



Science and Technology Committee

Oral evidence: variant Creutzfeldt-Jakob Disease (vCJD), HC 846

Wednesday 27 November 2013

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Written evidence from witnesses:

- [Professor James Ironside](#)
- [Dr Roland Salmon](#)
- [Professor John Collinge](#)

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

Questions 1-46

Witnesses: **Dr Roland Salmon**, Joint Chair, Advisory Committee on Dangerous Pathogens TSE Sub Group, **Professor James Ironside**, Professor of Clinical Neuropathology, National CJD Research and Surveillance Unit, University of Edinburgh, and **Professor John Collinge**, Professor of Neurology at the UCL Institute of Neurology and Director of the MRC Prion Unit, gave evidence.

Q1 Chair: Thank you very much for coming in. Periodically, we look over the work of the Committee and what is happening on broader issues of science in Parliament. It was suggested recently that we should have a close look at the current picture on CJD, hence this morning's session. Can I welcome you and invite you first to introduce yourselves?

Dr Salmon: I am Dr Roland Salmon. I am a recently retired consultant epidemiologist from Public Health Wales NHS Trust. Currently, I am one of the joint chairs of the Advisory Committee on Dangerous Pathogens TSE Sub Group. We are the Department of Health-sponsored committee that deals with a number of questions around the assessment of the risk and management of these diseases.

Professor Collinge: Good morning. I am John Collinge, a neurologist and professor of neurology at University College London at the National Hospital for Neurology and Neurosurgery. I am also head of the department of neurodegenerative disease at UCL. I direct the Medical Research Council's prion unit, which is a research unit specifically set up at the request of Government to tackle the problems posed by BSE.

Professor Ironside: Good morning. I am James Ironside. I am a neuropathologist and professor of clinical neuropathology in the university of Edinburgh, and I am also based in the National CJD Surveillance Unit which has been in the university since 1990, and is funded by the Department of Health and the Scottish Government to undertake surveillance and research on CJD in the UK.

Q2 Chair: To start with some definitions for our benefit, perhaps one of you could explain to us how vCJD affects humans and differs from other forms of CJD.

Professor Collinge: This is a group of diseases known as the prion diseases. They are all associated with a transmissible agent in the brain known as a prion. It is an unusual infectious agent, in that it lacks its own genetic material and consists simply of an abnormal form of the body's own proteins. The different forms of CJD are all associated with prions. There are basically three different ways a human can get one of these diseases. There is so-called sporadic, sometimes called classical, Creutzfeldt-Jakob disease, which is present all over the world and occurs at random in the population. We do not know what causes it; it happens out of the blue. It affects one or two people per million in the population every year all over the world. It is a rapidly progressive and rather dramatic dementia, which kills people in an average duration of four months from the onset of symptoms.

There are acquired forms of CJD where you are exposed to a source of prions in the environment. The original example of this was the disease kuru in Papua New Guinea, which was transmitted by cannibalistic practices. In western societies, we have had iatrogenic CJD, where people have been accidentally exposed to prions through medical or surgical procedures. There are quite a number of such cases, and they have occurred worldwide. Variant CJD is also one of these acquired prion diseases. We know it is caused by exposure to the BSE agent—the same prion strain that caused the epidemic disease in cattle in the UK and elsewhere.

Thirdly, there are inherited forms of these diseases. It turns out that one of a number of faults—genetic mutations—in the prion protein gene itself, which you can inherit from one of your parents, can also result in the spontaneous production of prions and one of the so-called inherited prion diseases, of which there are about 30 different types.

Q3 Chair: That is a helpful starting point. What role do you play now, and what role did you play in the epidemic in the 1990s? Some of you touched on this in your introductions.

Dr Salmon: In the 1990s, I was working as a consultant epidemiologist for the then Public Health Laboratory Service, which was a network of laboratories in England and Wales that dealt with infectious diseases and their prevention and control. Working in Wales as such, I was responsible for advice to the then Welsh Office about the risk BSE might pose to human health. Under that rubric, I think that was the time my concerns about the zoonotic potential of this were first alerted, confirmed by the work of James, John and others subsequently in the decade.

Professor Ironside: As I said earlier, the CJD surveillance unit was established in the university of Edinburgh in 1990 as part of the recommendations of the Southwood

committee, which was set up by the Government in the previous year to look at BSE and its potential impact on human health. The aim, or the mission, of the surveillance unit is to identify and study all potential cases of CJD in the UK to see if there has been any change either in the number of cases or perhaps the nature of the disease from previous years. This was set up by my colleague Professor Robert Will, a neurologist, who had had earlier experience, in the university of Oxford in the 1980s, looking at sporadic CJD, so that was a baseline to compare the changes. Our unit was set up in 1990, involving clinical, pathological and other workers, and in 1996 we identified this new form of CJD, now called variant CJD, which affects a different age group from sporadic or classical CJD. They are usually much younger patients with a different sort of illness. It is not such a rapidly progressive dementia but a longer illness with different clinical features and different changes in the brain on MRI scanning.

The other big difference between variant CJD and sporadic CJD is the prion; the infectious agent is much more widely distributed in the body. In sporadic CJD the infectivity accumulates largely in the central nervous system, but in variant CJD it is present outside the central nervous system in organs such as the spleen, tonsils and lymph nodes—anything that has lymphoid tissue in it. It appears that the agent can replicate in these tissues at an early stage in the incubation period when the patient has no neurological symptoms.

In collaboration with Professor Collinge's unit and others, we identified that the agent had biochemical characteristics and transmission properties similar to BSE. We know that the tonsils and spleen are also infectious in individuals with transmitted infectivity. Therefore, with variant CJD it is a different clinical picture: they are younger patients and there is a much wider distribution of infectivity in the body, which gives rise to concerns about secondary transmission from blood and the tissues that are often the subject of surgery—tonsillectomy or appendectomy.

Professor Collinge: I first got involved in this field in the late 1980s when I was a postgraduate student with the Medical Research Council working on the genetics of these diseases. I set up a research group soon after at St Mary's hospital, part of Imperial College, to work particularly on the genetics of these conditions. I became increasingly interested in the emerging epidemic of BSE and the risks it posed to humans, and was involved in the diagnosis of some of the first cases of what turned out to be variant CJD. My research group demonstrated and published in 1996 that the prion strain causing variant CJD—prions come in different strains—was the same as that causing BSE in cattle. I was funded at that stage largely by the Wellcome Trust, but in 1997 I was asked to set up a Medical Research Council unit specifically to focus on this area, with a serious critical mass of individuals, both to understand the basic biology of these conditions and also to develop some practical solutions with respect to prion decontamination, the development of diagnostics and ultimately the development of therapeutics for these conditions.

I also set up a specialist NHS clinic to manage patients with all forms of these diseases back at St Mary's in 1997. This was designated by the Department of Health as the National Prion Clinic in 2001. Subsequently, my research relocated to University College in 2001 where I have been since. The National Prion Clinic continues there, and sees the

majority of patients with these diseases in the UK, in close co-ordination with the surveillance unit.

Q4 Chair: We recognise that there is a very significant amount of skill in front of us. With all your experience, do you think that variant CJD continues to pose a significant risk to public health?

Professor Collinge: Absolutely. The study published recently in the *BMJ*, which you will have seen, is the latest of a series of studies to try to determine the prevalence of silent infection in the community, and is extremely concerning. We have known for many years that these diseases are associated with very prolonged incubation periods. If you inoculate animals with these diseases, as we do in the laboratory, and study them, there is a long latent period when the animals are completely healthy before the disease develops. The same thing occurs in humans. My unit has studied the end of the kuru epidemic in Papua New Guinea for some years. We documented patients there with incubation periods over 55 years. That is when prions are being transmitted from human to human in the case of kuru. When prions are transmitted from one species to another, typically the incubation periods are much longer, so we would anticipate incubation periods in BSE transmission to humans extending, at the extremes, up to and probably beyond the normal human lifespan.

This is a long-term issue. It is not like a flu epidemic that comes and goes in a few weeks or months; it is with us on a long-term basis, and it has always been an issue. Right at the beginning, we had no idea how many people would go on to develop the clinical disease. Thankfully, so far at least it has been a relatively small number, but there have always been concerns that it is easier to cross the so-called species barrier in the periphery to get an infection but not go on to develop the disease. This is well established with many infectious diseases. You can become a carrier of a disease like cholera or typhoid and live a normal life, but you pose a risk to others whom you can infect. It is well established that you can induce these sorts of carrier states in animals, and it is very likely that the same will be the case in humans. We have seen, particularly from the recent study that the Health Protection Agency has done, that there may be a very significant carrier rate in the UK population at the moment. The estimate is one in 2,000, although there is a caveat in that we do not know the sensitivity of that particular test to detect such carriers. There is really no way of knowing that at the moment, so it could be a significant underestimate of the number of infected individuals. It is simply the ones picked up by the test that constitute the one in 2,000, so I think there is a significant problem. We do not know at the moment how many of those people will go on to develop the disease in the half century ahead in which this will evolve.

