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THE FOUNDATION FOR SCIENCE AND TECHNOLOGY

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Towards novel tests for TSEs

A new technique developed by three scientists at the Serona Institute at Geneva may become the basis for more sensitive tests for abnormal forms of prion proteins, that responsible for BSE and vCJD in particular. What they have shown is that the abnormal (and infectious) forms can efficiently catalyse the conversion of normal into infectious protein in laboratory preparations if these are subjected to brief pulses of sound waves for 5 seconds every hour.

In experiments with brain tissue from hamsters infected with scrapie (the common TSE of sheep), the authors of the research have found that after 5 cycles of sonication, 97 per cent of the abnormal protein has been newly converted from the normal form. They also describe one experiment in which brain tissue from an infected hamster was diluted 10,000 times, but still gave detectable amounts of abnormal protein after 10 sonications.

Significantly, the research may also point to some of the reasons why previous attempts to replicate the conversion of normal into abnormal protein in the laboratory have been relatively unsuccessful. The experiments now described have used samples of brain tissue made homogenous in a blender rather than chemically purified preparations of the prion proteins. The explanation, the authors say, may be that there are factors in the whole brain that assist the conversion from normal to abnormal protein.

If that finding is confirmed, it will be a matter of some importance in the understanding of the mechanism of the TSEs to identify these unknown factors.

The authors' interpretation of their own technique is that sonication breaks up aggregates of abnormal prion proteins, thus increasing the chance that normal protein molecules will make contact with abnormal molecules and so be themselves converted into the abnormal forms.

As described, the sensitivity of the technique is estimated to be between 10 and 20 molecules of the abnormal protein (scrapie prion in hamster brain), but the authors say there is room for improving on the antibody technique used for assaying the outcome of the experiments, while it is clear that the laboratory conditions have not been optimized.

Source: Gabriela P. Saborio, Bruno Permanne & Claudio Soto, *Nature* **411**, 810–813 (2001).

Towards therapy for TSEs

The prospect that prion diseases such as BSE and even its human equivalent, Creutzfeldt–Jakob Disease (CJD), may be susceptible to treatment is raised by two separate development in the past few weeks, each of which involves as a prime mover Professor Stanley Prusiner from the University of California, San Francisco. Prusiner was the one who in the early 1980s insisted in the face of widespread scepticism that protein molecules such as prions are capable of causing infection. He was awarded a Nobel Prize for his work in the field a decade later.

In an article in *Nature*, Prusiner and colleagues from the Scripps Institute at La Jolla, California and the Department of Biochemistry at the University of Oxford show that antibodies again the normal form of a prion protein can prevent the formation of the aggregates that are characteristic of fatal prion diseases.

Although the experiments have been carried out with immature nerve cells of mice kept in laboratory culture, there is good reason to that they may be applicable in intact animals, perhaps even in people. The antibodies used in the experiments described are made artificially by genetic manipulation, which has the advantage that different parts of the prion molecule can be singled out as the operative parts. That in turn offers the advantage of suggesting which regions of the prion protein may be the best targets for the development of therapeutic drugs.

Meanwhile, on of the surprises of the experiments described is that the use of particular antibodies not merely prevents the conversion of normal to abnormal prion structures but also clears aggregations of abnormal protein from infected cells. The authors break with convention by using the word "cure" in their discussion of the possible application of their finding. They also discuss at length the difficulty of using antibodies, notoriously incapable of crossing the blood-brain barrier, in the treatment of intact animals infected with prion disease.

Prusiner is also one of the two principals in a drug treatment of a British patient diagnosed as suffering from vCJD, the human form of BSE. The experimental treatment, apparently devised after a random pharmacological test of drugs known to cross the blood-brain barrier, consists of treatment simultaneously with the anti-malaria drug mepaquine and the anti-psychotic chlorpromazine, variants of which are widely used in the treatment of schizophrenia. The patient treated in this way is said to have improved, but another (unidentified) is said not to have responded.

In Britain, the Department of Health said on 15 August that British patients would be offered the opportunity of access to this as yet unlicensed treatment.

See David Peretz *et al.*, *Nature* **412**, 739–743 (2001).

Slow decline of BSE?

The slow eradication of BSE from the British cattle herd is suggested by results of tests carried out on the brains of 10,032 cattle over thirty months old and slaughtered during 2000 and kept out of the food chain in Britain under current regulations. The Department of the Environment, Food and Rural Affairs (DEFRA) announced on 10 August that 0.42 per cent of the sample of brains showed evidence of BSE infection. This compares with an incidence of 0.45 per cent in samples collected during 1999. The difference is not statistically significant.

The interest of this development lies mostly in the development of techniques for testing for BSE. Most of cases of infection (39) were found by histopathology, which recognises lesions in brain tissue, but the others (2 in total) came to light in 'western blots' which recognise the presence of abnormally folded prion protein molecules even when they are not visible microscopically. A third case of infection was found by a putatively more sensitive test whose reliability has not yet been approved by the European Commission.

DEFRA press release, 10 August 2001

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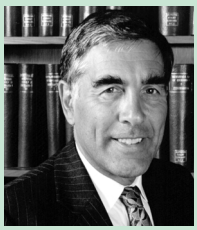
Lessons from the BSE Inquiry

by Lord Phillips of Worth Matravers

The BSE Inquiry — Implementing the Lessons Learned

The lessons learned from the 'Phillips Report' on the bovine spongiform encephalopathy (BSE) crisis were discussed at a meeting held on 3 April 2001. First speaker was inquiry chairman, Lord Phillips of Worth Matravers. The Chief Medical Officer, Professor Liam Donaldson, and the Chief Scientific Adviser, Professor David King, gave personal views of how Government was responding to the challenge. Extracts from a note of the general discussion, taken by Jeff Gill, are included with the accompanying text.



Lord Phillips of Worth Matravers

Now Master of the Rolls, Lord Phillips has been a Lord of Appeal in Ordinary since 1999. He was appointed to the High Court Bench (Queen's Bench Division) in 1987 and a Lord Justice of Appeal in 1995.

When my Committee's Report into BSE was published, I resolved that I would leave it to speak for itself. I have broken that resolution because of the object of this meeting. Having devoted nearly three years of my life to BSE, I thought it would be churlish to decline to assist in identifying the lessons to be learned from it. But I feel rather as if I have entered the lion's den.

We were of course looking at events up to March 1996. Lessons have been learned since then and, as we conducted what was a very open inquiry, lessons continued to be learned as we went along. I know that what I have to say will to some extent be a history lesson. Not altogether though.

When I accepted your invitation, I little thought that this country would once again be grappling with a major animal epidemic. Perhaps in the future someone will be asked to produce a report into the outbreak of foot and mouth and the adequacy of the response to it. I shall be interested to see to what extent lessons learned from BSE have informed the response to foot and mouth. Two points we made in our report may well prove particularly apposite: "An effective system of animal disease surveillance is a prerequisite to the effective control of animal diseases…. An effective system of passive surveillance will depend on farmers and their veterinarians having the incentive and the facility for drawing instances of animal disease to the attention of the state veterinary service."

As I have read of the proliferation of the identified foot and mouth cases all over the country, I have had a feeling of *déjà vu*. On BSE we concluded that the infection must have been spreading over a substantial period during which individual cases were passing undetected. Foot and mouth differs from BSE in having a very short incubation period. Nonetheless, I cannot but wonder whether the epidemiologists will conclude that cases of foot and mouth must have been passing undetected or unreported for a considerable period before the first case was identified. Before scientists can make any contribution to Government they require reliable data.

This leads to another lesson from the BSE story: the importance of epidemiology and of an adequate number of veterinarians trained in that discipline. The rapid identification of meat and bonemeal as a vector for BSE transmission was a vital contribution by J. W. Wilesmith to the design of measures to eradicate the disease. Dr Wilesmith was, of course, head of the epidemiological department of the Central Veterinary Laboratory; indeed, he was the only qualified epidemiologist on the staff.

Conclusions were, however, drawn about the epidemiology of BSE that proved to be unsound. It was thought at some stage that the cases identified around the country were index cases contracted from infection with scrapie via meat and bonemeal as a result in changes of rendering methods. It was also thought that the incidence of the disease would plateau at three to four hundred cases a month.

