Faculty of Public Health Medicine Queen Elizabeth the Queen Mother Lecture

BSE and the Principles of Public Health

Sir John Pattison

Foreword by John Wyn Owen

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To mark the 90th birthday of our Patron, Her Majesty Queen Elizabeth the Queen Mother, the trustees agreed to sponsor an annual public lecture, under the aegis of the Faculty of Public Health Medicine, to be given by an eminent worker of any discipline resident and working in the UK on a topic embraced within the main theme of 'Public Health'.

Professor Sir John Pattison's lecture, which is reproduced in the following pages, is particularly timely, given the current Philips Enquiry into the BSE episode and a heightened awareness of the risks to public health from globalisation of trade and travel. There is an ever growing range of new and serious challenges which will need to be faced by the public health infrastructures at a national level. It is important to ensure that adequate scientific investigation, technical support and the capacity of public administration and the political processes are able to respond promptly, effectively and responsibly.

The discipline of public health is increasingly coming into the spotlight and effective communication of public policy is a major challenge, but as yet is insufficiently addressed.

John Wyn Owen, CB
February 1999

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Professor Sir John Pattison was educated at Barnard Castle School, the University of Oxford and the (then) Middlesex Hospital Medical School.

Between 1975 and 1977, he was Senior Lecturer in Virology at London Hospital Medical College at St. Bartholomew's Medical School; and from 1977 to 1984 Professor of Medical Microbiology at King's College Hospital Medical School. Since 1984 he has been Professor of Medical Microbiology at University College London, Dean of UCL Medical School (1990-1998) and is at present Vice-Provost of UCL. From 1992-1995 he was Chairman of the Physiological Medicine and Infection Board and a member of the Medical Research Council. He was a member of the Board of the Public Health Laboratory Service (1989-1995) and editor-in chief of Epidemiology and Infection (1980-1994). He is currently Deputy Chairman of the King's Fund Management Committee, Chairman of the Spongiform Encephalopathy Advisory Committee and senior medical advisor to the Medical Research Council. Sir John's own research interests have been concerned with aspects of medical virology, particularly rubella virus infection and original work on the identity and consequences of infection with the human parvovirus B19.

BSE and the principles of Public Health

There are many definitions of Public Health but increasingly, these days, it is used in its broadest sense. Unsurprisingly, given my background, I want to focus on a narrower, more restrictive aspect of public health – the threats from, and the control of, infectious diseases.

When I was teaching microbiology and virology to medical students I found it was possible to devise a single slide to summarise the general principles of the subject. It indicates a source of a pathogen, various routes of transmission to susceptible individuals, the infection of many and the development of disease in some. Specific therapy is sometimes applicable but more desirable is the prevention of disease by eliminating the source, preventing transmission or raising the resistance of the host by immunisation. These principles were worked out a long time ago so they are not modern. They may be illuminated by genetics, proteomics and so forth but they are not, in essence, altered by them. They are not intellectually demanding, are rapidly learned and equally rapidly ignored. The consequence is that we are constantly reminded of them by specific and often alarming examples of transmissible diseases which are either novel or are re-emerging after a period of being relatively well controlled.

The transmissible spongiform encephalopathies (TSEs) which have emerged in the last 10-12 years are good examples of this. The very name TSE indicates much about the diseases. Clinically and pathologically they are dominated by changes in the brain, a spongiform appearance by light microscopy is characteristic and, at least under certain circumstances, these diseases are transmissible from one individual to another either within a species or between species. With respect to transmissibility many of the general principles of communicable diseases apply but there is one feature of TSEs which marks them out from other transmissible diseases, namely the nature of the agent involved.

No conventional virus nor any unique nucleic acid has been identified in TSE tissue. By contrast an abnormal form of a protein, known as PrP and widely expressed in tissues, is characteristic of affected animals. PrP is a membrane glycoprotein which is sensitive to digestion with proteinase-K whereas the abnormal form, PrP^{Sc}, uniquely associated with TSEs is relatively resistant to such digestion. The primary amino acid sequence of PrP^{Sc} is the same as the normal cellular protein and the difference between the two is conformational, with a higher beta sheet and a lower alpha helix content in the abnormal isoform. The normal function of PrP has not yet been elucidated by PrP^{Sc} usually accumulates in the central nervous system and lymphoreticular tissues of TSE infected hosts. Mutations in the PrP gene are associated with familial spongiform encephalopathies in humans and polymorphisms in the PrP gene correlate with relative susceptibility or resistance to TSEs in humans and animals. The precise mechanism by which spongiform encephalopathies are transmissible is not clearly understood. However it is assumed that transfer of small amounts of PrP^{Sc} results in the interaction of the resistant isoform with the normal cellular form to generate more PrP^{Sc}. Equally it is not clear whether PrP^{Sc} and the infectious agent are one and the same or whether another molecule is involved. Either way, the prion theory of TSEs predicts that the infectious agent consists only of protein(s). Elucidating the precise nature of the transmissible agent of