We also do not know the difference between people who develop the disease after a particular incubation period, and those who are long-term carriers, or what factors might trigger a change between those different states. All this will emerge over quite a long period of time. In the meantime, although carriers may live to 100 and not show signs of the disease, they pose a risk to others, because they will have high levels of infectious prions in their tissues and, therefore, could pass that on to others, for example if they are a blood donor, if their blood was used to produce blood products, if they contaminate surgical instruments, or if they are an organ donor. The risk of secondary transmission is

relevant to the large carrier pool of 20,000 to 30,000 people who now seem to be in the UK, according to this study.

Dr Salmon: In a sense, I am the generalist here, with two specialists. My work used to involve the investigation of outbreaks of infectious disease. In 1996, I went out and about with some of the doctors from Professor Ironside's unit as they went to see cases of variant CJD. The perspective from the bedside is that you would want to prevent as many cases as possible, because even on the scale of diseases that people get, it is a particularly devastating and unpleasant experience.

Is it a significant risk? If, by that, we mean are we likely to get a big number of cases, I remain guardedly optimistic that we will not. Could it go on and on? In other words, could it become self-sustaining through the kind of routes Professor Collinge was outlining? That is the concern, and that is why a lot of effort is going on to try to interrupt those routes of transmission, because ideally we want to get to a position where this simply dies out, and the sooner the better.

Professor Ironside: I share Professor Collinge's concerns. I was involved in the work in the paper published recently in the *British Medical Journal*. My colleagues and I did a study in the 1990s which found something similar, but in a smaller number of patients.

Q5 Chair: In your written evidence in all three cases there are a significant number of references to other people's work. We want to get to the bottom of whether your definition of "significant" is more than simply protecting the interests of your laboratory. Forgive me for putting it as bluntly as that. How widely held are your views, Professor Collinge?

Dr Salmon: Perhaps I may interrupt. I do not have a laboratory.

Chair: I know you don't—you can start.

Dr Salmon: I do not find my views too much at variance with those of my colleagues. To prevent this becoming a self-sustaining epidemic has to remain a significant concern for public health authorities.

Q6 Chair: Is that widely held across the profession?

Dr Salmon: Yes.

Q7 Chair: If a lot of leading scientists hold this view, is the response from Government at the present time adequate, or is there more they should be doing?

Professor Ironside: The Government have done a lot to try to deal with the threat posed by variant CJD transmission. For example, from the very earliest stages after we identified variant CJD, the national blood authorities did consider what the implications for their practices might be. This was before we had any knowledge that blood might be infectious in this disease, so they were highly precautionary. A large number of steps have been put in place to try to reduce the risks of the transmission of variant CJD through blood. There have also been other steps to reduce the risk of transmission through surgical instruments.

Some of these can be questioned, but transmission through blood is particularly important, and I think the measures in place are sufficient. We have had evidence of transmission of variant CJD by blood transfusion. So far there have been only four instances, and they all seem to have occurred before one of the precautionary steps—leukodepletion, the removal of the white cells in the blood—was put in place. It is very important that these steps should be maintained to contain the threat.

In terms of vested interests, I would be very happy if we had done a study and found a negative result and that there were no patients infected. I think that would be absolutely wonderful, but unfortunately that is not the case, and we have to accept the reality of the situation as we find it.

Professor Collinge: Similarly, I am sure I speak on behalf of my whole unit when I say that nothing would delight us more than the disappearance of variant CJD, and we have dedicated the last 15 years to try to develop solutions to these problems. James has pointed out some of the measures that the Department of Health have taken. I was involved in directly advising the then Health Secretary, Frank Dobson, on leukodepletion, which was an important measure, but the reality is that those measures taken on blood safety are of uncertain efficacy, and indeed uncertain necessity. We do not know whether they are required or are effective. What we need to do to manage this risk effectively is determine the level of risk in blood—I think that blood is the major issue in public health terms. To do that it is necessary to have a blood test. We do not infect each other by being exposed to appendix material; it is really blood that is the issue, and how many people are carrying this in the blood. A blood test has been a very important goal in this field, and a huge amount of research has gone into that worldwide. My unit reported the first such blood test in *The Lancet* two years ago. This test is now in clinical use at the National Prion Clinic. We use it for diagnosing variant CJD. This is a prototype test; it is not one that the National Blood Service could routinely use at this point in time, but it could probably be developed into that.

The next stage of looking at such a test is to be clear that it does not have a significant false positive rate before one starts doing other studies. With support from the Medical Research Council, we looked at 5,000 US blood donors, with samples kindly provided by the American Red Cross. They were all negative by the test, so there is not a high false positive rate with it. The next step we want to take is to compare a large sample of UK donors with a large sample of American donors—that is, comparing an exposed population and an unexposed population and seeing if there is a significant difference between them. If there is, that tells us two things: first, that the test is capable of detecting people carrying or incubating the infection, which at the moment we do not formally know, although it is likely from animal experiments; and, secondly, it gives us a first snapshot of what may be present in blood. If that was the result we found, it should create the momentum and perhaps the commercial business interest to turn that into a real high-throughput test, which is not something my laboratory or academics can do. Our attempts to persuade commercial companies to take that on have come to nothing, because at the moment they do not see a business case there. To my mind, this remains the key issue: first, to determine the extent of the problem and then to be able to manage it effectively. With such a test, infected units of blood could simply be discarded and would not go into NHS treatments. People having high-risk surgical operations where there is a risk of

contamination could be tested, for example. You would be able to manage the problem. You would know what it was and you would be able to deal with it.

It is a little frustrating that, having spent 10 years of my life at the request of the Department of Health developing these tests, it is stuck at the moment in a so-called valley of death situation: academics can take it so far and companies are waiting on the other side of the valley, but there is no way of getting across the gap.

Q8 Stephen Metcalfe: There have been a number of studies over the years, the most recent one being published in October of this year, showing the prevalence of carriers to be about one in 2,000. How accurate do you believe that particular study is compared with the others, and what makes a reliable study? What are the key indicators that can give us confidence that that is an accurate number?

Dr Salmon: The first thing to say is that that is a replication of an earlier study and gives a measure of the same order of magnitude. If part of the scientific method is to replicate the findings of others, that is precisely what has been achieved here. You are quite right: whereabouts in the evolution of the disease does deposition in the appendix take place, and what does that say about whether or not infection may or may not be present in the blood? In a sense, this is the point Professor Collinge made. He has a pessimistic take on that—that the appendix may underestimate the amount circulating in the blood. The fact that it has been replicated is one cause for us to have confidence. The second thing in place at the moment, which will reinforce that confidence if it turns out as expected, is to look at other populations that presumably were not exposed to the dietary epidemic, i.e. appendixes taken out before about 1980 or after 1996, which should take you outside the period when infection was more widespread in the food chain.

Professor Ironside: As Dr Salmon says, the results of the recent study in the *British Medical Journal* essentially replicated the earlier study that David Hillson and I did, and which was published in 2004. It was a very similar order of magnitude. What these studies are trying to do is estimate how many people in the population are infected with variant CJD but show no symptoms. How could we better ascertain that figure? We probably need more than one blood test; we need a screening test and a confirmatory test, as we have for other infectious diseases in blood transfusion medicine, but we do not have that.

The next best thing we can do is to look at tissues infected with variant CJD that are removed from otherwise asymptomatic individuals—the tonsils and appendix. The appendix seems to be the more valuable tissue in that case. It is not the best study we would like to do, but it is the only one we can do at present. The methods used in that study have been optimised and refined since the earlier study that we did in 2004, but, yes, we know it is not perfect. We found that some patients who died from variant CJD had had their appendixes removed earlier in their lives. We managed to find at least two of those appendixes and stained and tested them for prion protein deposition, and those were positive. So we knew on an a priori basis that you can detect abnormal prion protein in the appendix before the onset of neurological symptoms. What we do not know is exactly at what point in the incubation period this occurs. Is it very early in the incubation period, or is it later? If it is later, that might give you an underestimate of the total number, as Professor Collinge said.

We accept that the confidence intervals around these figures are large, but it is the best we can do at present until a blood test or tests are developed. It is not a very good comparison, but going back to the early days of HIV infection, before we knew what the virus was and before we had a blood test for it, how could we estimate how many people were infected? It was incredibly difficult to do. That is the kind of situation we are in, although we are probably a bit better because of the tissue prion deposition. I hope that is an answer to your question.

Q9 Stephen Metcalfe: Yes, thank you. We can have as much confidence as is available at the moment that this is an accurate number. Professor Collinge, you mentioned that one in a million people are infected and dying around the world. Is that correct?

Professor Collinge: Of classic or sporadic CJD.

Q10 Stephen Metcalfe: If the figure of one in 2,000 is accurate, what are the implications of that? Will the number of deaths from variant CJD increase in future?