These conclusions provided a false basis for policy decisions and were taken with the assistance of scientists. A period of grace was allowed to use up stocks of cattle food containing meat and bonemeal before the material was banned. Precautions in relation to human health were based on the premise that the risk of transmission was very small because BSE was likely to behave like scrapie. It seems likely that policy decisions now being taken in relation to foot and mouth must depend critically on advice from the epidemiologists in relation to the origin, timing and spread of the disease.

Open communication

Perhaps the most important single lesson we learned is the importance of open communication of information to the public. In the months after BSE was first identified, there was an embargo on the disclosure of any information about this new disease. There were several reasons.

MAFF scientists were reluctant to claim credit for identifying a new disease in cattle before they were sure of their ground. A scientist who has made a discovery will naturally wish to take the credit for it but will wish not to rush into print until his or her conclusions have been peer-reviewed. There will often be tension between this understandable caution and the desirability that both government and public should be promptly informed of possible hazards.

Another motive for the initial suppression of information was a fear of provoking a disproportionate reaction, especially on the part of foreign importers of British meat and livestock. In the event, this fear proved groundless. Foreign importers did not react strongly enough. Last week I was cross-examined by a committee of French senators investigating the spread of BSE in France. Why, they asked, did

Britain continue to export meat and bone-meal after it had been learned that they could infect cattle with BSE? I said that we sold them abroad because we continued to sell them here as pig and poultry feed and that Britain, in accordance with European law, had informed the other members of the EU of the outbreak of BSE and the perceived reason for it.

After the first few months there was a new policy, for which Mr John Gummer (then Secretary of State at MAFF) was largely responsible, that information should no longer be concealed from the public. This nonetheless went against the grain. There was in government a deep-seated culture of confidentiality. It was dangerous to keep the public too well informed because they were bound to over-react. And so, throughout the period up to 1996, the way that information was put before the public was weighted. There was a campaign of reassurance, if not of sedation. There was no misinformation nor concealment of information, but a failure to admit to the public that there was uncertainty, that there was risk and that the early reassuring conclusion that BSE was scrapie was less and less convincing. The public was repeatedly assured that it was safe to eat beef, and that there was no evidence that BSE was transmissible to humans.

Human transmission

When the Government announced in 1996 that BSE had probably been transmitted to humans, the public reaction was that it had been deliberately misled. There was a breakdown of trust in information provided by government and, to a lesser degree, by scientists.

We concluded that trust could be restored only by a policy of openness. The public must be given factual information in full and without spin. The public must be told what advice is being sought from scientists, and then, what advice scientists have given. In particular, where there is uncertainty, government must not shrink from saying "we are not sure".

There was one area where we had difficulty in deciding whether a policy of complete openness was desirable: immunisation. Those responsible for the safety of medicines reached an informed view that the risk of BSE being transmissible through vaccines was very much less than the risk to which children would be subjected if their parents stopped vaccinating them. There was great concern that if the public was told that there was even the remotest risk of transmission from vaccines contaminated with BSE, parents might cease to vaccinate their children. This concern may well have been realistic. Care was taken to avoid saying anything about vaccines that

might spark off such a reaction.

Was this paternalistic approach one that we should endorse? In the end we decided that it was not — that in the long term the public will learn to trust information they are given about risk only if they are given the truth, warts and all.

Winning back the faith of the public in the information that they are given will be a long job. Just as important is winning the confidence of the media. The suggestion that the public is being deceived makes good copy. Witness a recent newspaper headline "Whitehall Funds Hush-Hush Production of GM Fish". I suspect that all the information in the article that followed was in the public domain. That shows how difficult it is going to be to establish a climate of trust in government information.

Scientific advisory committees

Government must also be much more eclectic in the use of scientific advisory committees. It is an understandable reaction when confronted with a difficult problem involving scientific issues to set up an advisory committee. It is not always the best solution. Before setting up a committee, it is important to identify which questions need to be answered and how urgently.

Towards the end of 1987, the incidence of BSE was growing but animals showing symptoms could still be sent to the abattoir and enter the human food chain. Lord Montagu of Beaulieu seems to have been the first to ask "is it safe to eat these animals". There were three possible answers to that question — "yes", "no" and "don't know". If the answer was "don't know", that should have been sufficient to inform policy: the risk could not be taken and sick animals would have to be removed from the food chain. MAFF indeed concluded that "don't know" was the answer, but passed the question to the Department of Health. The Chief Medical Officer and his advisers didn't know the answer and it was decided to set up a working party.

That inevitably took time. It was not until 21 June 1988 that the Southwood Working Party met for the first time and immediately advised that, because of the uncertainty, carcasses of animals affected by BSE should be condemned and destroyed by incineration. That was a decision that could and should have been taken at least six months earlier.

Policy decisions on BSE undoubtedly needed to be informed by scientific expertise. The Government's approach was to set up a committee, first the Southwood Working Party and later SEAC, with the widest possible terms of reference, and to refer all policy questions to them. The committees did pretty well, but the policy, by no means a disaster, had several shortcomings. Too much weight was accorded to views that were necessarily provisional for lack of data. (That was particularly true of the Southwood Report.) Questions were neither precisely formulated nor targeted on the particular areas of expertise of the committee: a striking example is the reliance placed on SEAC's views on the efficacy of slaughterhouse practices.

The workload of SEAC was quite unrealistic for a part-time committee. At some meetings, the agenda was too substantial to be properly considered in advance or adequately discussed at the meeting. Where that happens, civil servants tend to do the pre-thinking for the committee and prepare papers pointing the committee towards particular conclusions. In such a situation, the calibre of the chair of the committee is all important.

Also, the views of committees were not always clearly communicated or properly appreciated. Thus SEAC's advice was not merely not communicated to the public, but not communicated within government to all who could have profited.

Our report sets out several lessons to be learned about the use of committees. Their members should be the best experts available, even if their interests at times put them in a position of conflict. (The best are almost bound to engender such problems.) Committee members should be given a realistic appraisal of the time required of them: when they are not public servants, they should normally be paid. On committees' input to policy, we advised that there should be much more of a dialogue with government than was the case with BSE. The scientists' input will often be only one of a number of considerations that should inform policy. The views of the public have a legitimate bearing on policy, which is why we recommended that lay representation on expert committees is desirable.

We advised that full use should be made of expert committees in contingency

planning and, more fundamentally, that there should be contingency planning. Once again, foot and mouth demonstrates the soundness of that lesson. It will be interesting to learn — if we learn — what contingency plans were in place to deal with an outbreak of foot and mouth. Scientists had obvious contributions to make to plans for containing and eradicating the disease. Did contingency planning go further than that? Was advance consideration given to the competing interests of the agricultural and tourist industries? We shall have to wait to learn the extent to which lessons from BSE informed the handling the current epidemic.

Important lessons are also to be learned from BSE about the form of advice given by advisory committees. It should normally be in writing. Assumptions underlying the advice should be made clear. The advice should identify areas of uncertainty and their extent. It should also be capable of being understood by lay persons, particularly because we concluded that advice should usually be made public.

Planning research

On the question of research, there is tension between the desire of a government department to carry out its own research and the benefits that flow from competition. Professor Ferguson Smith was concerned by the number of research projects initiated by MAFF without competitive tendering and, still more pertinently, that the progress and the results of these programmes were not peer-reviewed.

The scale and diversity of the research projects needed called for coordination of the research effort. The attempts made to achieve this foundered. A number of the bodies involved were prepared to contemplate having a research 'supremo' — so long as they provided the supremo — while the research councils were concerned that their independence might be mortgaged to MAFF. (That worry may have been justifiable: the Permanent Secretary had agreed with the Chief Veterinary Officer that "the responsibility for coordination should not pass out of the ministry's control".) We concluded that coordination of research effort is desirable in order to identify gaps in research, determine research priorities and identify the best sources of expert assistance. We identified a need for a well constructed plan for funding research from the outset.

Understanding of risk

I have only had time to refer to a few of the major lessons of relevance to scientists to be learnt from BSE. There is one more that I should touch on before I close: the need to educate the public about risk. Risk assessment is, consciously or unconsciously, an element in many of the choices that we all make in our daily lives. Unless the public has some understanding of this concept, it is impossible for scientists to communicate adequately their conclusions in situations of uncertainty.

