but not everybody has been. All definite and probable cases have been MM.

We have a possible case, as I think I gave you in written submission, who we think is pretty likely to have had variant CJD and who was MV. There are well-documented cases of variant CJD infection—at least we presume infection—for example, from a TMER study, haemophilia and the appendix study, who have been MV or VV, but no definite or probable case, as they are currently defined, has yet been shown to be other than MM.

**Q190 Stephen Mosley:** Does that mean that if someone was MV you would automatically rule them out from having vCJD?

***Professor Knight***: No, certainly not. That would be completely wrong. We have always been of the opinion that MV and VV individuals are likely to be infected. We have always been of the opinion that some of them will develop disease. We cannot know for sure, but we have always thought that was reasonably probable. We have always thought it is likely, on the basis of a variety of bits of data, that people with MV or VV, if they developed disease, would do it with a longer incubation period—we cannot be sure about that—so we would expect them to appear later. We have also been of the opinion, based particularly on certain animal experiments, that sub-clinical infection—genuinely sub-clinical infection, where people might never become ill at all during their lifetime—would be more likely in non-MM genotypes, but we have never for one minute said that people who are not MM would not get variant CJD. You look puzzled by that.

**Q191 Stephen Mosley:** No. There has also been a suggestion that an individual who died from vCJD infection might have contracted it via blood transfusion after the introduction of blood safety measures in 2002. Are you aware of that? Is there any evidence of that?

***Professor Knight***: When you say "after the introduction of blood—

**Stephen Mosley:** Someone who received blood transfusion after 2002.

***Professor Knight***: I am not sure about the specific case you are referring to, but the difficulty here is that the attribution of cause of prion disease is in general a matter of judgment. We know that there are lots of people who have developed variant CJD and who do not appear to have any risk factor other than the consumption of BSE-contaminated food, but there is no individual in whom we can prove that they ate a particular piece of contaminated food. It is impossible; we have no way of doing that.

Likewise with blood; it is not that we have had a unit of blood in which we detected infection, and that person has then been infected. When we first had a case who had had a blood transfusion from a donor who later went on to have variant CJD, and then they developed variant CJD, it seemed likely that that was the cause, but when we worked it out statistically it was not absolutely certain. But when we got the other two cases—indeed, one pair had been infected by a donation from the same donor—at that stage we were instructed that the odds of this happening by chance were about one in 100 million, or something like that, in which case you have to go along with that.

But there are people who have variant CJD and have had a blood transfusion in the past. Then they developed variant CJD, and the donor of that blood never developed variant CJD. The question is: is it possible that the person developed variant CJD because of asymptomatic infection in that donor, or is that just irrelevant? You have to make some kind of judgment on that score.

We looked at that carefully recently. I submitted a pre-publication paper to the committee, which is not in the public domain, whereby we tried to analyse all of our cases to see whether there was any justification for thinking that somebody who had variant CJD and had had a previous blood transfusion from a donor not known to have variant CJD could in fact have got it through blood transfusion. Our conclusion was that there was no very good evidence that any of those cases had obtained it through blood, but if you ask me whether it is possible, of course the answer is yes, it's possible.

**Q192 Stephen Mosley:** What controls are in place to make sure that you diagnose things correctly with vCJD, and is there any peer review of that?

***Professor Knight***: What happens in our unit is that we have a case, we collect information and we then classify the case according to a diagnostic classification protocol. That protocol has been published in peer review journals; it has been presented at a wide variety of scientific meetings; and it has also been discussed endlessly with international colleagues. There have been European collaborative systems in place for a long time now. When "Diagnostic classification of cases" appears on the committee agenda, it is one of those things that usually produces sinking hearts, because you know it is going to be a very long and difficult debate to try to get everybody to agree on the classification criteria. In the end, they are very rigorously discussed and reviewed, and we have come out with very robust ideas.

Those classification protocols are then put into practice. We apply them to patients, follow them up and see how well they work. Therefore, we revise them. We have had revisions of them. We revised them  I am trying to remember exactly when; I think it was 1998  to include 14-3-3 protein in the CSF. More recently, we revised them to include MRI; and we are about to revise them again to include other diagnostic tests. There is a great deal of rigour in that.

What happens in the unit when there are difficult cases  sometimes  there are  is that they are classified completely independently by me and my colleague, Professor Will. If we agree, that is fine, and, if we do not agree, we have to sit down and discuss the classification. Our whole methodology has been reviewed on more than one occasion; we have had meetings with the Department of Health, who clearly are our main funders, and

they have had external and international review members who reviewed our methodology, so I think it is fairly rigorous. We have close colleagues in the National Prion Clinic, and we meet monthly. We go through all the referred cases with the National Prion Clinic and discuss our diagnostic conclusions mutually. As far as it can be, I think it is a fairly robust process.