Professor Collinge: We do not know the answer to that. My best guess is that the majority of those individuals will be carriers and probably will not show signs of the disease. There is quite a lot of work from animal models on inducing a carrier state—when prions jump from one species to another—but we cannot be confident in that. We do not understand why some people are carriers and some people just have a long incubation period. You cannot formally distinguish those things very easily, other than with the passage of time. We do not know, but we cannot exclude the possibility that there may be many more cases of variant CJD in the future.

The problem I am most concerned about at the moment is the fact that, regardless of whether these individuals are in the incubation period and will develop the disease in five, 10, 50 years, or whatever it is, or whether they will be healthy carriers for the rest of their lives and die of something else, they still pose a potential risk to others via iatrogenic transmission, particularly with blood transfusion. We cannot at the moment identify these individuals without a simple blood test.

Q11 Stephen Metcalfe: What is the worst case scenario in terms of increasing deaths?

Professor Collinge: The worst case is that all those individuals ultimately develop variant CJD. I am sure that will not be the case, because inevitably some people will die of something else given the length of the incubation periods. The worst case is that all these people will develop the disease if they live into their 80s or 90s, for example. Another aspect of the worst case is how many secondary cases will be spawned in the meantime by those people being blood donors, organ donors or tissue donors of various sorts, or contaminating surgical instruments. That is harder to quantify.

Q12 Stephen Metcalfe: You talked about having developed a blood test and needing to commercialise it. Presumably, that would go some way to reducing the uncertainty about prevalence. Are there other things we can do as well?

Professor Collinge: The blood test is really the only way to do that; it is the only readily accessible human tissue that you can screen in large numbers. You cannot screen large numbers of tonsils or appendixes in normal individuals, so it has to be blood to get the epidemiological information we want to manage the situation.

Professor Ironside: Research is going on elsewhere looking into the screening of other body fluids, of which urine is one. A group with whom we collaborate seems to be doing well in detecting prions in urine samples. Whether this will be scalable-up we do not know, but if we have more than one different type of blood test, or blood and urine, or blood and something else, it would really help to clarify the answer.

One thing we have not mentioned today is genetic susceptibility to variant CJD. The gene that makes the prion protein has a variable region at position 129, and there is what we call a polymorphism there. That polymorphism, which is a bit like polymorphism in blood groups for example, seems to affect susceptibility, or more precisely, the incubation period of these diseases. Of the patients who have died with pathologically confirmed variant CJD, all who have been tested for this polymorphism have belonged to one particular group—the so-called MM sub-group. The appendix study and other work we have done has shown that the other sub-groups, the MV and VV, are susceptible to infection, but the incubation period in these other genetic sub-groups may well be longer. Indeed, this is borne out by the work Professor Collinge did on kuru, which showed very long incubation periods in other genetic sub-groups. This is another factor we need to concern ourselves with when speaking about the worst case scenario. Some of that will be determined by genetic variability in the population.

Q13 Sarah Newton: I would like to carry on from my colleague and ask questions of Professor Collinge and perhaps Professor Ironside as well. Going back to the whole idea of a blood test, you very well described the point you are at—trying to cross the valley of death to get that blood test, or range of blood tests, to be able to detect prevalence. What more can the Department of Health do to enable you to cross this valley of death so that we have a blood test, or some blood tests, to help diagnose?

Professor Collinge: At a simple level, they could fund the next study. I was asked to see the then Public Health Minister, Anne Milton, and the Chief Medical Officer when we published the paper in *The Lancet*. We discussed the issues, and I explained what I thought the next steps were, which is what I have explained to this Committee. They were very complimentary about the science behind the test and congratulated me on it, but felt that it was now time to seek a commercial partner to turn it into a screening test that the National Blood Service could use. I explained that we had tried to do that with considerable help from MRC Technology, the organisation that helps MRC units like mine to seek commercial partners, but none of them was interested because there is not an obvious business case for them. They want academics to take it further and show that the test actually works to detect carriers, and that there is a problem there for which it is going to be used. That rather drew a blank.

At a simple level, this study can be done. It is straightforward. We just need to collect 20,000 samples. We have already been in discussion with UK Biobank, which has a large sample collection, and their committee has agreed that we can have access to their samples. The American Red Cross are very happy to provide us with 20,000 anonymous

American donor samples. It is just the logistics of doing all the testing, which involves people and money. It is completely straightforward, but to my mind it needs to be done.

Q14 Sarah Newton: It needs to be done. Roughly, what would be the time frame for that work, and how much would it cost?

Professor Collinge: It depends on how many people you put on it. We developed this as a laboratory prototype; we are not a company. It works very well; it is robust, but it is quite laborious to do in the laboratory. The whole study could probably be done in a year to 18 months and would cost about £750,000.

Q15 Sarah Newton: Have you been back to the Department since then? That was some time ago.

Professor Collinge: Yes, I went to see Sir Paul Beresford, one of your colleagues, who asked me to accompany him to see the new Public Health Minister, and we talked about this again. She wanted time to think about it. I have not heard from them again since.

Sarah Newton: When was that?

Professor Collinge: It was about a month ago.

Sarah Newton: Would anybody else like to comment on that before I move on to my next question?

Dr Salmon: I have a brief comment. The £750,000 Professor Collinge mentioned would help him develop further the work he is doing. I am not sure I know what bringing a test into widespread use would cost as a commercial development—I am not sure he does—but it would represent a cultural change for Government to be involved in a commercial development like that. It is possibly one that would require even more cultural change from the Treasury than from the Department of Health. I might share with you a little quote from our old colleague Professor Hugh Pennington, who many of you may have seen on the television. In the *London Review of Books* in 2000, he wrote that the Treasury's "dark presence lurks throughout the whole BSE saga as insidiously as the agent of the disease itself." I am sure that is hyperbole. None the less, while we should be very conscious of what would be a very helpful next stage, there is a stage beyond that in commercialisation that may yet also prove a barrier, and would also require perhaps a little bit of a cultural shift in the way Governments round the world choose to work these days.

Professor Collinge: I hear what you are saying, but I suspect that if you were to find the same numbers in blood that the HPA found in appendixes, and by doing so demonstrated that the test was capable of detecting those cases, there would be a clear momentum and case for a company to develop this. We suspect that the sort of development work a company would need to do, which would basically be to adapt our laboratory test to their proprietary platforms to allow high-throughput screening in National Blood Service laboratories, would cost in the order of a few million pounds. I am no business person, but if this were to be a test routinely used on millions of blood units per year, I think the business case would be fairly obvious. At the moment it is not, because they do not know

whether the test would detect such individuals, and they are not sure that they are there to be detected.

Q16 Sarah Newton: Let's assume for one moment that this blood test is developed. How would you see it being used? Clearly, there are two groups of people. There is the screening of blood or organs already donated before there is a secondary link passing over to someone. There is also a big question in my mind about testing people who may themselves be carriers. They face the diagnosis of something that is fatal and has no cure at the moment, and may not be exhibiting characteristics that will affect their health for many years to come. It raises quite a lot of ethical issues about how you would go about using that blood test.

Professor Collinge: You are absolutely right. The Department of Health has wisely done studies on that already, anticipating the arrival of a blood test. There are issues. The important thing is to exclude infected units going into the national blood supply—ethically, that seems to me to be quite clear—and to control other transmissions during medical procedures in the NHS.

In addition to the 20,000 or 30,000 people that the Health Protection Agency study predicts are infected and are carriers in the population at the moment, there are 5,000 or 6,000 people in the UK who have been notified by the Health Protection Agency that they are at increased risk of developing the disease as a result of receiving either blood from a person who went on to develop variant CJD or blood products that are implicated, or who have been exposed to contaminated surgical instruments. Many of these people want to know whether or not they are infected. They have already had their lives blighted by being told this, and told that the risk is essentially unknown. A number of these people have come to see me in clinic and asked whether they can be tested. We have not made the test we developed available in that situation, because I do not think we know enough for it to be a useful thing to offer people in clinic, but if we got the next stage of that information it may be that we could offer the test and provide some predictive value for people who want to know about their own lives.

Professor Ironside: I agree that the individuals who have been identified as being at increased risk of variant CJD would be a group to which this or any other form of screening test could be applied. The ethics of the situation you described are not entirely novel. If you go back to the earlier days of HIV infection before drugs became available to treat it, the question was: was it ethical to test individuals? Did you have to get the consent of the individual to be tested, because then you were giving them this burden of information which would not give them any benefit because they would get this terrible disease and die from it? That situation has changed entirely, so we do not know what might happen in the future for prion diseases in terms of treatment.

The Health Protection Agency considered these issues before and commissioned a survey from Populus, a copy of which I happen to have with me, and which I can share with you afterwards if you like. It looks at what the use of such a test and what its implications might be for different groups in the population. It has some quite interesting results, but that could be used as the beginning of a basis for wider debate on these issues. I agree that it is a very important issue.