When in March 1996 the Government announced that BSE had probably been transmitted to humans there was an immediate drop in sales of beef. The supermarkets slashed prices and immediately cleared their shelves. What kind of risk assessment led to this consumer reaction? It is easier to identify the need to teach the public about risk than to work out how it should be done. A start must be to discuss risk openly, and to acknowledge uncertainty. Perhaps pupils need to be taught about risk at school as part of their basic education.

A leader in *The Times* recently stated that my report raised as many questions as it answered. That is not a bad epitaph for a report. BSE and now foot and mouth raise fundamental questions about modern agriculture. They go far beyond questions about what is sound and what is safe and what is profitable, which are topics on which the scientist has something to offer. They are questions about the kind of country that we would wish our children and grandchildren to live in. We did not in our report seek to answer these profound questions. They do, however, underline one simple truth: that the scientists cannot be expected to provide all the answers. ❐

Lessons for the health field

by Professor Liam Donaldson

Professor Liam Donaldson FMedSci

Professor Donaldson is Chief Medical Officer (CMO), the Government's principal medical adviser and Head of the Medical Civil Service. The appointment is located in the Department of Health. The CMO is the professional head of all medical staff, with responsibilities both on public health and the NHS .

BSE, a newly emergent disease in cattle in the 1970s, in 1995 became an emergent disease in humans known as vCJD; so far it has killed about 100 people. Why was not BSE recognised at the outset to be a potential zoonosis, a disease with the potential to cross-over into humans? Why was not the full panoply of communicable disease investigation brought to bear on the problem?

If such situations are to be avoided in future, we need to learn the lessons of risk assessment. My aim here is to point to the main lessons already being learned on the health side of Government from the Phillips report. I have three main topics: the concept of risk in the health field, the role of organisational culture, and the question of how the public should be informed about risks.

Spectrum of risk

BSE is just one of several health risks that have hit the headlines in the past year alone. There have been concerns about mobile phones, electricity power cables, side effects of medicines, food safety and many others potential or supposed hazards.. There are also risks to health from certain behaviours or personal lifestyles, such as the well documented risks from cigarettes, poor diet, lack of exercise, obesity and illicit drugs. A third and sometimes forgotten area of risk are the adverse effects of medical care: an estimated 850,000 hospital admissions in the United Kingdom every year result in harm some of which could have been avoided and which costs the National Health Service an estimated £2 billion. It is important to consider how lessons learned from BSE can be applied across this broad spectrum of risk.

discussion

The need for openness. The Phillips report was seen as pointing to a fundamental change in the methods of Government. Openness, as practised for example by the Food Standards Agency with its public board meetings, entailed a step into unfamiliar territory, but it seemed to work. Some business had to be done in private, for example when the Agency was given access to scientific information which had not yet been peer-reviewed, but the normal rule was to make its deliberations public.

Transparency also had an international dimension: the UK was part of a wider community and needed to integrate its approach to openness with that of the rest of Europe. There was real anger in France because the UK had continued to export meat and bonemeal after it had been identified as potentially carrying BSE. Strictly speaking, nothing had been done wrongly, in that the meal was not exported for use as cattle-feed, but plainer warnings should have been given.

There was evidence from social science research that openness was necessary but not sufficient to gain people's trust. Scientists could make predictions about the ozone layer, but would not necessarily be believed. This might be a problem of how to deal with the unfamiliar, given that people seemed to cope quite happily with unreliable scientific predictions in the shape of weather forecasts, every day. Perhaps the answer was to have a 'radio doctor' and a 'radio vet' to make health issues more familiar.

Not only do health risks cover a wide spectrum, but we are alerted to them in a variety of ways: for example, through research studies, surveillance of environmental hazards and through claims made by individuals, investigative journalists or representative groups. It is by thinking about the ways in which risk comes to our attention that we can learn how to respond more effectively and how to pick up warning signals as early as possible.

Too often, we have been caught unawares. With BSE, the risk was one which at first relatively few people suspected, but which proved to be a matter for genuine concern. On the other hand, in many of the areas where a perception of risk arises, some of the public are can be misled by exaggerated claims.

Thus a tabloid newspaper may report case studies showing people suffering from cancer and may claim that, because they were exposed to a particular environmental chemical the link between the chemical and cancer is established. An apparent cluster of a rare disease around an industrial site raises the alarm – and the presumption is that there must be some cancer-inducing pollutant. Such claims must be investigated thoroughly, but even in cases shown to be statistical flukes, that interpretation at present carries no weight with the public and the media.

The breakdown of trust that Lord Phillips refers to means that it is much more difficult now than a few years ago to deal with an association between a hazard and a health effect that is clearly not significant. Part of the problem is the difference between science and journalism, which use evidence in very different ways. Timothy Johnson, in the New England Journal of Medicine a few years ago, put it well: "anecdotal evidence, which is on the lowest rung of the evidentiary ladder in science, is often the basis of general news reporting".

We also have to acknowledge that the public consensus on what level of risk is acceptable or tolerable will vary in different fields. For example, since 1995, the Medical Devices Agency has reported 31 deaths associated with the use of infusion pumps caused by human error in routine handling of infusion pumps. Efforts to reduce errors of this kind have been successful: the number of deaths fell from 11 in 1995 to four in 2000. These four deaths have hardly been remarked upon, yet four deaths in the Hatfield rail crash in October 2000 led to national soul-searching, public disquiet and very dramatic action. Comparing risk and the level of risk and our tolerance of error and risk in different fields are questions we have only just started to explore.

Organisational culture

Whether patients are at higher risk from unsafe practices in one hospital rather than another depends partly on the organisational culture in the hospitals. Similarly, the outlook for a child in an "at risk" family depends partly on the organisational culture of the social services department and the other local agencies responsible for the child protection. Our hopes of avoiding "another BSE" equally rest largely on the ability of the organisational culture of central Government, the departments and the Civil Service to respond to future events. These organisational matters are, of course, dealt with in Lord Phillips's report.

The traditional culture of the Civil Service culture has been advisory rather than that of decision-making. Confronted with a problem, the tendency is to gather information to illuminate the issues rather than to move into active problem-solving mode. There is a tendency to gather information and to diverge away from a decision rather than to converge towards action. That is quite different to the management culture in other organisations.

This has contributed in the past to a very diffuse notion of accountability in the Civil Service. Someone writing advice to ministers on risk issues is likely to focus on his or her department's position rather than asking what their domestic neighbours would think of the advice being offered for the protection of their health as members of the public.

The traditional Civil Servant is a generalist, moving from job to job in different areas of work. This approach has its disadvantages. For example, some lead officials in key areas lack knowledge of the areas concerned and are expected to compensate for this by "knowing who to ask". But the ability to assess scientific information, the ability to know who to talk to or how to weigh up different opinions are not skills that can be acquired within a few weeks of taking up a new job. They are fundamental skills that need to be part of basic core training.

My last observation on culture and organisations is that an inability to work in teams is a recurring feature of organisations that go wrong. We have to guard against the possibility of damaging departmental rivalries. The tendency in some areas of the Civil Service for individuals to advance their careers by catching the eye of ministers is also disruptive: it encourages people to be unwilling to share the limelight with others. On the positive side, the Government is addressing some of these questions, aiming at better management of the day-to day work of the Civil Service and a clearer line of accountability.

There are also issues in thinking about our tolerance of risk, particularly in the field of health care. Traditionally, we have been prepared to tolerate harm and risk to individuals in pursuit of innovation, or as part of a "learning curve". That attitude

discussion

Rules for advisory committees. In discussion, the Government's promulgation of formal guidelines and codes of practice for advisory committees was seen as a welcome outcome of the BSE experience. The Southwood Committee had been set up as an informal working party and then found itself making policy. It was noted that the committee had recommended that meat and bonemeal should not be sold for feeding to cattle, but did not realise what large stocks were held on farms.

The Government was being advised on the current outbreak of foot-and-mouth by a group of scientists assembled for the purpose. It was asked how the members of such a group should be chosen. At one time there had been an attempt to draw up lists of experts on different subjects, but a degree of improvisation was probably unavoidable. If different people active in a given field were asked to list the top experts, their answers tended to be reasonably convergent. It was important also for expert committees to include people with mud on their boots.

is no longer the norm, placing an added burden on those making decisions on the behalf of the public.

Informing the public

The public perspective on risk and health is often very different from the official or scientific perspective. The public will not be interested in risk described in population terms; they ask, "what does it mean for me and my family and what should I do about it?" The mathematics of risk can be confusing – just what does the risk "one in a million" mean to the man or woman in the street?