prion diseases is one of the major issues in biology. However there are practical public health implications of the unusual nature of these agents. The first relates to their relative resistance to physical and chemical inactivation, a property that has been recognised for many years. This means that the usual sterilisation methods including prolonged treatment with steam under pressure cannot guarantee sterilisation of instruments or materials. The second practical implication is that molecular typing methods for the various strains of TSE are at a relatively early stage of development compared with those of conventional viruses and bacteria. Such techniques are vital for epidemiological studies of any transmissible disease and usually involve the detection of foreign antigens or antibodies to them or the genome of the parasite. Such approaches do not apply in TSEs and the issue is referred to again below.

Prior to 1980 a variety of TSEs of animals eg. scrapie, mink encephalopathy and humans eg. Creutzfeldt-Jakob Disease (CJD) and kuru were known. Then in 1986 the first description of bovine spongiform encephalopathy (BSE) in indigenous cattle in the UK appeared. As is typical of new diseases the condition was first defined by its clinical signs (notably nervousness, heightened reactivity to external stimuli and difficulty of movement particularly of the hind limbs) and the pathological appearances of the most severely affected organ, in this case the brain which showed obvious spongiform change. During the next 2-4 years the disease was shown to be transmissible to mice and cattle and thus BSE was a novel transmissible spongiform encephalopathy.

Initially the origin of BSE was taken to be a strain of sheep scrapie which had transmitted to cattle. However, to date, there is no evidence

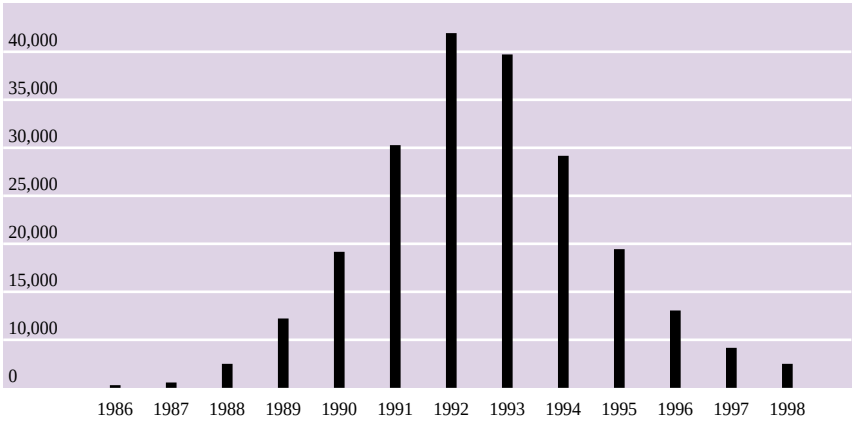

Figure 1. Number of confirmed cases of BSE per year in Great Britain since its first recognition in 1986.

that makes this any more likely than that BSE was a low incidence cattle disease all along. Whatever the origin the vast majority of the epidemic has been caused by the recycling of ruminant protein back to cattle in the form of meat and bone meal made from the rendered remains of sheep and cattle carcasses. It is not possible to identify a single change in the rendering process which allowed BSE to emerge in the 1980s. A variety of changes (eg. continuous rather than batch processing, reduction in the use of hydrocarbon solvents) had taken place in the 1970s and these were not confined to the UK. Possible relevant factors which distinguish the UK from other countries are the high ratio of sheep to cattle and the particularly high inclusion rates of meat and bone meal in cattle, especially dairy cattle, feed. Whatever the origin of BSE it is clear that by the early to mid 1980s the UK rendering processes did not inactivate the agent of BSE and a major epidemic was being created by re-cycling contaminated bovine remains to cattle.

