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B S E AND SLOW VIRUSES

There are a number of rare transmissible agents in man and animals which attack the central nervous system and cause the brain's grey matter to degenerate. Since 1985, cattle have succumbed to a bovine form of this disease(BSE) in increasing numbers, leading to a series of control measures by Government. Debate continues however, on the public health implications of BSE.

This briefing note examines the current state of knowledge of 'slow viruses' such as BSE, the evidence relevant to the public health implications and uncertainties which remain.

THE SLOW VIRUSES

The slow viruses (so-called because of their transmissibility and long incubation period) are a group of agents which cause progressive neurological disorders which are ultimately fatal. The agents responsible have not been characterised but they are believed to be simpler than a virus. They do not trigger any immune response by the body, nor can they be grown outside the body of an animal. They are identified through their effects on brain tissue, which degenerates to give a spongy appearance - hence the generic term of spongiform encephalopathies (SE). Versions of the slow viruses have been found in several animal species and man. Some have been known for hundreds of years, while others have only been diagnosed recently (Table 1).

TABLE 1: SLOW VIRUSES IN DIFFERENT SPECIES

Species	Disease	First Recorded
Sheep/goats	Scrapie	1732
Man	Creutzfeldt-Jakob Disease (CJD)	1920
	Kuru	1900
Mink	Transmissible Mink Encephalopathy	1947
Cattle	Bovine Spongiform Encephalopathy (BSE)	1985
Deer/ Antelopes	Chronic Wasting Disease	1967 1980's
Cats	Feline Spongiform Encephalopathy	1990

The nature of the infective agents and their *modus operandi* are only incompletely understood. All are unusually resistant to sterilisation procedures which would remove bacteria and viruses. The only way of unambiguously determining if an animal is infected is to inspect the brain, or inject its tissue into the brains of mice and wait (months to 2-3 years) to see if they develop the disease. There is no current method of detecting infection in living animals lacking symptoms. A more technical description of what is known of the nature of the slow viruses is given in the box below.

TRANSMISSION

The routes by which slow viruses can be transmitted are critically important in determining if disease in one species or individual is a threat to another. Unfortunately, because we cannot identify the infective agents, all conclusions on transmission in real life have to be based on circumstantial evidence using epidemiology, or inferred from laboratory experiments. With scrapie, sheep can infect one another (transmission from ewe to lamb is believed to be both *in utero* and through ingestion of the highly infectious placenta after birth), and the disease is therefore endemic and difficult to eradicate. In other species (mice, mink, humans), the corre-

What do we Know about Slow Viruses?

Examination of infected brains fails to reveal any conventional micro-organisms such as bacteria or viruses. Dissolving the tissue with a protein-dissolving enzyme leaves twisted filaments ('fibrils'). These are comprised of a protein normally present in the brain, but which sticks together to form fibrils in infected tissues.

The fibrils can be infectious, but pure natural protein is not. Research has yet to discover the infectious component of the fibrils, but has been underway for some time. It is not clear whether the modified protein is somehow capable of directing its own replication and modification, or whether small quantities of genetic material from the slow virus exist to take over and direct brain cell function.

Many different strains of slow virus exist. Scrapie, for instance, has over 20, each having a characteristic incubation period and lesion type/location. When scrapie is transferred to another species (eg in laboratory mice), the dominant strain may change. This ability to adapt suggests that the slow viruses do contain some genetic information.

Susceptibility to scrapie is influenced by genetic factors, and a gene which controls the onset of the disease has been located in sheep. While this offers a possible method of introducing resistance into flocks, it would not prevent sheep becoming infected.

TABLE 2: CHRONOLOGY OF SOME BSE-RELATED ACTIONS	
Nov. 1986	BSE first identified as a separate entity
April 1988	Southwood Committee set up
June 1988	BSE made a notifiable disease
July 1988	Ban on feeding ruminant protein to ruminants Compulsory slaughter and destruction of carcasses
Feb. 1989	Southwood Committee report published Tyrrell Committee set up (interim report June '89)
Nov. 1989	Ban on specified offals for human consumption
Feb. 1990	Voluntary ban by industry on use of specified offals in rendering

sponding disease is not normally spread from one infected individual to another, and the disease is said to occur in a 'dead-end' host (the spread of Kuru in the Fore tribe of New Guinea has been attributed to the ceremonial handling or ingestion of infected human brains). Whether transmission occurs with cattle (e.g. from cow to calf) has not yet been established.