**Q193 Stephen Mosley:** You have talked about the increase in sporadic CJD. Is there any evidence to suggest that that might be at all BSE-related?

***Professor Knight***: There is no evidence to suggest that. I think there is a bit of evidence against it. For example, countries like Australia have slightly higher annual mortality rates for sporadic CJD than we do, which, if we were hiding variant CJD in our sporadic CJD, would be a bit difficult to explain. As I said, the annual mortality rates for sporadic CJD have increased in the UK, but they have increased in an extremely parallel way. I wrote down some figures in anticipation that you would ask me this. For example, over the same sort of period, we went from an annual mortality rate of 0.39 to 1.37 in sporadic CJD. That is a fairly big step, but Germany went from 0.44 to 1.1; Italy, 0.48 to 1.76; Canada, from 0.07 to 1.44, which is a huge increase; and Australia, where there is no scrapie or BSE, from 0.96 to 1.5. If you look at the mean rates for the UK, they are lower than Australia, so, if some cases of variant CJD are masquerading as sporadic CJD, it must be a tiny number.

***Dr Mead***: I agree with a lot of what Richard said. Having attended many of these monthly meetings where we co-ordinate cases, I do not have the slightest doubt about the integrity of the classification system. While there might of course be debates on individual cases, I think it is done entirely honourably.

However, I am not so confident that some CJD we are seeing could not be BSE-related. There are very strong currents going on here in terms of generally increased awareness of the disease and better ascertainment. The reality is that the vast majority of elderly people never even get a diagnosis of dementia, never mind seeing a GP to get a diagnosis, never mind seeing a neurologist. There are big questions. Massive under-ascertainment in the elderly could be going on. Over the last few decades there have been huge increases in CJD diagnosis in the elderly, and I do not think that process has come to an end. One can make international comparisons, but with all these currents going backwards and forwards, it is very easy to conceive of a proportion, which could be a significant one, of prion disease in the elderly, that increase being BSE-related. It is very difficult to be certain that is not happening. It would have to be a very large increase for it to be obvious, but that is my view in any case.

Perhaps you would allow me 30 seconds to make some comments about some other things Christine Lord said that are relevant to the MRC prion unit. She made accusations about blood samples that I would like to counter, if that is okay. The situation with blood samples is particularly complicated. There are very few; many of them are separated into different fractions, and those go into different tubes with different chemicals; and many of them have different consent requirements based on what the families or patients themselves told us when blood samples were taken. That puts a lot of binds on us in terms of how we can distribute those samples. I know from discussions with Professor Collinge, when Christine was keen that we move samples around to different companies that he

spent many hours trying to negotiate this with her in the context of some of the problems and constraints we had. We really do bend over backwards to try to take into account the wishes of loved ones who have donated samples.

**Q194 Pamela Nash:** I would like to continue the questioning about the relationship between the Government and the surveillance unit and patients. When a patient is referred to the surveillance unit, I take it they have already had a diagnosis, or suspected diagnosis, from their own clinician.

***Professor Knight***: Yes, usually, although clinicians sometimes ring us up—I am sure they ring up the National Prion Clinic to discuss a case they have not formally diagnosed or told the patient or relatives about, because they are a bit uncertain and want to know whether they should be thinking along these lines. When it comes to us, we try to visit the case personally, interview the family, examine the patient and collect all the clinical data. We do that only with the consent of the family. Clearly, a visit by the National CJD Research and Surveillance Unit cannot be undertaken with consent unless the family and/or the patient knows that CJD has been considered. Therefore, at that stage the clinician has told the family and/or patient that CJD is what they either think or suspect.

**Q195 Pamela Nash:** To be clear about that, the surveillance unit would never be in the position of being the first contact that family would get—to tell them. They would already know that from the clinician, so the first they heard of vCJD would not be from the surveillance unit.

***Professor Knight***: No. All I can say is that our unit's practice is that we would never be able to arrange a visit, speak to the family and all the rest of it without their consent, and initially that would be after they had been told what the suspected diagnosis is. Of course, it may be that the diagnosis is not confirmed; it may be just a suspicion. There are cases we visit that do not have CJD.

