PART ONE

Background and Introduction

1.1. Transmissible spongiform encephalopathies (TSEs), otherwise known as prion diseases, are rare, fatal, degenerative diseases affecting the central nervous system (CNS), that occur in humans and certain other mammals.

1.2. There are several recognised TSEs, including Creutzfeldt-Jakob Disease (CJD) in humans, bovine spongiform encephalopathy (BSE) in cattle and scrapie in sheep. These and other TSEs are summarised in Box 1.

1.3. TSEs are in many ways unique, and exhibit biological properties that are different from those of other microbiological diseases[1,2,3]. A useful summary about these diseases has been published previously by the Spongiform Encephalopathy Advisory Committee (SEAC)[4]. Some of the important features relevant to occupational exposure are summarised below:

(a) TSEs are caused by unconventional infectious agents currently thought to be infectious proteins (apparently without nucleic acid) known as prions which do not share the normal properties of viruses or bacteria. The CNS contains the highest levels of infectivity which is associated with accumulation of a modified host-encoded protein, prion protein. In TSEs, prion protein undergoes a structural change (involving re-folding) to a conformer with an increased beta – sheet structure. This conformational change renders the abnormal prion protein more resistant to degradation, and is associated with infectivity. The abnormal form of prion protein is only found in TSEs, but the mechanism and site of its conversion are still uncertain.

(b) A common feature of all TSEs is the appearance of microscopic vacuoles in the grey matter of the CNS, giving a sponge-like appearance, from which the conditions derive their name. This change is accompanied by the accumulation of the abnormal form of the prion protein in the CNS.

(c) The commonest form of CJD occurs as a sporadic disease, the cause of which is unknown, although genetic factors (particularly the codon 129 polymorphism in the prion protein gene (*PRNP*)) influence disease susceptibility. The familial forms of human TSEs (see Box 1) appear to have a solely genetic origin and are closely associated with mutations or insertions in the *PRNP* gene. Most, but not all, of the familial forms of human TSEs have been transmitted experimentally to animals. There are no known familial or genetic TSEs of animals, although polymorphisms in the *PRNP* gene of some species (sheep for example) may influence the length of the incubation period and occurrence of disease.

(d) Although TSEs are not contagious, they are experimentally transmissible by inoculation and in some cases by oral challenge. Some animal TSEs, such as scrapie, are naturally transmissible to sheep and goats and chronic wasting disease (CWD) is naturally transmissible to several North American species of deer and elk, but how this is effected is still uncertain. Transmissible mink encephalopathy (TME) and BSE are feed-borne diseases. Transmission of TSEs to humans has occurred from both human and bovine sources, resulting in iatrogenic CJD and variant CJD respectively (see Box 1). Other animal TSEs, including scrapie, do not appear to cause human disease.

(e) TSE agents are not uniformly distributed in the tissues of affected individuals and infectivity levels vary at different stages of incubation. In general, during the clinical disease, CNS tissues (including the retina) pose the highest risk, lymphoid tissues, cornea and dura mater are lower risk and most body fluids and other tissues negligible risk (for more detail see Tables A1 and A2);

(f) TSE agents exhibit an unusual resistance to conventional chemical and physical decontamination methods. They are not significantly affected by disinfectants like formalin and ethylene oxide, and infectivity persists after standard autoclaving (e.g. 134°C for 3 minutes). They are also extremely resistant to high doses of ionising and UV irradiation and some residual activity has been shown to survive for long periods in the environment;

(g) All TSEs are invariably progressive and fatal once clinical signs appear; there is currently no known effective treatment or prophylaxis, although this is an area of active research and clinical trials in humans have been established.

(h) There have been no confirmed cases of transmission of TSE to humans as a result of occupation. If TSEs could be transmitted in the occupational setting this would be most likely to occur from exposure to infected tissues or materials by direct inoculation (e.g. puncture wounds, 'sharps' injuries or contamination of broken skin), by splashing of the mucous membranes or, exceptionally, by swallowing.