The diseases are most readily induced in laboratory animals by injections (particularly to the brain). With humans, Creutzfeldt-Jakob Disease(CJD) has also been transmitted through grafts or injections of contaminated material. Eating infected tissues has also caused disease in the case of mink, mice, primates etc, and is one possible cause of recent cases of feline SE. Comparisons of the efficiency of transmission by different mechanisms suggests that ingestion is a relatively ineffective method of infection - up to 40,000 times less effective than intra-cerebral injection.

THE BSE OUTBREAK

The current outbreak of BSE was first recognised in 1986, and has now grown to around 1000 new cases each month (Figure 1). The epidemiological evidence points strongly to the cause being an infectious agent in protein concentrates which contained meat and bone meal. Table 2 lists some key actions subsequently taken.

It was assumed that the source of infection was scrapie from infected sheep tissues used in rendering processes[1]. As the BSE outbreak spread, scrapie would be supplemented by the BSE agent itself from infected cattle tissues, increasing the amount of slow virus entering the rendering process. An alternative hypothesis is that BSE may be a bovine form of slow virus which had been previously present but not recognised in cattle. The true origin cannot be unambiguously determined.

Irrespective of the exact origin of the infection, the key to its spread has been attributed to an increase in infected material rendered and to changes in rendering industry processes which may have reduced process severity (a combination of temperature, time and solvents used), allowing more of any infective agent to survive.

1. Rendering is a cooking and separation process whereby animal wastes (fats, bones, offal, carcasses etc.) are processed to extract fats and proteins (primarily tallows, and meat and bone meal).

Once the infection is present in feed concentrates, the large output of modern rendering plants can spread it through the extensive distribution networks of the major feed compounders. The geographical distribution of cases (more are encountered in the south than in the north) has been related by the Central Veterinary Laboratory to the extent to which feed compounders used meat and bone meal, and the severity of the process used by the rendering plant supplying them.

Measures subsequently taken (Table 2) are designed to avoid new cases of infection of ruminants through infected feed. If infected cattle cannot transmit the disease to other cattle or calves, BSE will work its way out of the cattle population as affected animals die. If secondary infection does take place, as with scrapie, BSE would prove more persistent. Depending on the efficiency of transmission, the disease could just take longer to die out or could, in the absence of new measures, become endemic like scrapie.

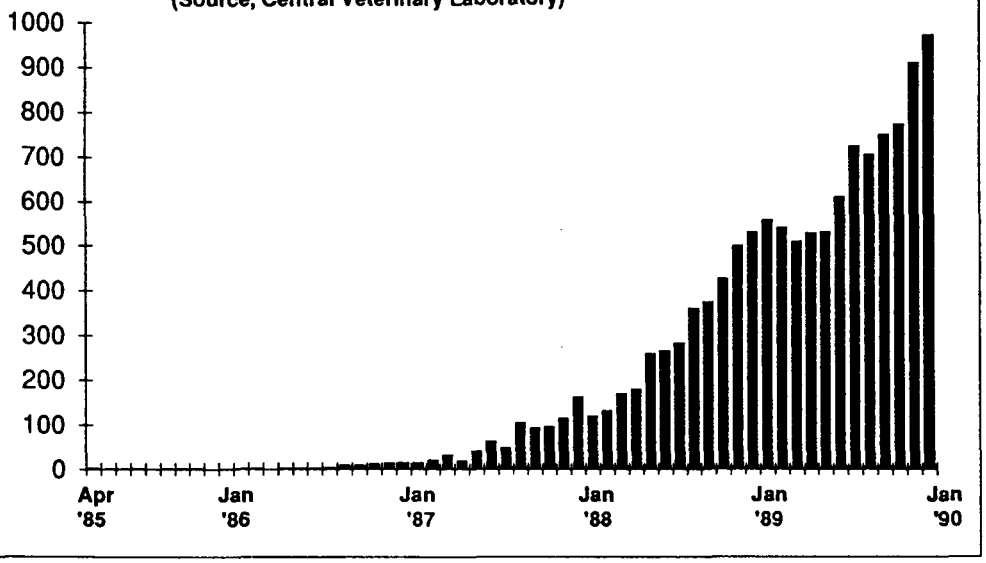
The 1989 report of the Working Party on BSE (the Southwood report) estimated the number of cases of BSE which would be expected to arise if cattle were 'dead-end' hosts. Given no change in exposure, 350-400 cases per month (0.1% of the cattle population each year) were expected until 1993, when numbers would start falling (the incubation period is 2.5-8 years). The actual number of cases (Figure 1) is higher than predicted, which may reflect the increase in exposure arising from infected cattle being rendered into meat and bone meal at the beginning of the epidemic, before this practice was banned. There is still no direct evidence of cattle infecting one another, though studies will not provide more definite answers until 1991/2 or later.