Up to March 1999 there have been 174,015

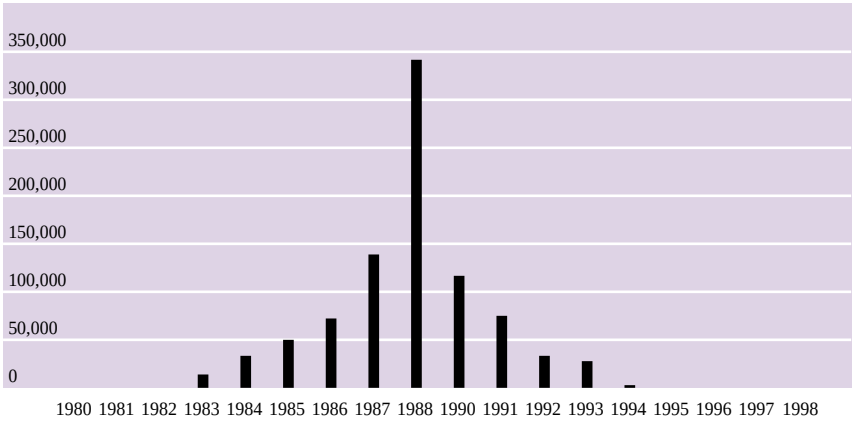

Figure 2. Estimated annual occurence of new infections with BSE in Great Britain (adapted from the work of Professor R.M. Anderson and colleagues).

cases of BSE in the UK. Some cases occurring in 1985 were diagnosed retrospectively and there were undoubtedly others at this early stage of the epidemic that were missed. Subsequently the annual incidence of cases peaked in 1992 and is now in rapid decline (*Figure 1*). The majority of cases have occurred as a result of infection in calfhood with about two thirds of the UK dairy herds having at least one case. By contrast, only one sixth of the beef suckler herds have had a case and, in the majority of these herds, BSE has occurred in animals purchased from dairy herds. The within-herd incidence has been relatively low even when the epidemic was at its height involving only approximately 3% of adult animals within affected herds.

BSE occurs most frequently in animals aged 4-5 years. Many animals in the UK are slaughtered at a younger age than this so, even if they were infected with BSE, they would not have had a chance to develop the disease. Using back calculation methods developed for the analysis of the AIDS epidemic it has been demonstrated that it would have been necessary to infect almost one million animals in the UK herd in order to end up with the 174,015 clinical cases of BSE to date. The pattern of these infections rose dramatically up to 1988 (*Figure 2*). In July of that year the UK Government introduced a ban on the feeding of ruminant protein to ruminants and this had an immediate affect on the annual incidence of infection (*Figure 2*). This ban remains the main control measure in relation to the cattle epidemic and illustrates the principle of interrupting a route of transmission of a transmissible agent to susceptible hosts. The ban was not completely effective due to cross-contamination of ruminant feed with ruminant protein incorporated in pig and poultry feed in the feed mills and possibly continuing exposure of cattle via pig and poultry feed on the farm. As a consequence there have been over 38,500 cases of BSE in animals born after the ban on ruminant protein in the ruminant feed. One case has appeared in animals born as late as 1995. Accordingly the feeding of mammalian protein to all farm animal species was prohibited in 1996 with a view to completely closing this route of transmission.

Calculations have also been made on the number of cases of BSE that would occur in 1996 and in subsequent years (*Table 1*). The calculations are based on a dominantly food-borne source of infection but include some cow-to-calf transmission. This was included because a long-term cattle study indicated an increased incidence of BSE in calves born to mothers in the late stages of the incubation period of the disease. The results are compatible with a cow-to-calf transmission of approximately 10% which is not, in itself, sufficient to perpetuate the BSE epidemic. The predictions which commenced in 1996 are shown in table 1. The actual number of cases

in 1996 was 8,016, for 1997, 4,149 and for 1998 the final observed number will be close to 3,100. It is predicted that there are very few new infections occurring each year now that the food-borne source has been closed off and the cow-to-calf transmission is so low. Thus the BSE epidemic is fast disappearing, an offspring cull is taking place, after which it is difficult to conceive of any practical and justifiable measures which could accelerate the decline.