Q17 Sarah Newton: We have focused very much on blood tests because they seem a lot more advanced. Professor Ironside raised urine tests. How quickly could they be developed? What are the barriers to them being developed? Could you talk to us about what more could be done to advance those tests?

Professor Ironside: Those tests are at an earlier stage than the blood test that Professor Collinge has demonstrated. They are being developed by a scientific collaborator with us in the USA who has looked at urine samples from patients with variant CJD, obtained with the necessary consents for research purposes. That work has been submitted for publication. It is under review at present, and we are just waiting to see what the outcome of that is. It is at an early stage, but I believe it shows potential promise.

Q18 David Tredinnick: I think I am right in saying that since 2009 there have been 12 probable or confirmed cases of variant CJD. What were the likely sources of the infection?

Professor Ironside: In the surveillance unit, we have identified three individuals who died with variant CJD, and who appear almost certainly to have contracted the illness from blood transfusion from a donor who was infected with variant CJD. I do not think any of these cases are in the recent group you mentioned, so the source of the infection in most cases of variant CJD in the UK, apart from these three cases, we assume to be oral consumption of meat or meat products infected with BSE. Because of the incubation period we discussed earlier and the fact that BSE contamination of the human food chain was likely to have occurred in the UK over a considerable number of years, it is not surprising that we have this time spread of cases, and as Professor Collinge says, we simply do not know how long this will continue. The cases we have seen so far of variant CJD may just be in those who are most susceptible and those who have the shortest incubation period from BSE exposure. For the other genetic sub-groups, we will have to wait and see, but, apart from the three I mentioned, we believe the others are all due to oral infection.

Q19 David Tredinnick: How sure can we be that the food chain is no longer infected with BSE?

Dr Salmon: I declare an interest here, which I did put in. I am a member of the board of the Food Standards Agency.

Substantially, we can have a lot of confidence, certainly in the UK-produced elements of the food chain, because diagnoses of BSE are now virtually absent in UK cattle. From a peak of 30,000-plus diagnoses in 1992, we are now down to literally two or three a year. It is a little bit of a scientific mystery, not to say scientific concern, why these two or three odd cases continue to occur, but the burden of infected material entering the food chain is now pretty much negligible. The law to prevent parts of the animal that could be infected going into the chain—the brain, spinal cord, dorsal route ganglion and parts of the small intestine—is very actively pursued by the meat inspectors of the Food Standards Agency. Indeed, in response to a reduction in the testing of cattle, they increased the number of inspections they were doing at meat-cutting plants and abattoirs to make sure that specified offals were not getting in. I for one feel perfectly confident about that.

Q20 David Tredinnick: Do you think the chances are that similar epidemics caused by animal-to-human transmissions will happen in the future?

Dr Salmon: Yes, I do. The one thing we learn from the emergence of different epidemics of prion diseases, be it kuru in New Guinea, chronic wasting disease of mule, deer and elk in the United States, transmissible mink encephalopathy, BSE or variant CJD, is that these prions are ubiquitous in nature. From time to time, they take aberrant forms that can lead them to clump together and be toxic, and problems can develop within a relatively short space of time. For all the ones I mentioned, you are probably looking at less than a decade, so it is part of prudent social management to have the scientific wherewithal to be able to confront new problems in infections of this kind wherever they emerge.

Professor Collinge: The key thing is that we learn the lessons of BSE here and do not reintroduce recycling of tissues within the same species. Whatever the source of BSE was, prions arise spontaneously in all mammalian species, as Dr Salmon mentioned. If you start feeding them back to each other, as happened with humans in Papua New Guinea from kuru, a prion disease epidemic is essentially inevitable over a period of time. The prions survive normal cooking processes. They survived the heat treatment involved in producing the cattle feed that fuelled the epidemic. It is important that we learn that lesson and do not relax the restrictions and start going back to doing it again, because inevitably a problem like that will arise at some stage in the future.

Professor Ironside: I emphasise my strong agreement with that point. A lot of these regulations are directed from Europe, not just in this country, and it is very important that that lesson is learned.

One other thing that has happened since BSE was identified is that screening for BSE in animals has revealed other forms of prion disease in these species that we did not know existed. There are now atypical forms of BSE; there are atypical forms of scrapie in the sheep population. I am sure that more will exist. If we allow recycling in these animals, it will amplify the problems, so that is a key part of the control.

Q21 Jim Dowd: Professor Collinge and Professor Ironside, you have already answered some of the questions that I want to look at in the case of secondary transmission. Before I do that, the phenomenon of the carrier, as I suppose you would call it, is not solely limited to vCJD. It is well known in typhoid and various other conditions. There are cases where, for example, the disease is carried in the female line but manifests itself only in the male line, and there are others. Has any work been done on carriers, in the sense of what it is they have which means they are immune to the disease but the disease is still prevalent?

Professor Ironside: In humans, it has been very limited. I mentioned genetic susceptibility and polymorphism in the prion protein gene. I believe it is more likely that the carriers in the population belong to the other genetic groups that have not been identified as yet with confirmed variant CJD. That is just one gene; there may also be others that have an effect. This has been better modelled in animals, and I would look to Professor Collinge for his views on that.

Professor Collinge: We have been studying it for some time. I am not sure that genetics is going to have a huge bearing on it. You can induce a carrier state in mice by crossing a species barrier in an inbred group of mice that are all genetically identical. It is relatively easy to do when you cross the species barrier. What the so-called species barrier means is that, although you can transmit prions from species A to species B, in practice it is usually quite difficult, thankfully. It is rather unpredictable. In two chosen species, the prions might jump relatively easily; in some it hardly ever occurs. In work done in my laboratory, which we published back in 2000, we were looking at this for a completely different reason. It was thought that prions from a hamster could not infect a mouse. It was thought to be a complete barrier and was the subject of some research interest. We did that experiment for a completely different reason, but when we infected a bunch of mice with hamster prions we found that none of them ever showed any signs of disease; they died of old age at the same range of ages as non-inoculated animals, but it turned out they were all infected and had very high levels of prions in their brains—in fact, similar levels to those in animals that had died of the disease. It became apparent that what we thought of as a species barrier defined in clinical terms was incomplete, and that it can be rather easier to cross these barriers than we previously thought.

But there is an additional step required to get invasion of the brain in a neurological disease, and that appears to be what we are seeing in humans. Becoming infected following exposure to BSE may be much easier than we thought, but, thankfully, developing the clinical disease still seems to be a rarity. We do not yet understand what mediates the transition between those two states, and that is an important area of research.

Dr Salmon: I think you asked the question in the spirit of infections more generally, including infections with bacteria and viruses, which are the sorts I am much more familiar with. It is very difficult to give a general answer because the biological properties of each of those different agents lead to different mechanisms in different circumstances. In things we do know—you used the example of typhoid—there is incomplete treatment with a number of viral infections; hepatitis is a good example. It is the age at which you are infected. Very young children who are infected often become lifelong carriers. There are clearly final common pathways in the immune system, but there is sufficient inter-organism variation that it is probably not terribly helpful to think of this as a general phenomenon.

Q22 Jim Dowd: Could you confirm that the only known cases of person-to-person transmission were the four back in the 1990s from contaminated products? Is that right?

Professor Ironside: Yes, that is correct. Three patients developed variant CJD and died from the disease. In the fourth infection, the individual died from an unrelated cause five years after the blood transfusion, but examination of the spleen and other lymphoid tissues at post mortem found evidence of prion protein accumulation, similar to what we were looking for in the appendixes. We have now transmitted the infection experimentally from the spleen of that patient. The patient had no neurological symptoms, was at increased risk because of receipt of a contaminated blood transfusion and died without symptoms of disease but yet was infected, and the spleen was capable of transmitting the infection. That is a very interesting case in point.

Professor Collinge: To add a caveat to these answers, we are talking about BSE causing variant CJD, which is the case. Variant CJD is associated with a particular strain of prions that had not been seen in the human population before, but studies we and others have done in so-called transgenic mice—mice that have been genetically engineered so they make the human form of the prion protein, in its two different forms, the M and the V form—suggest that BSE is able to trigger it. It has been known for a long time that these strains are not immutable; strains can themselves mutate. You can infect an animal with a strain and it will propagate a different strain.

This appears to be the case with BSE when we look at the human transgenic models. Sometimes BSE can induce the formation of different strains in all three of the different genetic types in humans. Often, these strains are seen in classical CJD. We have to consider the possibility, but I think the likelihood, that BSE will also trigger the production of what looks like classical CJD. It would not be called variant CJD because it does not have the characteristic pattern of neuropathology, or the characteristic biochemical features of variant CJD, but it is in itself related to BSE exposure. It is possible that some cases of what we call classical CJD are related to BSE exposure. The number of cases recorded in the UK of classical CJD by the surveillance unit has been steadily rising over a period of time. That is attributed in large part to the fact that we are getting better at diagnosing this disease. I am sure that is true in large part, but it is still possible that a proportion of that rise is related to BSE and, therefore, could also relate to secondary transmission cases as well as primary transmission cases.