Abroad, BSE has been confirmed in Ireland. It has also been suggested that cases exist in other countries (including France and USA) which have been attributed to other diseases such as rabies.

FACTORS RELATING TO HUMAN HEALTH

The human slow viruses have been extensively studied. Kuru has steadily declined since exposure to infected brains was stopped in the 1950's, suggesting there were no other routes of transmission. CJD occurs throughout most countries at a low level (in the UK around 30 cases per year). In view of the clear similarities with scrapie, many studies have looked for a link either with eating sheep or occupational exposure to infected animals. While such epidemiological evidence cannot rule out the possibility that some individual cases of CJD originate from scrapie, these studies have yet to produce any conclusive evidence that human CJD has been caught from infected animals. Surveys of those who should be most at risk - shepherds, butchers, vets and abattoir workers show no higher incidence. Neither is there a relationship between the incidence of

FIGURE 1 : Numbers of Suspected BSE Cases each Month from April 1985 to January 1990 (Source, Central Veterinary Laboratory)



CJD in different countries and the incidence of scrapie in their sheep population.

Scrapie is endemic in most countries. While its true incidence in the UK is unknown, losses of 10-20% have been reported in some flocks. **If we have been eating sheep for hundreds of years, many of which have been infected with scrapie, is there is any basis for being more concerned at the consumption of beef products originating from cattle with BSE?** The answer will depend on whether there are differences between the infectivity of the BSE and scrapie agents and also on the levels of exposure involved. Relevant factors could include:

- Sheep are traditionally slaughtered by different methods than cattle, which may have led to less of the highly infected parts (brains, central nervous and lymphoid systems) entering the human food chain.

- Latest results suggest that BSE isolates contain new strains of slow virus which have not been previously obtained from sheep. It will not be clear whether this has any implications for infectivity for some time.

The infective agents do not proliferate in muscle tissue, offals are banned for human consumption, and all affected animals are destroyed. Thus human exposure to BSE-infected tissue has been reduced or eliminated. However, prior to the implementation of the ban on the use of offals for human consumption, some exposure will have taken place. Should the BSE agent be significantly more infectious to humans than scrapie, it is possible that human cases could follow after the incubation period. The results of research into the susceptibility of primates to infection are of interest here. So far, tests at the MRC's Clinical Research Centre show no effects on Marmoset monkeys 28 months after their brains were injected with BSE and scrapie-infected brain. This contrasts with earlier experiments where exposure to human CJD in the same manner caused disease as early as 18 months after injection.

Meat and bone meal will still contain scrapie, since infected sheep are still rendered. Depending on the effectiveness of the industry's voluntary ban on use of specified offals, BSE may also be present. Feeding meal to ruminants is now banned, but still allowed for pigs and poultry. This practice is viewed as unlikely to lead to further human exposure, since both poultry and pigs are killed for human consumption after only a few months. Thus even if the scrapie/BSE agents were able to infect these species, the long latency period of the disease would mean that there was insufficient time for the infective agent to proliferate in the animal.

Nevertheless, based on experience with sheep, there may be initial sites of infection (primarily the lymphoreticular system) before later spread into the central nervous system. The possibility of small amounts of the agent entering the human food chain cannot therefore be excluded if pigs or other species were to become infected. So far, the limited evidence suggests that pigs may be less susceptible than other species to slow virus infection, since experiments have failed to transmit Kuru to pigs from infected tissues. Other experiments feeding BSE-infected tissue to pigs are going on.

ISSUES

Meat/Bone Meal Sterilisation.