1.3. The unconventional nature of the agent, together with the appearance of BSE in the mid-1980s and variant CJD in the mid-1990s, has led to a considerable amount of scientific research. This in turn means that there is a need for updated guidance on safe work practices in laboratories and

small and large laboratory animal accommodation as new information on these diseases continues to emerge. There is also a need to provide guidance for health practitioners on the risks from humans infected with TSE agents.

Scope of this guidance

1.5. Health and safety law sets out a series of general duties on employers, employees and self-employed people. There are specific regulations which cover work with biological agents such as those causing TSEs, notably the Control of Substances Hazardous to Health Regulations 2002 (COSHH)[5]. These require employers to assess the risks in all cases where there may be exposure to biological agents and when appropriate introduce measures to either prevent or adequately control exposure. COSHH applies whether there is a deliberate intention to work with the agent (such as in a research laboratory) or whether exposure is incidental to the work (such as in a hospital ward or operating theatre).

1.6. This guidance is therefore divided into three main sections as follows:

- Hazards and risk associated with workplace exposure to TSE agents (including information on health and safety law);

- Containment and control measures for laboratory work with TSE agents, materials and infected animals (i.e. where there is deliberate intention to work with the agent or where laboratory workers are handling material that may contain the agent;

- Infection control of CJD and related disorders in healthcare settings (i.e. where any exposure to the agent is incidental to the work).

1.7. The purpose of this document is to provide guidance to employers on the precautions to control the risk of exposure of employees and others to TSE agents from work activities. The guidance applies to many occupations that involve contact with people or animals infected with TSE agents, or potentially contaminated material. It should also be drawn to the attention of those responsible for advising others who may come into contact with TSE during the course of their work. Included in these groups are:

- laboratory staff (including experimental animal house staff);
- healthcare workers (including infection control staff; medical and nursing staff particularly in neurology, ophthalmology, neuro- or ENT-surgery, oral and maxillofacial surgery; and dentistry; sterile services supply staff and medical engineers);
- staff involved in hospice and community care;
- pathologists (including veterinary pathologists), pathology laboratory staff, post mortem technicians;
- funeral, cemetery and crematorium workers;
- local Consultants in Communicable Disease Control (CsCDC) and Health Protection Teams.

1.8. Additional advice for veterinary surgeons and those involved in the transportation, slaughtering and processing of cattle and cattle products can be found in a separate Advisory Committee on Dangerous Pathogens publication "BSE Background and general occupational guidance"[6]. Guidance on handling meat-and-bone-meal (MBM) material[7] and an information sheet on common zoonoses in cattle[8], which will be of interest to farmers and others involved in animal husbandry, have also been published by the Health and Safety Executive. Details of these publications are given in the References.

Box 1 Human and Animal TSEs

The human TSEs occur in 3 groups:

- Idiopathic diseases: Sporadic CJD and sporadic fatal insomnia
- Familial diseases: Familial CJD, Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia
- Acquired diseases: Human agents: Kuru and iatrogenic CJD
  Bovine agent: Variant CJD

All human TSEs are very rare; the world-wide incidence of CJD is about 1 per million people each year. Sporadic CJD accounts for around 85% of all human TSEs; familial TSEs account for around 10-15% of cases and the remaining smaller numbers include the acquired human TSEs. In sporadic CJD the usual age of onset is late middle age (average age 65 years). Most patients present with rapidly progressive dementia with focal neurological signs including ataxia, myoclonus, visual disturbances and rigidity. Death usually occurs within 4-6 months of clinical onset. The clinical features of familial TSEs are much more variable, even within affected families. Some patients exhibit clinical features which resemble sporadic CJD, while in GSS most patients present with ataxia and other movement disorders before the onset of dementia. In sporadic and fatal familial insomnia, patients usually suffer from prominent sleep disturbances before the onset of other neurological abnormalities.