Q23 Jim Dowd: It might be a mistake to say that the changes put in place subsequently, particularly those related to the blood supply, have not been 100% effective; it is just that we cannot identify it.

Professor Collinge: We do not know how effective. The principal protective measure was leukodepleting blood—removing the white cells from blood. That advice was given to the Department of Health on the best guess at the time, that infectivity was most likely to be white cell-associated. Subsequent work showed that it was present in all the different fractions in the blood. Leukodepletion is only going to be taking out a proportion of the infectivity, probably about half. Leukodepletion on its own is a good thing to do, but it is not solving the problem.

Q24 Jim Dowd: Generally, is it your view that the UK blood supply is free of variant CJD prions, or not?

Professor Ironside: I do not think we can give that guarantee. From the results in the recent *BMJ* paper, there are likely to be individuals who are identified as having prion accumulation in their appendix. We do not know who these individuals are because the study was anonymised for ethical reasons. The individuals could be blood donors, for example. We simply do not know. The blood supply could contain variant CJD infection. Will all that infection be removed by the steps put in place by the national blood authorities? These steps should result in a substantial reduction in that risk, although not complete elimination, so we have to be vigilant about that effect. It is part of our job as the surveillance unit to take a very close history of all sorts of medical procedures, blood donations and transfusions, and there is a particular study in place with the blood

authorities to look at this. We do not have a closed mind as to whether a disease just like variant CJD, or some other form of prion disease, could be transmitted by blood, so that situation is under constant review.

Q25 Mr David Heath: I should like to deal with surveillance for a few moments, so Professor Ironside is the obvious candidate for the first question. It seems to me you have a difficulty with this disease, with its long latency, in that, first, people die from other causes before the disease has a clinical dimension; secondly, there is a real risk of confusion with other dementias in old age. Are you satisfied that your surveillance system at the moment is giving you a reasonably accurate picture of what is happening?

Professor Ironside: In terms of variant CJD, we cannot be sure that we are identifying all cases, particularly in the elderly population where the differential diagnosis of a progressive neurological disease includes much commoner diseases such as Alzheimer's disease, Parkinson's disease and other related disorders. This has been the subject of ongoing debate with the Department of Health. To address that, we have submitted an outline proposal to the Department for a more targeted approach to the elderly, to look at whether some of the dementias occurring in the elderly might in fact be due to variant CJD. That is under consideration at present.

Q26 Mr David Heath: How would that help, unless we were able to do post mortem brain tissue examination?

Professor Ironside: When I say "surveillance", I mean the whole surveillance picture; it is not just saying, "This patient might have variant CJD"; it is following it up to autopsy. It might eventually include a blood test, urine test or whatever test became available, but now, because of the response of the NHS to the challenges of dementia, and the Prime Minister's challenge on dementia, the structures are there, because of the memory clinics and other things where elderly patients are being investigated better at an earlier stage in the illness. We can identify individuals who perhaps have more atypical forms of dementia and follow them up very intensively to see whether any of them might have variant CJD. They may well have other rare forms of dementia as well, but it seems to me a good opportunity, now that we have these structures in place, to undertake the investigation.

Q27 Mr David Heath: Would making vCJD a notifiable disease help?

Professor Ironside: This question has been posed several times before. Our view generally has been that probably it would not help. To make a disease notifiable you need to have a very precise disease definition. If we take the idea Professor Collinge suggested, that in individuals with different genetic backgrounds and different incubation periods the disease might be different, in the elderly it might be rather different from its manifestations in younger people, because of co-morbidities. That is another reason. In other countries in Europe where CJD has been made notifiable, it has resulted in a reduction of the numbers identified because of—how can I put this?—the lack of willingness of the medical profession to engage with regulatory authorities in terms of notifying the disease. If we have a professional-based voluntary system, it is more likely to achieve the goal than a compulsory one.

Q28 Mr David Heath: Would you both concur with that view?

Professor Collinge: Certainly, the differential diagnosis of dementia in the elderly is not done well in this country and most other countries. There is a lot of diagnostic nihilism: “What is the point of the diagnosis? You can’t do anything about it.” There are no effective treatments yet for any of these neurodegenerative diseases, although thankfully there are things on the horizon, including with CJD. I would be pretty cautious. We may well be missing significant numbers in the elderly. Given the way these people are investigated, I do not think it would often be picked up or differentiated, given that it is more likely to be called Alzheimer’s disease.

The other problem is the falling autopsy rate in this country. When I was a medical student and junior doctor, autopsies were carried out on a significant proportion of people. Now it is a rarity, so that last check on your diagnostic accuracy as a physician has gone, so I suspect we may be missing significant numbers in the elderly.

Dr Salmon: While I think I understand the human dynamic behind the falling post mortem rate, it is a considerable burden to try to understand what the accurate level of diagnosis among the elderly may be. Would notification help? As a doctor who has worked in public health and was therefore part of the regulatory process, if you have a good informal reporting network, as you have here, no, it probably would not. The problems start to occur when you get a more plural health organisation, however—particularly once you start to get more commercial elements. Indeed, countries that rely on notification often have to introduce it for those reasons.

Q29 Mr David Heath: I think the consensus I am hearing is that notification probably would not help, but, if we had an effective screening test, that would make a significant difference.

Professor Ironside: I agree with Professor Collinge that more needs to be done to explore the issue of variant CJD in the elderly by a targeted approach, including autopsy. As a pathologist, of course I would be very anxious to support that.

Q30 Pamela Nash: Gentlemen, both within your own areas of research and beyond, we are interested to know what key areas of CJD are being looked at going forward. We would also be interested to hear whether there are any areas that you think should be looked at where, as far as you are aware, research is not being funded at the moment.

Professor Collinge: Speaking as a doctor looking after these patients, for me developing effective treatment is the main thing I am concerned about. That is about half of what my MRC unit works on. This is very challenging. There are no treatments for any of the degenerative brain diseases. This is becoming a very serious issue, as I am sure you all aware, particularly with respect to the increasing numbers of patients suffering from Alzheimer’s disease as the age structure of the population changes. We are going to have to do something about this as a society. As you extrapolate these curves, it is clear that it is going to become unmanageable in the years ahead, so effective treatment that slows down

the onset of these diseases and ameliorates their symptoms is a very important target for western societies.

Q31 Pamela Nash: While we are on that subject, can you tell us more about how prion research might affect or increase our knowledge about Alzheimer's and related diseases?

Professor Collinge: Yes, absolutely. As to what is going on in these diseases, it turns out that one of our own proteins in the brain—the prion protein—changes its shape and sticks to more of the same proteins, forming aggregates or polymers. Essentially, it is a seeding process in the brain. You get seeds of disaggregated material which are able to grow and propagate, and this damages the brain. Some years ago this was thought to be something going on principally in the prion diseases, although there were some other rarities in which this phenomenon was seen, but over the last five to 10 years it has become increasingly apparent that this fundamental molecular process is going on in all degenerative brain diseases. In Alzheimer's disease, two proteins do this: one is called A-beta and one is called Tau; in Parkinson's disease, it is a protein called alpha-synuclein. They are different proteins, but the same process of seeding protein polymerisation seems to be what is going on. There is huge interest in this in the research community at the moment. You will hear people talking about prion-like mechanisms in Alzheimer's disease and Parkinson's disease, for example.

Apart from that generic similarity between the diseases, and therefore the potential for generic treatments of some of these conditions, there was a rather surprising finding, at least to me, from Yale university in the United States, published in the journal *Nature* four years ago. We know that in Alzheimer's disease what damages brain cells are things referred to as A-beta oligomers, which are small clumps of the A-beta protein. Things are toxic usually by binding to some receptor in the body which mediates that toxicity. The group at Yale was trying to identify receptors for this toxic material and found that one of them is the prion protein. It appears that the prion protein is a direct player in Alzheimer's disease itself, not just in terms of analogous molecular mechanisms. This is particularly important to my unit because we have been working for some years now to develop effective treatments for these diseases. Our target is the prion protein, so the drugs and antibodies that we have developed to hit the prion protein may potentially have a role in Alzheimer's disease too. There are a number of ways in which these diseases come together at a research level.

The treatments we have been developing are twofold. One is that we have been developing monoclonal antibodies to treat CJD. As you may be aware, the most important new drugs being developed now are not the classical small-molecule tablets; they are antibody treatments. We have shown that we can cure mice of prion infection by using these antibodies. The Medical Research Council funded us to genetically engineer the most suitable of these antibodies to turn it into a human version. You cannot treat patients with a mouse antibody because the human immune system will reject it. You have to make a human version of the antibody, which we have done. This antibody has now been manufactured and is going through safety testing with a view, we hope, to future clinical trials. That is very promising. These agents are extremely powerful in animal models. One of the advantages of working on prion models is that they are not really models. One of the difficulties in doing research into Alzheimer's disease is that animals do not get the

disease, so the experimental models that people use in animals are, by and large, not very good. Because animals get the same disease, we can be much more confident that if the drug works in a mouse it will work in a human.