The possible problems associated with recycling animal wastes and tissues are not new - the Royal Commission on Environmental Pollution warned in its 7th report (1979) of the danger of transmitting disease-bearing pathogens to stock and thence to humans, through the recycling of animal wastes. The Southwood report pointed out that the increased efficiency of modern agriculture allows productive use to be made of animal waste which would otherwise create major disposal problems. However, these practices also open up new pathways for infection to animal and man, which the report concluded should be eliminated, e.g. by proper sterilisation of such animal products.

Current MAFF regulations require renderers to use conditions which are effective in killing *Salmonella* bacteria, but these are not effective against slow vi-

ruses. Hospital autoclaving procedures to inactivate scrapie and CJD have been defined (134°C under pressure for 18 mins), but the effectiveness of rendering processes in inactivating scrapie had not been studied by MAFF or the industry prior to the BSE outbreak. Thus it is not currently possible to define the process conditions necessary for complete sterilisation of meat and bone meal.

In view of the several years that will be needed to produce precise guidance on process inactivation of scrapie and BSE agents, some believe it prudent to review rendering process conditions now to see if their severity can be increased to reduce, if not eliminate, slow virus activity. There are different views in the industry on the practicality of such an approach - some suggest interim adoption of conditions equivalent to those used for hospital sterilisation, while the industry association believes that renderers cannot replicate the same environment as surgical autoclaving. MAFF appears reluctant to introduce official guidance or regulation until the results of joint MAFF/industry research are available (see below). Discussions on an EC draft regulation are, however, underway which may specify minimum acceptable processing conditions for rendering plants across the Community.

Key Uncertainties and Research Needs

Despite the extensive research over many years on slow virus diseases, many gaps in knowledge remain. They have been enumerated in detail by the Consultative Committee on Research into Spongiform Encephalopathy (the Tyrrell Committee), and MAFF has committed £12m over the next 3 years to pursue 20 of the 27 projects recommended. Some of the more important projects are designed to find out:

- **The nature of the infectious agent.** Despite analysis of the tell-tale protein fibrils (see box on page 1), the nature and *modus operandi* of slow viruses are still undefined. This impedes the search for a specific test for infection before symptoms show, as well as being an essential precursor to a search for a cure. Research is underway, but it is impossible to say when this fundamental gap may be remedied.

- **Conditions of inactivation.** These have been defined for hospital sterilisation procedures, but the effects of different rendering processes on activity are still unclear. Work relevant to industrial processes is being planned with support from MAFF and the industry, but is not yet underway. Given the delays inherent in testing using mice, conclusions are unlikely to be available for several years.

- **Infectivity and transmissibility of BSE.** Experiments to establish the transmissibility of BSE to other species (including primates) and from cow to calf are underway. Of the many tissues taken from infected cows, only brain has been shown to infect mice so far, but because of the long latency period, full conclusions will not be available for some years.

Policy Principles

Most experts see the absence of an epidemiological link between scrapie and CJD as indicating that BSE is unlikely to be a significant health threat to humans. Expert committees have thus recommended certain actions be taken because it is impossible to demonstrate that a risk does not exist rather than because a positive quantifiable hazard has been identified. This inability to prove a negative is a common problem with which public policy-makers have to grapple. Responses may be guided by one of two principles.

The first is to base policy on an assessment of risk made from the best available scientific evidence, incorporating appropriate safety margins to safeguard public or environmental health. The second, known as the precautionary principle, places a greater emphasis on anticipating possible consequences before scientific evidence is available on their exact importance. The latter approach is increasingly being proposed to deal with environmental issues where conclusive scientific proof of cause and effect is difficult or slow to obtain.

Government actions have included a number of precautionary measures based on expert recommendations. These are, in the view of both UK and EC experts, sufficient to stop the spread of BSE, and British beef is not considered to be a danger to public health, in the light of current knowledge. Nevertheless, there have been calls for the precautionary principle to be applied further in view of the uncertainties which will remain for some time. Such an approach could attempt to eliminate the current low but unquantifiable risk of slow viruses spreading to non-ruminants, either by restrictions on the use of meat and bone meal or by ensuring adequate sterilisation. The risk of maternal transmission will also not be quantified for some time, raising the issue of whether calves born to cows which subsequently become infected should be capable of being traced so as to allow follow-up studies or action.

FURTHER READING

Additional details and background information are available from POST, 2, Little Smith Street, London, SW1P 3DL. Tel: (071)-222-2688.

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