Where underpinning scientific knowledge is weak, then lay logic and interpretation come into play. The traditional language of risk is confusing to the public; words like "safe" or "unsafe" have been discredited, phrases like "minimal risk" or "hypothetical risk" are not understood. Combine this with the breakdown of trust, and it is not surprising people fear they are not being told the whole truth, and suspect that their interests are being subordinated to commercial or political interests.

In thinking about better communication with the public, we've learned that we must be more open, we must be better at conveying uncertainty and we must be better at conveying the level of risk in terms that are meaningful to members of the public.

A final word now on the media. The media and the public health and governmental perspectives on these matters are very different. The media look at the facts as they seem, we like to think that we look at the facts as they are. The media move to a story line very quickly, we like to have the context properly set. The media often presume that the truth is being withheld whilst we believe that the science is uncertain.

We live at a time when blame and retribution are the prominent in media coverage of what has gone wrong. It is important that there should be proper accountability, but we also have to ask whether the climate of blame and retribution can go too far. If the first and, sometimes, the only questions that are asked are always, "who knew what when?" and "what did they do about it?", is that not likely to create an atmosphere of fear in which people will not be open about problems, but rather, will tend to conceal them? The concept of honest failure seems no longer to be recognised.

At the Department of Health, we have been are trying hard to approach things differently since the BSE enquiry. I like to think that we have started to address some of the problems, drawing on a number of fundamental principles: high quality assessment of science, consistency of approach across all risk areas and having a clear framework for intervening against risk.

In the wake of the BSE crisis, we have taken steps towards improvement in three areas: to understand the depth and breadth of the concept of risk and achieve consistency across the different fields; to tackle the difficult task of transforming our organisational culture; and, finally, to get the tenor and the style of the communication of risk to the public right. ❐

The lessons for Government

by Professor David King

Professor David King ScD FRS

Professor King is Chief Scientific Adviser to the Government at the Office of Science and Technology, DTI.

The Phillips Report is an invaluable audit of the actions of a Government faced with a crisis, and of how one department interacted or did not interact with others. As Chief Scientific Adviser, I was involved in preparing the Government's initial response to that report, which came out in February. (A fuller response will appear later this year.)

Between 1996 and the appearance of the report in November last year the Government took several actions. I draw attention to my predecessor's documents 'Guidelines on the Use of Scientific Advice' and 'Guidelines 2000' and the Code of Practice for Advisory Committees. Those give very sound advice, and we are trying to move on them.

Let me begin with the issue of openness and transparency, because I think that that is where a change is needed most. Openness is essential if we are going to be believed — science policy makers or Government members — when we stand up and make statements. But of course we have to be sure that our statements are correct. And that is sometimes more easily said than done.

On the question of the need for horizon-scanning, which Lord Phillips

discussion

Public perceptions of risk. There was a particular problem in communicating with the public about risk. The schools tried hard to get the concepts of risk and probability across in the maths syllabus, but with limited success: people still bought lottery tickets. Scientists needed to learn how to become more effective communicators than the media. One tool was graphical presentation. A graph showing forecasts of the course of the foot-and-mouth epidemic on different assumptions made a very persuasive case for the rapid culling of animals on infected and contiguous farms.

One problem was the use of large numbers to convey small risks. Participants in one focus group, when asked what a million meant, said simply that it was a very big number. Other ways had to be found to illustrate relative risks, for instance by saying that the radiation left over from Chernobyl had the same impact on health as smoking two cigarettes in a lifetime.

It was argued that risk could not be discussed in isolation. What mattered was the trade-off between benefit and risk. Thus the sales of mobile phones had increased even after possible risks to health had been identified, because the benefits of using them were obvious. In the case of genetically modified foods the benefits to consumers were not so apparent. When beef first came under suspicion the supermarkets were able to sell their stocks off cheap, because customers decided it was safe to eat so long as the price was low enough. People differentiated between risks which they could run if they so chose — for example smoking cigarettes or cycling round London — and those which they could not control, such as the risk that the food they bought from the supermarket might make them ill. The public seemed more and more conscious of food-borne disease even as the real risk declined.

⇨ **A detailed summary of the discussion is available on www.foundation.org.uk**

has mentioned in relation to the current FMD crisis, how much horizon-scanning was there? How prepared were we for a foot and mouth outbreak in this country? Should we have anticipated an FMD crisis in the UK? Were there real risks associated with foot and mouth outbreaks elsewhere from which infection might be transported to the UK?

If you ask a team of experts what potential problems are coming up, there will be as many answers as there are experts — multiplied by some large number. So horizon-scanning must include an evaluation of the likelihood of alternative scenarios. Horizon-scanning, which itself requires careful analysis, is the most difficult task we have taken on.

The concern about public confidence in scientists and science policy makers is also an issue that goes beyond the particular crises. Witness the public attitude towards GM foodstuffs and the bio-science-cum-biotech area. Indeed, the fundamental question has now arisen whether or not Britain is to be a user-friendly climate for the development of these new technologies.

On the current FMD crisis, let me say something about the initial response. The first case of infection was recorded on 20 February and, a month later, the number of reports of new infections was increasing alarmingly. That signalled a need for a step change in the national response. Sir John Krebs at the National Food Standards Agency called a meeting of epidemiologists, scientists active in the area, MAFF scientists and myself. The epidemiologists told us, with one voice, that the epidemic was, in strictly scientific terms, out of control: the number of new cases was growing exponentially, with a doubling rate of something like nine days.

The day afterwards, Sir Richard Wilson, Cabinet Secretary and head of the Civil Service, called a meeting of heads of departments at which I gave a report of the Krebs meeting, saying what the epidemiologists had said. Since then we have been meeting twice daily, with the code-name COBR, essentially under the chairmanship of the Prime Minister. It fell to me to set up a science-based team to inform COBR on how to act through the crisis. This team has played a crucial role in bringing this epidemic under control.

The science team includes a wide range of experts, among them epidemiologists, animal biologists and others knowledgeable about foot and mouth. The team has been relatively open and dynamic in the sense that if somebody has suggested bringing somebody in who has, perhaps, an outlying opinion, we have brought that person into the team.

We had two main growth models to inform us: a University of Cambridge model that includes each farm outbreak — a so-called granular model — and an Imperial College model that is, by contrast, a continuum model. Both predicted exponential growth, and despite using quite different technology, both produced similar predictions. At the initial meeting called by John Krebs, the Imperial College team's projection from an outbreak corresponding to about 30 to 35 a day was that incidence would rise to something over 400 reports a day. Integrating the curve suggests that something like one-half of the livestock of Great Britain would be lost.

Factoring in the contiguous cull policy and time-lag for slaughter demonstrated that we would be able to get the disease under control. The policy that we are now implementing [in early April]is based on improving the time of cull of an infected premises to 24 hours from time of report to time of cull, and culling of contiguous premises, based on 48 hours to achieve that. Events over the next week or so should show how accurate our predictions prove to be. In fact, while the prediction was that at this time we'd be hitting about 70 reports a day, for the last week we have averaged 45, so the situation begins to look quite promising.

The question of vaccination has been at the top of many people's minds and we have included vaccination, in various regimes, in the models. We are continually being asked questions such as 'what will happen when cattle that are currently in sheds are let out to pasture?' and that is also being modelled.

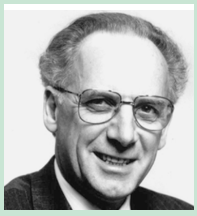
Finally, in relation to the fundamental questions on modern agriculture raised by Lord Phillips' talk, I feel that FMD is raising precisely the same questions as did BSE, and once the current crisis subsides, we shall then begin to start talking about what is fundamentally wrong, and what needs to be corrected. The lessons for Government from FMD, following on the lessons from BSE, are, I think, going to be very profound. ❐

Current knowledge of TSEs

Sir Brian Heap & Keith Root

The science of BSE

A meeting to discuss current scientific knowledge of bovine spongiform encephalopathy (BSE) took place on the publication of the policy document "Transmissible spongiform encephalopathies" by the Royal Society and the Academy of Medical Sciences. The general discussion is summarised by Jeff Gill.



Sir Brian Heap CBE FRS

Sir Brian is Foreign Secretary to the Royal Society, Visiting Senior Fellow, School of Medicine, Cambridge University, and Senior Visiting Scientist, The Babraham Institute, Cambridge.