The second line of research is to develop classical small-molecule drugs to bind to the prion protein and stop the molecular process taking place. This is a collaboration we have had for some years, funded by the Department of Health, with GlaxoSmithKline, the country's major pharmaceutical company. That is also producing very promising results. We now have small-molecule drugs that very significantly affect the progression of the disease in mice when taken orally. We have two potential treatments for CJD on the horizon, and the mechanisms by which these two treatments work are somewhat different. It is also possible that we may use these in combination in patients.

There are always safety concerns with any new medicine, but if the antibody proves safe in patients with sporadic CJD, on which we intend to conduct the first clinical trials, in principle, one could then use an intravenous injection with one of these antibodies to treat people who are infected, but before they showed signs of the disease. Therefore, these carriers or people incubating the disease could potentially be treated to eradicate the infection before it ever showed any signs. Obviously, you would need a blood test to identify those individuals, but it comes back to the ethical question: what is the point of telling somebody they have a disease you cannot treat? It may be that soon we will be able to do that and offer people a way of curing the infection so it never shows in the brain.

Professor Ironside: I would agree that progress in treatment of these diseases is very important. In addition to the work that Professor Collinge's group is doing, there are groups in other centres internationally that are doing this. It is very important that the results of these should be viewed in total, because it may well be that a combined approach as indicated will be important here.

However, even after we have treatment or screening tests, we also need to have better means of diagnosis of patients at the earlier stages of disease so they can start treatment before they become too neurologically damaged. We are working on a number of different approaches with new technology, some of it shared with colleagues in the States, to look at urine, blood and cerebral spinal fluid tests. We hope that that will aid early diagnosis.

As to the relationship with other prion diseases, I agree that there are likely to be common mechanisms. We know that Alzheimer's disease and Parkinson's disease spread in the brain in very predictable circuits, and in order to treat these diseases at an early stage, we need to inhibit the spread of disease, so we need new approaches to do that.

The problem in these diseases, as was mentioned, is that the animal models of the diseases in general are not very good. Obviously, they do not get the human diseases, so it is important that there are available samples of tissue from individuals who have these diseases for research so any finding in an animal model can be translated into the human situation at a very early stage. This early translation is very important.

Finally, although this probably sounds self-serving, the reality of the situation is that if we are to detect changes in variant CJD and the emergence of other diseases, we need to have an effective surveillance system in place for a longer term. Our current funding from the

Department of Health ends in March 2015. We are hoping that that will be continued, but that remains to be seen.

Q32 Pamela Nash: That was an excellent plug.

Dr Salmon: My interest is very much around prevention. We have heard about how the similarities between these diseases and others offer exciting possibilities for treatment and cure, but they also have implications for the prevention of a number of diseases. If we consider sporadic CJD, the orthodoxy is that somehow it is spontaneously genetic. You have heard these words today. Yet the cases of sporadic CJD in the UK are more clustered than you would expect to occur by chance, which implies that at least some may have an environmental cause.

If you look at work in Scandinavia, where they have complete health records and registries, you find that the rate of sporadic CJD correlates with the number of operations of all descriptions that people have had. There is a suggestion that at least a component of what we call sporadic CJD may be acquired from the environment somewhere. By that reckoning, given that these other diseases have similar mechanisms, and certainly can in certain experimental circumstances be transmitted among animals, we have to ask ourselves the question: could any of these other ones have environmental components such that, if we could identify them, we could reduce the proportion? When you are talking about Parkinson's disease or Alzheimer's disease, reducing it by even a small proportion prevents a lot of illness, because they are common. I offer that thought as a longer-term research aspiration.

I offer just a couple of observations about secondary prevention. One of the things that have intrigued me for years is the fact that the variant CJD cases we know about in the UK have an onset of 26 years and people die at 28 years.

Q33 Pamela Nash: As a lay person, what do you mean by “secondary prevention”?

Dr Salmon: Secondary prevention is where you are exposed to the agent in some way but prevent the disease from progressing, as opposed to primary prevention where you are kept away from the agent in the first place. In the UK, 26 to 28 years is the modal age of the variant CJD cases. It has been that from the start of the epidemic to now; it has never changed, which suggests that something at a certain age is relevant. The favoured explanation is that it is something to do with our immunological or genetic make-up. The slight downer to that is that one other European country that has a lot of cases is France. They have 27 cases, an appreciable number. The age of the cases there—diagnosis and death—has always been 35 or 36 years, so it is substantially different. The French are culturally different from us in a number of ways; I work with them and I know, but I never assumed they were genetically different. Here is an observed difference that is probably telling us something about what else is going on with us when we are exposed to food-borne transmission. I think there are things we could learn here.

Q34 Pamela Nash: That is fascinating. Is research going on into that at the moment, or is it something that you think should be explored further?

Dr Salmon: I certainly think it could be explored further. I know it is an observation that has been made by both James's unit and his French counterparts. I offer it up to you because it suggests there is a line of inquiry among all these diseases which says that, even if we cannot prevent exposure to the agent, there may be certain other things we can do to make people better able to resist infection.

Q35 Mr David Heath: With regard to the French, there is certainly a strongly-held view in animal health circles that there was massive under-reporting of bovine infection in France. Could that be relevant to what you are saying?

Dr Salmon: I cannot comment on animal reporting; I simply do not know enough about it, but the human surveillance has been very efficient for a long time.

Professor Ironside: We have very close collaborations throughout Europe. There are surveillance programmes in each country. We learn from one another's experience. There is a European umbrella of surveillance systems, if you like. My colleague Professor Will is very heavily involved in that and actually ran this. Looking in detail at what is going on in the cases in France and the UK has been under way for a while. What is the source of the French infection? Was it foodstuff imported from the UK, which was one theory? I was astonished that anyone in France would eat food imported from the UK, if you listen to their opinion of British food. You ask whether that was reported and I couldn't comment on that, but that is one theory under exploration. Although there are not any major genetic differences there may be other explanations, so we collaborate very closely with our French colleagues to answer that. It is a very interesting observation that has been known from the outset. The reasons for that are still not entirely clear, but a number of ideas are being pursued at present.

Q36 Pamela Nash: I would like more of an insight into the funding of research. Is it still mostly public funding? You mentioned a joint project with GlaxoSmithKline. Could you tell us a bit more about the private sector and charitable contributions as well, from your experience?

Professor Collinge: Most of my funding comes from the Medical Research Council, which provides core support for the unit, which is renewed on a five-year basis. We are just coming up to our renewal now. Our funding runs out in March 2015.

Q37 Pamela Nash: You have an opportunity to plug your financial situation as well.

Professor Collinge: It looks like we have the same cycle. Every five years we go through an intensive peer review process, and they decide whether we get any money for the next five years, and how much. We get money from other sources. The Department of Health have funded quite a lot of research, including the collaboration with GlaxoSmithKline that I alluded to. GlaxoSmithKline have not provided any cash in that collaboration; they have provided in kind support, which is of immense value. The money to employ my staff and run the laboratories at UCL has come from the Department of Health and MRC. GSK have provided us with an enormous amount of resource and expertise. They gave us access to their small-molecule library, which is the major asset of any pharmaceutical company.

There are 2 million drug-line compounds, for example, that we have screened at UCL. It is more in kind support.

I used to be a Wellcome principal fellow and they generously funded my research. When I became an MRC unit director I had to let that go; I had to make a choice, but virtually all the money for the unit comes from the MRC and the Department of Health. We still have some research funding from the Wellcome Trust but it is of a much lower order, and some other charities fund our research. Patient groups have been generous in supporting our research too.

Professor Ironside: Our funding for core surveillance is from the Department of Health and the Scottish Government. We have project funding from the Medical Research Council and we have some funders in Europe and North America, but this field is not one that the commercial sector is interested in funding. We have tried that and it just has not been successful.

Q38 Pamela Nash: Because of the numbers involved.

Professor Ironside: Yes. As John says, they cannot see a business case.

Professor Collinge: To complete the story, one thing I forgot to say is that our Department of Health funding has finished. The Department of Health have had a separate pot of money to support CJD research, which has supported colleagues in Edinburgh as well, but that has now finished. The funding we have had from them for our clinical research and therapeutic studies terminated six months ago.

Q39 Pamela Nash: Do you get funding from the Scottish Government?

Professor Ironside: The Scottish Government contribute 10% of the cost of the surveillance for CJD in the UK as a per capita contribution in terms of population size.

Q40 Pamela Nash: In that case, do you also get money from the other devolved Administrations?

Professor Ironside: I do not know what the arrangements for that are. I know that the Scottish Government contribute 10% of the cost to the Department of Health, and then we have a research contract with that Department. It is one contract, but it is supported by the Scottish Government.