**Q196 Pamela Nash:** What is the next stage for you in contacting the patient and/or the family?

***Professor Knight***: Sometimes we are informed shortly after death. If it is after death, we usually wait a bit of time and then we contact the family through their GP and arrange a visit later on to speak to the family. If they are alive, through the local clinical services we arrange a visit to that patient on the ward, because at this stage they are almost certainly on a hospital ward somewhere. The local team arranges for the family to be there so we can see the family at the same time, and then we visit.

**Q197 Pamela Nash:** What training do members of staff of the surveillance unit who carry out the questioning and visits get to deal with what is clearly a sensitive situation for quite vulnerable families?

***Professor Knight***: Sometimes the visit is conducted by myself or Professor Will, in which case I suppose the only training that I can say we have had is that we have been dealing

with prion disease since 1980, and we have been clinical neurologists for 35 years. That is the only training we have had.

The junior staff who go out are usually fairly experienced trainees. They are obviously medically qualified; they have usually done two or three years of general medicine and a couple of years of neurology, so they have a lot of clinical experience in dealing with patients. Normally when we choose these individuals, we concentrate very much on their interpersonal qualities. We want people to go along who will be sensitive and good at dealing with patients, not simply people who are interested in the science of this.

When we employ a new person, we overlap so that for the first few visits they go with someone who has been doing this for two years, or one of us. They see how it is done and get some apprenticeship training, as it were, and then go on their own. Very often, they are accompanied by one of the unit's nurses. Both of them are very experienced senior nurses, one of whom had training in psychiatric nursing and one of whom had training in neurological nursing, so again they have a lot of experience of talking to people.

**Q198 Pamela Nash:** You will be aware that Ms Lord spoke about that relationship and experience in her evidence. Have you ever had complaints to the surveillance unit about the conduct of staff on visits to families and patients?

***Professor Knight***: I suppose I should be able to answer that question absolutely, but it is a long time. I cannot recall any time when I have had a specific complaint from a patient or family about a visit.

**Q199 Pamela Nash:** Is that something you would keep a record of?

***Professor Knight***: Yes, of course you would. There are times—I am sure Simon will say the same thing, because we discuss this at our monthly meetings as well when comments are made about things that have happened, but very often, when you look into it, it is very difficult to find anything that actually happened. The trouble is that sometimes it is very confusing. For example, in one particular incident somebody said something that was not quite right. When we looked into it, it was a member of the local clinical staff, not one of our units, but the patient's family got them all a bit mixed up. Sometimes it is quite difficult, but it is never anything major. I have never had anybody come back and say they found the whole process unacceptable.

Of course, we talk to our junior staff, because, after all, we are sending them out to other people's hospitals for two or three years, and they are seeing patients who are seriously ill and are going to die, and families who are very distressed. Doing that kind of job for two or three years has effects on people, some of whom are relatively young. We go into it in some detail. What they say is very much my own experience, and Simon will probably say the same thing. A lot of families like this process in a curious way; they find some kind of solace in going through the patient's life and everything that has happened, and talking about it. Quite often, you end up in little cul-de-sacs where they remember some kind of family gathering and you talk about that. A lot of them find it quite helpful.

On the technical side of things, from our point of view it is a joint deal. We want to research information, but we are also going to give them information. Simon would probably say the same thing. They get a lot of information from experts in their disease, which they would otherwise perhaps find difficult to get.

**Q200 Pamela Nash:** One other thing mentioned by Ms Lord in her evidence was that families had been asked not to speak publicly about the fact that their relative had vCJD, or about the specifics of the case—for instance, if the relative had given blood before. What is your response to that?

***Professor Knight***: That was probably the most astonishing thing. I have absolutely no idea as to the basis of that comment. I can categorically state of course, I cannot give you any evidence—that we would never ever give such advice, and, for the life of me, I cannot think why we ever would give such advice. I cannot think what on earth the purpose of that would be. Anybody who knows anything about me is hardly going to suspect me as an agent of the establishment.

**Pamela Nash:** What an accusation!

***Professor Bird***: In 20 or so years of dealing with TSEs, I have had nothing but absolute admiration for the quality of the work done by the CJD surveillance unit and for the protocols it has introduced that are adopted internationally. I have to say I found that evidence very surprising.

***Dr Mead***: I agree entirely with Richard. I find those comments completely surprising. We monitor very closely the work of the doctors in our team. I visit a lot of patients myself. I have never made a comment like that; I have never heard any of my staff or colleagues make a comment like that. I am not sure why on earth we would make comments like that, so I was completely surprised. I agree with the comments about complaints. We have a large file full of "thank you" letters, which overwhelm any problems there have been.

**Pamela Nash:** Thank you very much.

**Chair:** I thank the panel very much for their comprehensive responses this morning.