Dr Keith Root

Dr Root of the Royal Society was secretary to the committee producing the policy document summarised here.

BSE is the cattle form of a range of transmissible spongiform encephalopathy (TSE) diseases, which include scrapie in sheep first reported in the eighteenth century. BSE was identified in 1986, since when nearly 180,000 cases have been confirmed. More than 5 million cattle have been culled as a result of schemes such as the ban on cattle older than thirty months entering the food chain (the OTM rule). The total cost is estimated at well over £1 billion. Moreover, since 1996 there have been 88 confirmed deaths in the UK from a distinct new variant of CJD (vCJD), with a further 13 cases awaiting confirmation. The infective agent for vCJD appears to be distinct from that in classical CJD cases; it is biologically indistinguishable from BSE.

The prion protein, PrP, is the product of a naturally occurring gene that is similar among mammals and which may be present in all vertebrates. PrP itself is a naturally occurring cellular membrane glycoprotein, but there is also an abnormal form, PrP^{Sc}, which is found in insoluble stable aggregated particles and is associated with the destruction of brain cells. It is self-propagating and infectious. Its insoluble β-form is resistant to degradation whereas the normal glycoprotein, largely in an α-helical form, is soluble and easily degraded. If the gene for PrP is deleted from mice, the animals are resistant to infection by prions.

Susceptibility to infectious diseases is influenced by the genetics of the host, and it is known that some sheep breeds are particularly resistant to scrapie. Within the PrP gene, the site encoding for the amino acid at position 129 along the PrP protein, which can be either methionine or valine, is particularly significant resulting in a spread of incubation periods in mice from 100 to 500 days. The shorter incubation periods are found where both copies of the gene encoding for this position are the same (homo-zygous). So far all vCJD victims have been homozygous for methionine at position 129, which may indicate that the current victims were those genetically disposed to have short incubation periods. Other genes on other chromosomes are also believed to influence susceptibility, and continuing genetic studies are important to deepen our understanding of susceptibility to TSEs.

This paper summarises the Policy Document 8/01 published by the Royal Society (ISBN 0 85403 5591) and presented to the meeting of the Foundation of Science and Technology on 5 June 2001. The full report can be found at www.royalsoc.ac.uk and www.acmedsci.ac.uk

Origins of BSE

We are still not sure when, or how, BSE first appeared. The Phillips Report suggested that the BSE epidemic in cattle started in the late 1960s from a chance mutation in a food animal sent for rendering, creating a new form of prion, probably from cattle. Meat and bone meal (MBM) remain the chief suspect as the vehicle of dissemination; certainly the BSE epidemic declined after the ban on MBM in 1988.

In contrast to the Phillips Report, Paul Brown of the US National Institutes of Health has come down strongly in favour of the idea that a scrapie agent acquired an altered host range during its passage through cattle. Other suggestions have included the idea that BSE could have emerged from an exotic zoo species, through the action of an organophosphate insecticide or as an autoimmune disease. Our conclusion is that it is still uncertain how the disease began.

Mechanism of infection

Once in the body, prions can reach the central nervous system through two main pathways. First, as with viruses that affect the central nervous system, invasion may occur via the peripheral nervous system. If PrP^{Sc} is removed experimentally, the spread of the infectious agent is inhibited, indicating that the presence of the prion protein rather than an immune response is necessary for spread of the agent within the body. Second, prions can colonise the immune system, being taken up by white blood cells such as antibody-secreting cells (B cells) and cells that trap antigens.

For all the TSEs, transmission between animals of the same species is readily achievable. After intracerebral injection, all animals succumb over a wide dose-range. Incubation periods, although long, are remarkably constant. As the dose is reduced, incubation periods lengthen until a point is reached at which further dilution enables some animals to survive.

For all TSEs, transmission of prions between species is much less efficient on

first exposure. Where transmission is achieved, only a fraction of exposed animals succumb, usually with greater variation of the incubation period. However, once transmitted to the new species, most if not all animals succumb to disease after exposure to PrP^{Sc} recovered from animals of the same species. There is indeed a 'species barrier': it has been calculated that it needs 1,000 times more BSE to kill a mouse than a cow!

What is the agent?

The nature of the infective agent itself is not resolved. Is it PrP^{Sc} alone or PrP^{Sc} in combination with some other molecule? It has been demonstrated that if nucleic acid molecules are involved, they cannot be longer that 100 bases. The prion protein itself may have the capability to encode strain information by differences in its conformation and glycosylation; recent work on the aggregation of yeast prions *in vitro* supports this idea.

The novel form of human prion disease, vCJD, is associated with the same strain as cattle BSE, and differs from sporadic BSE. Although abnormal forms of the prion have been produced in the laboratory, none has yet produced the disease in experimental animals or been serially propagated — the acid test of the 'protein-only' hypothesis.

The association between BSE and vCJD infection has been confirmed in mice and macaque monkeys. Both young and older macaques succumbed to BSE with a similar pathology, although plaque deposition was greater in the younger animals. This may imply that vCJD cases have been missed in the elderly and hence not reported to the CJD Surveillance Unit.

If an animal does not display overt clinical signs of TSE, it may nevertheless be incubating one. John Collinge's group has shown that a strain of hamster prions thought to be non-pathogenic in mice multiplied to high levels in mice without causing overt clinical disease. The prions produced were pathogenic when transferred to both mice and hamsters.

Can the spread be stopped?

The cull of cattle over thirty months old has prevented spread of the disease and we agree that changes to the OTM-rule should not be considered before January 2002.

We also conclude that the present EU-approved tests for infectivity at slaughter are inadequate. Improved tests to identify infected animals and to detect the infective agent are urgently needed. The tests must be able to detect infection (scrapie and BSE) in the brain and other tissues of food animals (including sheep) before the onset of clinical signs. They are also needed to determine the prevalence of infection in food animals at an early stage of incubation as well as to detect vCJD infection at a very early pre-symptomatic stage.

A major priority is to commission tests that have an increased sensitivity of one or two orders of magnitude, to develop fast tests on blood or urine and to obtain tests that can be used in sheep. The Food Standards Agency should be encouraged to commission such tests; we commend the initiative of the Joint Funders Group (MRC, BBSRC, MAFF and the Department of Health), which organised a recent workshop to bring together academic groups and companies interested in developing diagnostic tests for TSEs.

Eradication of TSEs?

The European Commission has signalled unequivocally that the current ban on MBM, due to expire this summer, will continue. The Commission has also made clear that prohibiting MBM forever would not be a proportionate action and would have serious environmental, financial and world trade implications.

The Royal Society's statement in 1997 raised the question whether there is BSE in the national sheep flock. That would be serious because of the impossibility of removing all potentially infected lymphoid tissue at slaughter. (In cattle this is not such a problem.) It is likely that many sheep were exposed in the early to mid-1980s to infected MBM. Even if sheep were infected with BSE, because of the shorter life-span of sheep than cattle, the infection would have died out by now unless there was vertical and horizontal transmission of BSE in sheep. That question is being explored.

The only long-term solution would be to eradicate TSE diseases from food animals by breeding from animals resistant to infection, selectively culling infective animals when suitable tests are available, improving animal husbandry and possibly by the use of transgenic animals from which the prion gene has been deleted. For the immediate future, we support the National Scrapie Plan, and believe that it should be designed to remove TSEs from sheep and goat flocks.

Disposal of infective material

A recent report about the persistence of infectivity in samples heated to 600 °C was a surprise; it is urgently necessary that this finding should be fully investigated. (Quite brief heating to 100 °C in molar sodium hydroxide appears to destroy infection.)

We were surprised to learn that there are a few abattoirs in the UK where both food animals and OTM cattle are slaughtered. Under EU rules this work cannot be undertaken on the same day. Current science, if confirmed, would advise against such dual-use abattoirs, but this is a grey area where science advice could easily stray into policy, the responsibility of governments and politicians.

Quite apart from the considerable cost of storage, there is always a danger of leaks

summary of recommendations

The policy document contains eight main recommendations.