Dr Salmon: To make a general observation, although I did bits of funded research in the distant past, I always worked in a service capacity, but I am conscious that the UK has an internationally excellent research base in these diseases, not just in personnel but in laboratories, animal facilities, cell lines, animal lines, reagents and all these sorts of things. My worry is that, if the funding disappears from this, we will simply lose all the benefit of that, and that will be a considerable lost opportunity cost. I hope it has become apparent that this is a research initiative that has a much wider relevance than simply the narrow area of variant CJD and BSE.

Q41 Graham Stringer: I would have thought pharmaceutical companies would have been beating a path to your door if you are on your way to finding a cure for Alzheimer's, Huntington's or Parkinson's, if there is a relationship between these prion diseases. Is that not the case?

Professor Collinge: It is not. We have talked to most of them, again with the help of MRC Technology. There is modest interest in supporting CJD therapeutics, for which there might be a business case despite the rarity, but it is going to have to be taken further within the public sector for that to happen. The next steps are phase one studies in humans where you look at whether the drug is safe to administer to humans, and how it is distributed in the body when you do so. You then go on to the next phase of seeing whether it works against the disease.

Any development of new drugs is an extremely risky business. More often than not, it is completely unsuccessful. The pharmaceutical industry have endless failures, despite the huge resources they can put into these things. For academics trying to do this, it is correspondingly more difficult. The message we have is that they want to see it go further; they want to see those phase one studies to show we have got safety data in humans and initial signs of efficacy that these drugs are getting to the target and doing something. At that stage, they may well come in.

I come back to the phrase “valley of death”, with which I am sure you are all familiar. It is a rather chilling thing to say in the context of what we are talking about here, but it is very real. The pharmaceutical industry are also very risk-averse at the moment. There have been enormously high-profile failures of treatments in Alzheimer's disease that have cost them hundreds of millions of dollars. The average cost of putting a new drug on the market is about £700 million or £800 million. Huge risks are involved here, and they want to take it further. They want academics to take it through to proof of principle in humans, not animals now, before they will get involved and make a major investment. This is a big issue. How we do this in the UK is something I discussed some time ago with the MRC. We have to tackle dementia in this country. The pharmaceutical industry worldwide are pulling out of this area because it is seen as being too difficult; they are not getting shareholder return; they are under pressure to deliver on things that make money. Increasingly, academics will have to fill that gap and identify the therapeutic targets, as we have done in prion disease. They are a very clear target to hit, but we have to be able to take it further than we have done before, because pharma will not partner with us at the early stage where it is still in the laboratory. We have to get it out there to patients ourselves.

As soon as you take drugs out of the laboratory and towards patients, the amounts of money are much, much larger. Work on the monoclonal antibody has been funded so far by the MRC. We spent £8.3 million developing and producing that antibody. In pharmaceutical terms, that is incredibly cheap. The average cost of getting such a drug to market is about £700 million to £800 million. We estimate that the full cost of doing the phase one and phase two studies to take it to a point where it could be taken up and licensed by pharmaceutical companies is about another £15 million. We have applied for that money through the MRC's translational medicine and DPFS schemes, but the feedback is that this is high risk; it might not work; and it is a lot of money. All these

things are true in an academic environment, but we will never get anywhere unless we try. I should say that all these things were apparent when we started the project in the first place. Any attempt to develop a new drug for anything, let alone a novel treatment for dementia, is fraught with risk. We must have a different attitude to risk in public funding in the UK if we are going to get any solutions to the problems of dementia. It is no good getting people like me to spend 15 years developing these things and then say, "Well done, but now it's quite expensive. Go off and find a pharmaceutical partner." Pharmaceutical partners just will not partner you at that stage. At the moment, I am spending a lot of my life going round speaking to philanthropists and venture capitalists to see if they will help me get across the valley of death. So far, that has been completely unsuccessful.

Q42 Graham Stringer: To change back to David Heath's question about the reporting of variant CJD, Christine Lord in *The Sunday Times* said she believed there was massive under-reporting of it. What would be your response to Mrs Lord?

Professor Ironside: I can speak on behalf of the surveillance unit which is responsible for providing the figures to the Department of Health. My response to Mrs Lord would be that we are not concealing any information on variant CJD, or any other form of CJD. I would like to know the basis of her anxieties, so we can provide reassurance. We are completely open and transparent in how we report the information to the Department of Health. The figures we have provided are as accurate as we can possibly make them.

Q43 Graham Stringer: You talked a considerable amount, very helpfully, about contaminated blood leading to further infections. At the beginning, you mentioned contaminated surgical instruments. I was not clear what you were saying was the current situation in hospitals about contaminated surgical instruments. Are you satisfied that that problem is being dealt with?

Professor Collinge: Certainly not. This is a significant problem, evidenced by the fact that, a little over a decade ago, the Department of Health set up a directed programme and encouraged many groups to do research to develop novel means to decontaminate surgical instruments. Many projects were funded; there were probably 20. I think they spent over £10 million on this. My unit had one of those grants to do this. It turns out that prions stick very avidly to metal surfaces. When they are on there you cannot get them off. Experimentally, it is a very efficient route of transmitting the disease. We now use it in the laboratory. The basis of the blood test we have developed is getting the prions to stick to metal powder first before we detect them with an antibody, so ironically we use its affinity for surgical stainless steel to develop the blood test.

This is a significant problem. Prion diseases have been transmitted by contaminated surgical instruments. We know it can happen. In classical CJD, the prions are nearly all in the brain and spinal cord, and most surgery does not involve those tissues. In variant CJD, the prions are all over the place. A lot of them are in the so-called lymphoreticular tissues, like the tonsil, spleen, appendix, as you heard, and indeed blood, so a much wider range of operations is potentially implicated in risk here.

The research programme that I mentioned to you resulted in several solutions and products were produced, one of them by my unit. Here we were successful in getting a company

interested in it. DuPont picked up our technology and converted it into a product. Neither this nor the other products that were available, of which there were three, has ever been taken up by the NHS; they simply have not been used. These issues have been bounced around various committees, to the great frustration of me and others. The solution we developed was a combination of enzymes and detergents, if you like a sort of bespoke biological washing powder, which very effectively prion-decontaminated metal surfaces. We thought we were doing this in a simple way. It simply involves a pre-soak. We put the instruments in a bucket or whatever container of hot water and add a sachet of this material. We designed it to work at 50° C, which is the temperature at which water comes out of hot taps in the national health service. It is pretty simple with cheap ingredients. We spent five years on this, and it has gone nowhere. There were questions about it; it was said, “We don’t like it as a pre-soak. We will have to change our working procedures. We would like it to go into the hospital washer-disinfectors.” This could be done, but DuPont and other companies were simply not willing to invest in that given that the initial product got absolutely nowhere.

As far as I am aware, none of these things was bought at all in the NHS. It is perhaps not surprising. Many of you will be aware that the NHS is notoriously resistant to change and the introduction of new methodologies. Experience at local hospitals is, “We don’t want to do this because it will mean we will have to change our rotas. Doing these pre-soaks and things is all a bit difficult.” Why should they do it? It is an additional expense and inconvenience, and there is no central direction now to do this. The Department of Health do not tell people to do this, although they do with MRSA and C.difficile, following public outcry about those things. As for prions, they have never really told hospitals that they have to tick this box and they will be inspected to see whether they have done a proper risk assessment and, if necessary, they have used one of these products.

Absolutely nothing has happened despite all this research and effort. Currently, several hundred people have been notified that they have been exposed to surgical instruments. When James’s unit or my clinic identify a patient with CJD, one of the first questions we ask is, “Have you had any recent surgery, medical procedures or dentistry?” They often have and a look-back has to be done and a risk assessment made. If it is a significant incident, the patients exposed to those instruments have to be notified; they are not allowed to be blood donors. You are blighting those people’s lives. All of this has been avoidable for some years by applying research which the Department of Health have themselves funded. I find it quite extraordinary. The system of communication between Whitehall and the hospitals to say, “Look, this is a problem,” just does not work. The Department of Health acknowledge the problem; they have the CJD incidents panel reviewing every case. To give a typical example, if someone has developed CJD and it turns out they had an endoscopy of their intestine the week before, the hospital does not know which endoscope was used, so all of the hospital’s endoscopes, at £30,000 a time, have to be quarantined. It is not as though people do not acknowledge there is a risk here, but the solutions which have been produced with public money are just left on the shelf and companies have now discontinued manufacturing it. It is extraordinary.

Q44 Graham Stringer: Of the many extraordinary things you have told us this morning, to my mind that is the most extraordinary. I do not want to put words into your mouth, but you

are saying that 200 cases of patients being infected by contaminated instruments have been identified.