The transmission of spongiform encephalopathies is generally more difficult between species than it is within species. This has led to the concept of a species barrier and it expresses the relative difficulty of inducing disease in one species compared to another. Both agent and host factors are important in determining whether or not transmission of disease takes place. Clearly the major concern following the identification of BSE was whether or not it would transmit to the human population. However following identification in cattle an agent indistinguishable from BSE was recovered from zoo ruminants with a spongiform encephalopathy. Between 1986 and 1992 cases occured in bison, nyala, gemsbok, two species of oryx, greater kudu and eland. The source of the infection was the same meat-and-bone meal – containing concentrated feed responsible for the disease in cattle. These species are somewhat closely related to domestic cattle but in 1990 a case of spongiform encephalopathy was diagnosed in a domestic cat. Again the agent proved indistinguishable from BSE using strain-typing techniques similar to those described below for variant CJD (vCJD). Subsequently there have been 85 cases of feline spongiform encephalopathy (FSE) spread widely throughout the UK. The true incidence is almost certainly at least double that observed because diagnosis is patchy and the disease was not statutorily notifiable until 1994. Again it is believed that the route of transmission was oral and that the source of infection in this case was commercially produced cat food. A voluntary ban on the inclusion of specified bovine offal in pet food was introduced in 1989 before a statutory ban in 1990. The number of cases of FSE is now slowly declining (*Table 2*). Five of these cases were born after the ban on specified bovine offals in pet foods and one possible explanation is that these animals were exposed to long shelf-life products produced before the ban. A spongiform encephalopathy indistinguishable from FSE has been found in other members of the Felidae notably puma, cheetah, ocelot and a tiger in zoos in the UK between 1992 and 1995. The probable exposure here was through the consumption of bovine spinal cord in the raw meat that was fed to these animals. The clinical signs of FSE in cats in which ataxia, hyper-reflexia and behavioural

Year	New infections		Cases	
	Expected value	95% prediction interval	Expected value	95% prediction interval
1996	189	(155 – 11,300)	7,386	(6,541 – 8,856)
1997	95	(63 – 236)	4,111	(3,006 – 7,664)
1998	38	(21 – 214)	1,864	(1,153 – 7,052)
1999	12	(5 – 162)	682	(388 – 5,909)
2000	3	(1 – 86)	221	(128 – 3,660)
2001	1	(0 – 33)	72	(45 – 1,592)

Table 1. Predictions of new infections and cases of BSE from 1996 – 2001.

1990	1991	1992	1993	1994	1995	1996	1997	1998
12	12	10	11	16	8	6	6	4

Table 2. Number of cases of Feline Spongiform Encephalopathy in Great Britain by year of diagnosis.

changes are common features is, in general terms, very similar to BSE in cattle.

Thus in the 1980s and 1990s in the UK we had created a major epidemic of BSE in cattle by recycling contaminated remains back to susceptible animals via feed and transmitted the disease to exotic zoo animals and domestic and wild cats, all apparently by the oral route. Already at the end of the 1980s the possibility that BSE posed a risk to human health had been acknowledged. Accordingly important measures were introduced between 1988 and 1990 and once again these measures were based on sound public health principles. One of the most probable routes of transmission was interrupted a) by slaughtering and destroying sick cattle so they did not enter the food chain (1988) and b) by removing from the human food chain those bovine tissues, which by analogy with scrapie, were liable to contain the highest concentrations of the transmissible agent. The latter was the specified bovine offals ban of 1989. Then in 1990 the CJD Surveillance Unit was set up to monitor CJD in the UK to determine whether there were any changes in the incidence or the nature of the disease over time. Even if BSE proved to be capable of causing human disease it was unlikely that the first thing that would have been noticed was a marked increase in the overall numbers of CJD. Thus, and again using good communicable disease principles, the incidence of the disease in certain sentinel groups was carefully monitored. In this case the sentinel groups were those who, by virtue of their occupation, might have particularly close contact with BSE affected animals i.e. farmers, veterinarians and abattoir workers. By 1995 the third and fourth farmer to develop CJD since 1990 were recognised and the statistics showed that there was only a low probabililty that this had occurred by chance. Nevertheless the clinical disease in these farmers was typical of classical CJD and in due course strain-typing also indicated that these were cases of classical CJD. To date there have been no cases of CJD in veterinarians or abattoir workers during the past decade.

However in May 1995 the first teenager ever to be diagnosed with CJD in the United Kingdom died and in October of that year there was the death of a second teenager. From this point on other relatively young cases began to appear and the clinical and pathological features of these cases were similar to each other and different from classical, sporadic CJD. The patients were relatively young (mean age at onset 29, range 16-51), the duration of the illness relatively long (12-14 months as opposed to 4-5 months) and the early symptoms were often of a behavioural nature. On investigation the characteristic EEG pattern of sporadic CJD was not seen and neuropathological examination of the brain showed florid plaques and extensive cerebellar involvement with multiple PrP deposits. The recognition of this illness which came to be known as new variant CJD (nvCJD) now variant CJD (vCJD) led to the uncomfortable conclusion that the most likely explanation was exposure to BSE. In March 1996 there was only circumstantial evidence to support this. The hypothesis was biologically plausible, the cases were geographically limited to the UK, there was a temporal relationship between BSE in cattle in the 1980s and vCJD in humans in the 1990s and finally, no other persuasive explanation was available. Not unnaturally some were sceptical of the connection and the question “Is there really a link between BSE and nvCJD?” was frequently asked. The question was answered by the classic approach of comparing the types or strain of transmissible agent recovered from patients with that from the