- Basic research is crucial to further our understanding of TSEs and the multifactorial nature of their occurrence and transmission.
- High quality young researchers should be encouraged to enter this area by means of prestigious 5–10 year fellowships.
- Recycled animal protein should be banned for the foreseeable future, and alternative ways of disposing of carcasses explored.
- TSEs should be eradicated from food animals through the breeding of resistant animals and the selective culling of infected animals.
- Sensitive and inexpensive tests are urgently needed for routine testing of slaughtered animals and preclinical tests for use on live animals and humans.
- Further work is required on the destruction of the infective agent, sterilization of surgical instruments and the safety of blood transfusions.
- Urgent steps need to be taken to eliminate the possibility of cross infection in abattoirs handling both food animal slaughter and the culling of OTM animals.
- Good prospects exist for the development of new therapies, but research and development will require public financial support.

into the environment. Keeping MBM out of feed production for ever would cause environmental problems. In the UK alone, there are now more than 430,000 tonnes of MBM in store, with possibly a further 200,000 tonnes of tallow. Disposing of these materials in the EU as a whole would cost around £3 billion a year; suitable dietary-protein replacements and dispensing with the 'added-value' of animal by-products would reduce annual returns by a further £1 billion.

Accordingly, we have made a very preliminary study of the the disposal of MBM by microbiological digestion on an industrial scale and by anaerobic pyrolysis at 850 °C to yield gases of medium to high energy-content for electricity generation. Both are worth further investigation. Pyrolysis might yield a return of about £20 per tonne of product converted to electricity, to which should be added the significant cost of incineration.

The risk of cross-contamination is vividly illustrated by recent observations of the persistence of infectivity on the surface of metals. While no cases of CJD have been attributed to surgical instruments subjected to autoclaving, the conditions for sterilisation of surgical instruments should be defined for both vCJD and the sporadic version of the disease.

Prospects for therapy

By the time patients incubating CJD show clinical signs, neurological damage may be too severe for recovery. Suitable diagnostic tests are therefore crucial to identify early pre-clinical cases, particularly in high-risk groups, including relatives and haemophiliacs who have received blood products.

Work is hampered by not knowing what causes neurological damage: is it PrP^{Sc}, a toxic intermediate or some form of membrane-bound prion protein? Nevertheless, several research groups are exploring a range of avenues for prophylaxis and therapy. Schenk and colleagues have shown in transgenic mice with a mutation that causes Alzheimer's disease in humans that immunization with beta-amyloid peptide inhibits the formation of plaques in the brain; with prion diseases, a potential therapy might involve antibodies against PrP, which are effective in tissue cultures infected by mouse prions.

Resources

For research purposes, it is vital to maintain special containment facilities for qualified research workers, and to produce reagents and tissue banks with full documentation on provenance and infectivity, measured on an agreed standard. There are centres of excellence in TSE research in Europe and the United States. While the EU programme has brought some of these together, we conclude that there is scope for further collaboration, especially with laboratories in Switzerland and the United States.

Although recent research has considerably enlarged our knowledge of TSE diseases, on many questions (such as the origin of BSE), science has not yet explained things, merely described them. ❐

The nature of the BSE agent

by Professor Dominique Dormont

Professor Dominique Dormont,

Professor Dormont is Chef de Service de Neurovirologie, Service de Santé des Armées (CEA)

The unconventional character of the TSE agent raises a number of problems for diagnosis and treatment. The proteins that aggregate in nerve cells in the course of the diseases include PrP, the natural prion protein, which is either associated with the infectious agent or is the infectious agent itself. The protein that accumulates in infected individuals has the same primary sequence as the normal protein they had before infection. It is very difficult to understand how, with no modification of the primary sequence, aggregation within the cell should be the hallmark of these diseases.

Although one can use antibodies against PrP to study the aggregation of the protein, no antibody can discriminate between normal and abnormal PrP, which impedes the design of diagnostic tests. However, the protein in normal individuals is susceptible to proteolytic degradation by proteases. In contrast, in infected individuals, the prion partially resists proteolysis. This is the only way we now have to make a biochemical diagnosis of TSE: we must first demonstrate the aggregation of PrP and also that the aggregated PrP partially resists proteolysis. We can do that for the brains of infected cattle, but we cannot yet assay other parts of the infected animal with this technique.

The part of the PrP molecule that resists proteolysis in an infected individual can polymerise into fibres. When fibres were discovered in the brains of sheep with scrapie, it was thought that the agent of the disease had been discovered. But when the fibrous structures are broken down by sonication, the molecular fragments remain infectious. Fibres as such are not the agents of disease.

Since 1997, a clear picture of the tertiary structure of the normal PrP in mice, cattle and now humans has emerged. Unfortunately, we do not have such a clear picture of the abnormal PrP and so cannot have a true idea of the mechanism that leads to its aggregation.

There are two different hypotheses about the nature of the TSE agent. The most popular, the 'prion hypothesis', is that PrP is itself the agent But there are also scientists who believe that the TSE agent carries its own genome which we are not yet smart enough to identify.

On the majority view that the agent consists only of protein, the infectious PrP is distinguished by an abnormal tertiary structure. That could arise by one of two pathways. Either the protein is produced in its normal form and then converted, within the cell, into the abnormal structure or the PrP is misfolded as it is

produced. What really happens remains an open question.

Unanswered questions.
It is puzzling that that nobody has yet succeeded in reconstituting infectious material after denaturing natural abnormal PrP, and that it has not been possible to propagate infectivity from recombinant protein. That has led some people to suggest that the prion hypothesis might be wrong.

Other recent experiments suggest that we should distinguish between infectivity and resistance to proteolysis. It has been shown that recombinant PrP can adopt the abnormal tertiary structure and that the molecules then rapidly form dimers, oligomers and eventually aggregates that can be seen in the electron microscope, but are not infectious. It has also been shown that the interaction between normal and abnormal PrP in a cell-free system can induce resistance to proteolysis in normal PrP. John Collinge has, however, shown that the resistant PrP generated in these conditons is not infectious.

The molecular basis of the difference between various strains of the same TSE is also not yet understood. A strain is a natural isolate that has been serially passaged in mice with an identical genetic background. Different strains can be distinguished by their biological properties — the incubation period, the neuropathology pattern, the electrophoretic behaviour of the PrP resistant to proteolysis. It is well known that different strains of scrapie are associated with distinctive patterns of lesions in the brains of infected animals. So if you believe in the prion theory, you have to admit that there must be several different abnormal PrP conformations that are stable and transmissible even between species and even by the oral route.

Only one strain of BSE has been identified so far. Whatever the cattle affected, if you inoculate mice with a well defined genetic makeup, you always get the same disease, called 301C. So take the brain from an infected cow, then inoculate a sheep, a goat and a pig and, when those animals become sick, re-inoculate the same strain of mice. In each of the three cases, you end up with 301C disease. In the prion theory, what this means is that the abnormal PrP from cattle has induced the formation of abnormal PrP in three different genetic backgrounds (with distinct PrPs), yet the biological characteristics of BSE are unchanged.

What can be the molecular basis for strain diversity? It could be either that there are still unknown molecules associated with the PrP or that there is some covalent modification of the molecule. On the other hand, on the prion theory, it may be that there is a broad range of strain-specific refolding of the PrP, which must be capable of adopting several different stable conformations.

We may yet learn much from the experimental situations in which TSEs are transmitted to animals without accumulation of PrP resistant to proteolysis. Fatal familial insomnia is one of these, which can be transmitted to mice which, on the first passage, do not accumulate PrP.

In this connection, S. B. Prusiner has recently developed a test for the detection of abnormal PrP. This depends on the development of antibodies directed against a region of the PrP protein which is accessible both in the normal and denatured PrP, but which is buried inside the molecule in the abnormal form and so is not accessible to the antibody. By measuring the difference in antibody binding between the folded and the denatured protein, you can estimate the amount of abnormal PrP. By these means, Prusiner has demonstrated that part of the abnormal PrP is sensitive to proteolysis.

The current prion theory is therefore as follows. In the absence of infection, normal PrP is folded normally into the molecules expressed at the cell surface. But, in the process of folding, protein molecules go through a succession of intermediate states; at one of these stages, perhaps by the binding of a ligand that could be the abnormal protein itself, the folding process diverges from the normal pathway and leads, after more intermediate stages, to the aggregable abnormal protein. The intermediate at the bifurcation in the folding pathway already has an abnormal tertiary structure yet is still sensitive to proteolysis. So there is a clear distinction between resistance to proteolysis, which is linked to aggregation, and the misfolding of the protein which, in this theory, is the origin of the infectious agent.