Professor Collinge: Not infected, exposed. They have had to be notified that they have had a significant exposure to prions, because they are then expected to take certain precautions. They are not allowed to be blood donors. If they go on to have surgery, they have to notify the surgeon that they are a high-risk individual. Needless to say, this has a major effect on their lives, and quite a number of these patients come to my clinic for counselling. It makes me very angry, because all of this was avoidable.

Dr Salmon: Perhaps I had better say a word or two about how the process works. I certainly do not wish to cast myself in the role as an apologist for the Department of Health here, but there are perhaps one or two elements that it would be helpful to share. When it was acknowledged that transmission could take place by surgical instruments in the late 1990s, the CJD incidents panel was set up. This was broadly to address the circumstances where surgical instruments had been used on someone who went on to develop CJD and they were subsequently used on other people. Based on information from animal experiments and a certain amount of mathematical calculation by inference, because that was all that was available at the time, where it was felt that the risk to those who had had the surgical instruments used on them was more than 1%—an entirely arbitrary figure was chosen, but none the less one that stood the test of time—they were deemed “at risk for public health purposes”. They were approached and counselled to tell their healthcare providers, not donate blood and so on. I think that originally 375 people came under that rubric, and that number, with the passage of time, has gone down to 275 or 300. If we had had a blood test in those days, that would have made life hugely simpler.

I do not think it is fair to the Department to say that nothing was done. At this point, they took a very keen interest in the way the whole decontamination process was working in hospitals. Having turned over the stone, they found a number of things they did not like and, as far as I understand, instituted a number of general improvements within hospitals. You would have to talk to the decontamination scientists properly to get chapter and verse on this, but they tell me this and I have no particular reason to disagree.

With regard to specific products, it is perfectly true that they have not introduced any. I understand John’s frustration with plural committees around which things can circulate. I had understood that DuPont had been in dialogue with the Health Protection Agency, now Public Health England, about the commercialisation of this product, and that was where things rested. I am told that the barrier was having the product composed in such a way that it could be introduced into what is, in effect, a rather industrialised process that has to do a lot of instruments in a cycle. I appreciate his frustration. It certainly appears that the basis of a considerable development did exist here.

Professor Collinge: That is right. For the reasons I have given, what we had developed was seen to be inconvenient. They preferred to have a product that would go into the existing washer-disinfectors. That could readily have been done. For technical reasons, it required reformulation, which was beyond the competence of my unit, to do with surfactant technology and foaming in washing machines, which is not what we are expert in, but there was no commercial case. After all this work had been done, the NHS did not buy a single unit of that product. Is it surprising that the manufacturer just walks away? I think it is extraordinary. This has been bounced round I do not know how many

committees with all sorts of acronyms, sub-committees and working groups when patients are still being put in this position. People are having their lives blighted by being told they have been exposed to a contaminated endoscope, surgical instrument or whatever. I think it is disgraceful.

Q45 Graham Stringer: That leads into my next question. When I knew you were coming this morning I had a look at the Phillips report. One of the key issues in that report was how well the Government responded to scientific advice at the time of the BSE scandal. How have the Government acted on advice? You have just given us one example where it has not been so good. SEAC has been dissolved and the issue passed to the Advisory Committee on Dangerous Pathogens. Has that had an impact? Can you tell us a little bit about how you believe the Government are taking advice in this area?

Dr Salmon: I currently find myself as acting chair of the Advisory Committee on Dangerous Pathogens. This is a committee with a long pedigree. It started off as the Dangerous Pathogens Advisory Group, following the 1978 Birmingham smallpox outbreak. It has evolved down the years to deal with a variety of threats. I think it represents a reasonably natural home for dealing with agents like prion disease, particularly since we can set up sub-committees to attract expertise. I allow my colleagues to contradict me. I do not think that as a committee it functions any worse than SEAC did in the period I served on that committee. So far, so good.

There is a genuine problem, shared in a number of the scientific committees on which I sit, in getting the perspectives and time scales of science absorbed into the government mechanism. Governments, quite understandably, work on electoral and news cycles which are rather shorter. The sort of things we are talking about, which inevitably have time periods of 10, 15 and 20 years before they come to fruition, find it harder to get ministerial attention. I do not know the answer to that, but I do not find that to be specifically an issue with prion diseases.

I would hope that the ACDP provides a reasonably natural home for discussion of these sorts of elements. My personal experience is that it does, but, rather than take my word for it, perhaps through you I should pass the word to my colleagues.

Professor Collinge: Mercifully, I have not been on any of these committees for several years. I served on SEAC for many years, including during the crisis. It had its strengths and weaknesses, but when it emerged from the crisis it was a committee with a huge amount of experience and expertise, and it included some scientists of great international distinction. It was a shame that it was disbanded, and I did not see the point of it. It can hardly have been very expensive. We did not get paid very much, if at all. That was a bit of a shame, although some of that expertise is passed on to Roland's committee.

As to how the Government deal with scientific advice generally, we could spend the rest of the day talking about this. Getting thrown into the BSE crisis, and seeing the extremes of this, has certainly been very educational for me. One extreme was when the crisis was breaking on 19 March 1996. I was called back from a meeting in Paris to come to an emergency meeting at the Department of Health and, in an underground incident room, we discussed what needed to be done. There were only four of us there at the time. We came up with four options of increasing severity of what needed to be done. Thankfully, what

we eventually recommended was probably, given the benefit of hindsight, the right thing. What was very insightful to me at that moment was that we sent these four suggestions across the road to Downing Street. They came back to us and said, “We don’t want four options; we want you to tell us what to do.” I must say that the scientists felt rather uncomfortable at that point. Clearly, it is for scientists to advise and for Ministers to decide, but we now seem to have gone to the other extreme where there is a lot of scientific information.

I find it hard not to use the age-old cliché about things not being joined up, but that is what I have been describing. Research gets funded. You go away for several years and come back with an answer. Often, officials seem to be rather surprised that you have come back with an answer, but then it simply does not go any further. It goes round and round various committees, sub-committees and working groups, and nothing ever seems to happen. If it gets anywhere near the NHS, getting them to take anything up is a challenge in itself. For me, the big problem at the moment is not that the Government do not listen to scientific advice, but that the mechanisms of how these things are translated through to improved patient safety and care in the NHS simply do not work.

Professor Ironside: I declare that I was a member and deputy chair of SEAC for a while. I am now on the ACDP TSE group. It is not just SEAC that has disappeared. Other bodies like the CJD incidents panel, which dealt with the question of patient exposure to contaminated surgical instruments, no longer exist. That has left a gap. More worryingly, given the long time scale and history of these diseases, as these bodies are moved, there is a lack of memory and understanding of how we got to the position we are in now. You tend to get questions like, “Why don’t we do this?” The answer is, “We thought of that six years ago and it doesn’t work as a strategy.” There is a need to focus expertise in this and to make it more relevant to the needs of the NHS.

I share the comments about joined-up thinking. Various groups like that concerned with decontamination have been set up. I have no idea where that has got to. We asked a question about it at the last ACDP meeting. We need to have a report on what that group is doing and where it has got to. There is a lack of joined-up thinking. There is a lot of activity; it is just that I have no idea where it has got to and where it is going in terms of uptake by the NHS or Department of Health.

Chair: We will ask them.

Q46 Graham Stringer: Clearly, this is a problem of communication. What more could the Government do to reduce the public health risk from variant CJD?

Professor Collinge: I come back to the point I made earlier. The most important single thing that could be done is to develop an effective blood screening test which is properly quantifiable—the problem is that we are not reliant on mathematical models so we can measure what is going on in the system—and then institute proper risk management. That is the fundamental change. There has been unanimity on the advisory committees for years; it has just been very technically difficult to do.

Professor Ironside: I agree with that. I go back to the discussion we have already had about dementia in the elderly. This is a huge problem, of which CJD is a part. It is

essential that there is early and accurate diagnosis, and that is a huge challenge that faces not just the UK but many other countries. The UK has the added challenge of variant CJD that most other countries do not have.

Dr Salmon: Aside from the two elements my colleagues have remarked upon, I am not sure that more needs to be done to maintain progress now. I am worried about this quiet forgetting about what we have learned and things slipping back. We are already having discussions, inspired by the European Union, about whether we should be feeding fish proteins back into the food chain. There is a robust discussion going on about whether or not the UK should be allowed to produce de-sinewed meat, or whether it is mechanically recovered meat.

All of these things taken in isolation can be done in such a way as to be safe, but one wonders about two things: first, what the cumulative effect of all these different changes may turn out to be; and, secondly, if we consider de-sinewed meat, just how easy it is to police it so that authentically you get what you say you are getting. One thing we learned from horse meat, if anything, is that food authenticity needs quite extensive policing. I worry that, as this recedes into time, we will in a sense start to forget the lessons we have learned and simply set up the circumstances for a related but possibly different problem.

Chair: Gentlemen, we have gone considerably past our intended time with you because it has been particularly interesting. Thank you very much for your evidence this morning. The Committee will now go into private session.