putative source. Two approaches were used. In the first the size of the PrP fragments remaining after protease digestion and the relatively high concentration of the di-glycosylated form indicated that vCJD was distinct from the previously recognised forms of CJD. Moreover there were similarities between the PrP^{Sc} types recovered from cases of vCJD, BSE and FSE. The second approach determined the incubation period and the lesion profiles in inbred strains of mice and found that BSE, FSE and vCJD were indistinguishable and yet clearly distinct from classical CJD.

The second question concerns the route of exposure of humans to BSE. The working hypothesis since the recognition of the association between vCJD and BSE is that humans acquired the disease by the oral route due to the inclusion in the human food chain of the tissues that contain the highest concentration of the transmissible agent notably brain, spinal cord, dorsal route and trigeminal ganglia, retina and intestines. This remains the working hypothesis but so far there is no direct evidence to support it. Indeed it is unlikely that this will materialise since the retrospective analysis of the ingredients of the enormous variety of human foodstuffs is extremely difficult. However the main measures to protect public health have been concerned with the interruption of this route of transmission with first the banning of sick animals from the human food chain (1988), then the specified bovine offal ban (1989) followed by the ban on mechanically recovered meat of bovine origin (1995) and finally the beef on the bone ban (1997).

The third question that was asked immediately the announcement of a possible link between BSE and CJD was made in 1996 was “How many cases of new variant CJD will there be?” Estimates at the time ranged from “Not many more than there are at present” to “Some very large numbers”. Unfortunately the range still remains the same. Ideally in answering this question one would like to be armed with a sensitive and specific test for the transmissible agent in individuals who are incubating the disease. None is available at present but there are some promising leads. In one of the vCJD cases the protease resistant prion protein has been found in the lymphoid tissue of the appendix two years prior to the onset of symptoms. In cases with symptoms, PrP^{Sc} can be detected in tonsil and spleen. Thus tonsil biopsy and analysis can be used for the pre-symptomatic diagnosis of vCJD in the same way that it can for scrapie. Currently consideration is being given to large scale studies of the material resulting from routine tonsillectomies and appendicectomies. In the absence of such information the predictions have to be based on mathematical modelling. To date there have been 3 deaths from new variant CJD in 1995, 10 in 1996, 10 in 1997 and 15 in 1998. There is not sufficient information in this time series to narrow down the theoretically possible numbers for the future and certainly the pattern does not exclude the possibility of a large number of cases in the future. Moreover it may still be 3-5 years before this uncertainty about the future size of the epidemic will be significantly reduced.

The other classical communicable disease approach to predicting the size of an epidemic is to define and concentrate on the “at-risk” groups. The age range of cases of vCJD is strikingly restricted especially for a disease which probably has an incubation period of 10 years or more. The cases to date indicate that either susceptibility or exposure or incubation period is age dependent. The other striking aspect of the cases so far relates to a common

polymorphism at codon 129 of the PrP gene. Either methionine or valine is encoded and approximately 40% of the UK population is homozygous for methionine (MM), approximately 10% homozygous for valine (VV) and approximately 50% heterozygous (MV). In sporadic CJD 80% are MM, 10% VV and 10% MV. More than 30 cases of vCJD have been tested and all of them have proved to be MM.

Is the problem now under control? The cattle epidemic is disappearing fast. The necessary controls are in place so there is very little likelihood of further transmission from cattle to man. There is a theoretical possibility that BSE has infected sheep and is being sustained in the national flock. Preliminary work has not given any indication that this is the case but further research is needed. Meanwhile regulations governing ovine specified risk materials are in place. Whilst there is still the possibility of a sizeable outbreak of vCJD we must be concerned about the possibility of human-to-human transmission. Plasma products are now being prepared from non-UK plasma and blood is being leucodepleted prior to transfusion. The decontamination of surgical instruments which have come into contact with lymphoid tissue is under consideration.

It will be many years yet before we can be sure we know the final outcomes of the BSE epidemic and are able to count the cost. We cannot return to wholly extensive farming but we need to remain concerned about the possible consequences of the intensity of our production methods and any new developments such as genetic modification. Such developments will often be of benefit but occasionally may give rise to significant human health problems. In such a context we must continue to apply the important principles of public health.

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