I conclude that we need to keep an open mind about the nature of the BSE agent. ❐

discussion

Limiting the risk. In response to the document "Transmissible spongiform encephalopathies" (see page 10 for recommendations) the Food Standards Agency announced that it would examine the risk of cross-contamination in the eight dual-use abattoirs, which had not been in operation since 23 February due to foot and mouth disease. Professor Dormont and others noted that the nature of the infective agent in TSEs was not yet resolved, and in the discussion the scope for controversy was illustrated when one contributor proposed that TSEs were autoimmune disorders, while another declared that this possibility had been firmly ruled out.

There was dispute also over the likely future incidence of vCJD. One speaker argued that new cases were falling gently and future cases would be limited to a few hundred, but others disagreed. It was pointed out that all the victims so far had been of the same genotype as early kuru victims, with short incubation times. Later victims were liable to have longer incubation periods. It was also suggested that it was no longer necessary to invoke the precautionary principle in relation to vCJD. That principle should come into play when there was not only uncertainty but also scope for serious harm if the wrong decisions were made. In fact, the steps needed to minimise the risk of getting vCJD had been taken.

Diagnosis. The development of better diagnostic tests was seen as a big scientific challenge, and one speaker thought the effort devoted to it disproportionately small. Noting calls for measures to encourage high quality young researchers, one speaker wondered what was wrong with the existing researchers. Nothing, according to one response, but there was a recruitment problem, particularly for good postdoctoral scientists. One problem was that a budding science career needed quick results, and TSE research was a long haul.

On the problem of talking about risk and uncertainty, it was pointed out that an invariably fatal disease such as vCJD called for a different approach to risk from one with less extreme consequences. One speaker suggested that the media had not addressed the issues, though another participant thought the media were responding well to the Food Standards Agency's policy of openness.

⇨ **A detailed summary of the discussion is available on www.foundation.org.uk**

The potential human threat

by Professor Roy Anderson

Professor Roy Anderson FRS FMedSci

Professor Roy Anderson is head of the Department of Infectious Disease Epidemiology at Imperial College of Science, Technology and Medicine.

All the TSEs appear to have very long average incubation periods, but we do not yet understand why that is so. Good data on the distribution of the incubation period of a TSE in humans derives from Papua New Guinea, where kuru was transmitted by cannibalism occasioned by the death of a relative, when it is sometimes possible to define precisely the point of exposure. Epidemiological studies of kuru suggest a median incubation period of around 7 to 10 years.

Studies with laboratory animals point to several more subtle problems. Thus the genetic background of the host is an important determinant of the likelihood of infection leading to disease on short or fast timescales. So much is well known from experimental studies of TSEs in mice, but the possibility that there may be one of two amino-acids at position 129 of PrP (see page 9) in both cattle and people is relevant to the future occurrence of vCJD in people. For example, recent studies of kuru indicate that methionine homozygotes have the shorter incubation periods post infection, valine homozygotes have on average a longer period while heterozygotes (with two different amino-acids at position 129) have a still longer period. In the UK population, 40 per cent of people are homozygotic for methionine, 10 per cent for valine and 50 per cent are heterozygotic. All of the cases of vCJD so far recognised in the UK belong to the genetic group with potentially the shortest incubation period. In other words, cases in the other genetic groups may still be incubating over a much longer average period.

One of the more puzzling features of prion infections is that, for a given strain of agent and a host of well-defined genetic background (say an inbred strain of mice), the variance of the incubation period is much less than for infections of other kinds, by viruses or bacteria. Surprisingly, the pathogenesis of the TSEs against hosts of similar genetic backgrounds seems to be almost a deterministic process.

The agent can move round the body, from gut to brain for example, by various routes, but little is understood about the detail. Studies of scrapie in mice have shown the presence of the infectious agent both in the spleen (part of the immune system) and the brain, but over time, the concentration in the brain increases exponentially culminating in clinical symptoms and mortality. That is the basis for believing that, in cattle with BSE, animals in the late stage of incubation are likely to be more infectious to humans than in the early stage due to very high concentrations of the abnormal prion.

At the outset of the BSE epidemic, the mode of transmission was essentially indirect and horizontal, by the recycling of infected feed (that is, meat and bone meal feeds, or MBM). What about the thorny question of direct horizontal transmission, as by the contamination of pasture by, for example, faeces of infected animals? So far, there is no epidemiological evidence that BSE is transmitted in this way, although for scrapie in sheep, horizontal transmission must play a part: an endemic disease such as scrapie cannot be sustained by vertical (maternal) transmission alone.

In the BSE epidemic, roughly 180,000 cattle have been clinically diagnosed with the disease. The epidemic has been very well charted by veterinary epidemiologists since it became a notifiable disease. We thus have an extraordinarily detailed database about the evolution and spatial spread of the epidemic. We can, for example, identify hot-spots of BSE infection in cattle herds or holdings which may be very relevant to the occurrence of vCJD in humans both now and in the future.

Tip of the iceberg

The epidemic is now in a phase of rapid decline. Halfway through this year, we expect roughly 500 cases in total for 2001, compared with 1,300 last year. The decline has been abrupt, but the turnover followed by many years the ban on recycling of meat and bone meal from infected animals into animal feeds, introduced in late 1988 (see Fig.1). That reflects the long incubation period of the disease, which experimental studies suggest has an average period of 5 years. By statistical inference from the database of 180,000 cattle, one can infer the shape of the incubation period distribution, which is much broader than the distributions observed in the infection of genetically homogenous strains of experimental animals with a TSE agent of defined strain. That suggests that there is some genetic variability within the UK cattle herd that determines pathogenesis for BSE.

Along with knowledge of the life expectancy of the cattle host, the BSE incubation period in cattle tells us one very important thing — the cases of overt

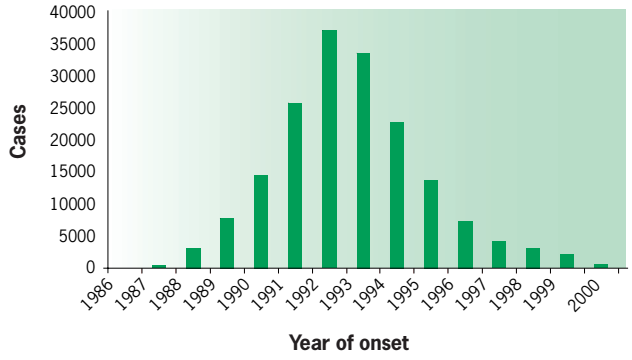


Fig 1 **The observed BSE epidemic in Great Britain.**

disease that we see in cattle are the tip of an iceberg. The average incubation period of BSE in dairy cattle is approximately 5 years. The average life expectancy of a dairy animal is between two and two and a half years. If the incubation period of the disease is five years and the life expectancy of the host roughly two years, the implication is that a great many diseased animals have entered the food chain without clinical disease being recognised.

A further complication in the interpretation of the incubation period distribution has been demonstrated by experimental infection studies in cattle by Wells at the Central Veterinary Agency at Weybridge. The incubation period in cattle is dose-dependent: smaller doses give longer incubation periods.

We can also glean some information about the risk of infection as a function of age. (There is an urgent need for research on the age-dependence of propensity to infection; there are as yet no data for cattle, sheep or even mice.) Analysis suggests that there is a peak of susceptibility in very young cattle. That may be relevant to the development of vCJD in humans.

Vertical transmission

There is experimental evidence for a rate of maternal transmission from mother to calf of about 10 per cent. As with other infections, the probability of vertical transmission increases to the point at which clinical disease is apparent in the mother. Further evidence comes from analysis of the entire database of 180,000 infected animals, tracing the fate of all the offspring of mothers who subsequently develop BSE. That yields a vertical transmission rate of about 9 per cent, which is consistent with the experimental study.

It is not always possible to distinguish between genetic inheritance and maternal transmission on epidemiological grounds. So far, there is no evidence from BSE in cattle that genetic inheritance of susceptibility has influenced the course of events. There is an urgent need to understand how vertical transmission occurs — is it via colostrum, is it pre-natal or is milk involved. We are completely ignorant about the mechanisms of transfer of the abnormal prion protein from mother to offspring. This is relevant to the safety of milk from infected animals for humans.

One of the key questions in the area of human health is to try to estimate what we have been exposed to in Great Britain over the past 20 years. A back calculation from the observed epidemic of reported BSE cases to estimates of how many infected animals were affected suggests that something like three-quarters of a million infected animals went into the human food chain before safety measures were put in place in 1989. So the depressing conclusion is that the population of Great Britain had very high exposure to the BSE agent.

What of the future? The epidemic is certainly in decline. Planly it is not self-sustaining. In other words, there is no evidence of infection directly by contaminated pasture that would result in endemic disease in cattle but this will not be certain until we have seen the tail of this epidemic develop over the coming 5 to 10 years.

Human disease

The link between BSE and vCJD was made in the spring of 1996 by the CJD Surveillance Unit in Edinburgh who noticed a shift in the average age of onset of CJD to younger patients. Classical CJD is a disease of the elderly, but the new variant CJD (vCJD) typically develops when patients are between 20 to 30 years of age. Subsequent studies provided strong evidence for a close association between vCJD and BSE, on the grounds of pathology and immunochemistry.

What is the human risk at present, given that the OTM rule (animals over 30 months of age are not allowed to be used for meat or meat products) is now enforced in the UK and other parts of Europe? We can estimate crudely how many late stage incubating animals with high abnormal prion densities (those with short incubation periods) are entering the human food chain at present. The answer is less than one. This suggests an extremely low risk, but it will not have vanished until 2005. In essence, our exposure now is essentially negligible compared to what we were exposed to in the past (Fig. 2). That doesn't of course mean to say that we should not attempt to reduce this to zero.

It is very disappointing, given our experience in Britain, that the BSE agent has started to spread and has become a serious problem in other European countries such as France, Germany and Spain.

One important need, throughout the European Union, is the testing for BSE in all cattle who may enter the human food chain or who may be used to produce products (for example, tallow) that we may be exposed to. It is now required to

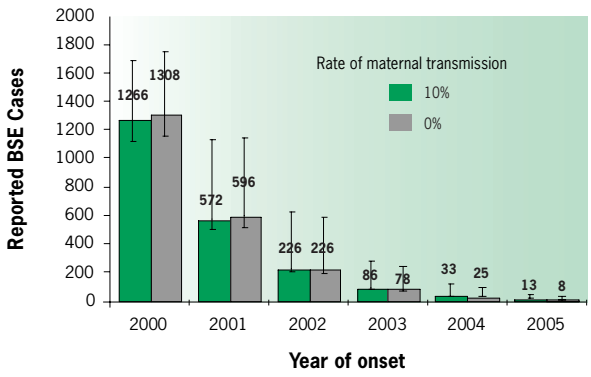


Fig 2 **Updated BSE case predictions 2001–5. The predictions are higher than those made in 1996, but still within original prediction levels.**

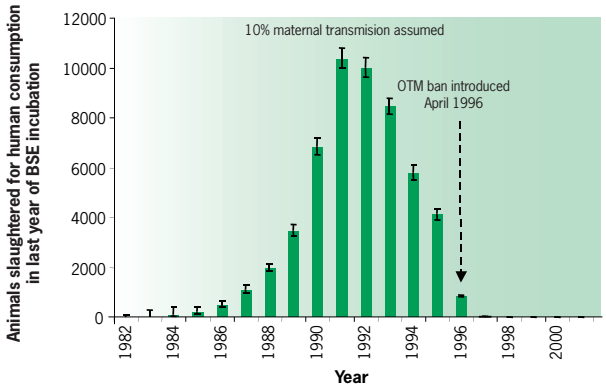


Fig 3 **Current risk: the effect of the OTMS (over thirty months scheme)**

test 'fallen cattle', which are cattle dying on the farm from injury or for unknown reasons, over 30 months of age. Of 106 fallen stock tested by the end of April, 12 were positive for BSE. The high percentage may be a statistical fluctuation in a small sample, or a sign of bias in the sampling given that fallen stock might have a greater than average probability of being infected by comparison with other animals in the herd. More significant may be MAFF's testing of 9,500 cattle older than 30 months of age where only 0.45 per cent were positive.

The implication for the UK of EC regulations that fallen stock should be tested for BSE, is that about 75,000 animals, together with about 325,000 OTM animals must be tested each year. The cost would be many tens of million pounds a year. Even so there is a problem: the current tests have unknown sensitivity to detect the BSE agent in animals at different stages in the incubation period. Possibly, they are sensitive only about three months before clinical onset of disease. We really need to calibrate the tests against material from cattle with known dates of infection, which is not easily done. Meanwhile, there is no way of interpreting the observation of a 0.45 per cent prevalence in 9,500 OTM cattle: the true prevalence could be n-fold higher.

The foot and mouth epidemic has brought further complications. So far, about 10,000 cattle aged over 5 years have been buried and about 50,000 have been burned. How is the ash from these animals, some of who will have been incubating BSE, to be safely disposed of?

Risk assessment

Risk assessment poses a difficult problem for scientist studying BSE and vCJD. What we have to go on are the history of the BSE epidemic, meat production and consumption patterns, incubation periods and observed vCJD cases. We know very little about many of the key parameters that determine risk to humans (such as the infectiousness of a defined quantity of the BSE agent consumed orally, and the incubation period distribution of vCJD in humans) and yet the precautionary principle demands that we carry out risk assessment. We can calculate with some degree of precision certain factors such as the volume of infected animals year by year, at given stages of the incubation period of BSE that could have entered the food chain (see Fig. 3).

In my own early involvement in SEAC, some risk assessment studies were presented that included statements such as, "the risk is 0.00001" — with no indication of confidence bounds. Yet the uncertainties are so many and so great that the confidence bounds could range over many orders of magnitude. The danger here is that numbers convey a sense of precision – when in reality great uncertainty lies behind them. Scientists have a duty to define clearly the degree of uncertainty involved in any such calculation. All estimates of risk entail some degree of uncertainty, but where BSE and vCJD are concerned, science cannot provide estimates of risk in many areas with any precision at all. We need to make that very clear, and repeat the message often!

Turning to the reported vCJD cases, the age distribution is markedly different from that in classical CJD: the disease has appeared in younger people between the ages of 15 to about 35. Remember that the cases are all in people with the homozygous methionine genotype and may reflect an early part of the epidemic.

How then do you make estimates of the future course of the vCJD epidemic, given the many uncertainties? All you can do is list all the unknowns, take some probability distributions for those unknowns, simulate millions and millions of times by drawing at random values from the unknown distributions and create a cloud of uncertainty of possible future scenarios of the course and magnitude of the epidemic. This has been done, but all one can say with any precision at the moment is that the future is extremely uncertain. We cannot exclude very large epidemics, or epidemics of small (a few hundred cases) to moderate size.

There has been much discussion of sampling surgically removed tonsils and appendix material to detect abnormal prion to improve precision in such estimates by providing information on the age specific prevalence of incubators of vCJD. Quite a large number of samples have been analysed; so far, encouragingly, all these samples have been negative. But the numbers of samples analysed so far are much smaller than those needed to lend precision to estimates of prevalence of, say, 10 per million. In addition a similar problem arises to that of testing for BSE in cattle. At present we have little knowledge of the sensitivity of the vCJD tests for people at different stages of the incubation period. This makes the interpretation of the tonsil and appendix surveys very difficult indeed.

Epidemiological knowledge of vCJD will accrue slowly but some recent patterns provide important new information. For example, there has been a cluster of vCJD cases in one district in Leicestershire. Recent investigations by the local health authority suggest that there seems to be a common association with the consumption of beef from a butcher's where there was a risk of contamination of meat with bovine brain. On the assumption that the exposure of all the affected individuals was roughly contemporaneous, the data provide an estimate of incubation period for the fast-developing homozygotes of between 11 to 16 years. It is important to note that the animals slaughtered by this butcher were thought to be around three years of age and therefore not necessarily in the late stages of incubation of BSE. This may imply that early BSE incubators pose a risk.

To summarise, there are many epidemiological research needs. Some of the most important are as follows. First, it is very important to carry out experimental work to understand the route of vertical transmission. Second, the sensitivity of diagnostic tests across the incubation period must be defined. Third, we need to understand why scrapie is endemic in the UK (what is the route of horizontal transmission). Fourth, we need to investigate the factors underlying what may be an increasing number of vCJD clusters. More generally, we must aim at the eradication of TSEs within all livestock. BSE may not be the only TSE capable of infecting people. ❐

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Professor Hugh Pennington FRSE FRCPath, University of Aberdeen
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26 June

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