Kuru occurred as an epidemic in the Fore-speaking people in the Eastern highlands of Papua New Guinea and was first reported in 1957. Its transmission was associated with funeral rites involving ritual contact with, preparation of, and consumption of the entire body (including brains) of relatives who had died of kuru. The similarity, especially of the neuropathology, between kuru and scrapie, a disease of sheep that had been shown to be transmissible some 20 years earlier, led to the subsequent successful experimental transmission of kuru to primates. A link was thus established between human contact with kuru-infected tissues, their consumption and the eventual development of kuru. The incidence of kuru has been markedly reduced following the abolition of cannibalism coupled with health education, although recent cases still arise

from historical exposure, indicating a maximum (to date) incubation period of around 40 years. The shortest incubation period in kuru is reported to be about five years.

The first case of iatrogenic transmission of CJD was identified in 1974 in a corneal graft recipient. Since then several hundreds of cases of iatrogenic CJD have been reported, most of which have occurred in recipients of human-derived pituitary hormones or human-derived dura mater grafts. Other rarer sources of infection include contaminated neurosurgical instruments and intracerebral electrodes. Incubation periods for iatrogenic CJD range from 1-2 years for neurosurgical routes of transmission to over 30 years in some pituitary hormone recipients. World Health Organisation guidelines on TSE's in relation to biological and pharmaceutical products have been published recently[9].

In 1996, the National CJD Surveillance Unit in the UK[10,11] identified a new form of CJD, which is now known as variant CJD. Variant CJD generally affects young adults (mean age at onset 28 years) with a clinical illness that lasts on average for 14 months. The initial features include psychiatric abnormalities and sensory abnormalities, which are usually followed by ataxia, myoclonus and other movement disorders and accompanied by dementia. At the time of writing, over 140 cases of variant CJD have been identified, over 90% of which have been in the UK. Considerable uncertainty exists over the likely future numbers of variant CJD cases in the UK; there has been a small but important decline in the incidence of the disease in 2002. There is a substantial body of evidence from multiple transmission studies to indicate that the agent responsible for variant CJD is biologically indistinguishable from the BSE agent, making this the only known human TSE which has arisen from infection from another species.

There have been no confirmed cases of transmission of TSE by virtue of occupation. There have been a small number of reports of sporadic CJD in healthcare workers (including a neurosurgeon, retired laboratory workers and a pathologist) but their link with their occupation is speculative. There is no evidence at present that occupational exposure to BSE is a risk factor for variant CJD.

The animal TSEs are:

- scrapie in sheep, goats and moufflon;
- bovine spongiform encephalopathy (BSE) in cattle;
- transmissible mink encephalopathy (TME) in farmed mink;
- chronic wasting disease (CWD) in deer and elk species;
- feline spongiform encephalopathy (FSE) in domestic cats and captive exotic felines;
- spongiform encephalopathy in captive exotic ungulates.
- Spongiform encephalopathy reported in primates in a French zoological collection.

BSE was first confirmed in the United Kingdom in 1986. Up to December 2002 about 183,000 native-born cattle in the UK are known to have been affected, and a total of over 3,000 native-born cattle in several other countries, including most countries of the EU. Current statistics can be found on the Defra webiste[12]. A few cases have occurred in these and some other countries following export of live cattle from countries with BSE.

Affected animals become unsteady on their feet, lose weight and become nervous, hence the term 'mad cow disease'. The BSE epidemic has been in continuous decline since 1992/3 in the UK as a result of successive bans on feeding ruminant-derived protein and subsequently mammalian-meat-and-bone-meal to ruminants. All animals suspected of having BSE are compulsorily slaughtered and completely destroyed. Ruminant or more extensive feed bans are now applied throughout the EU and in many other countries of the world, even those unaffected by BSE.

Scrapie occurs in sheep, and more rarely in goats and moufflon, and has been recognised for more than 250 years. Affected animals often scrape themselves against objects to alleviate itching, become unsteady on their feet and lose condition. It is endemic in flocks in many countries, but there is no evidence that it can be transmitted to humans.

TME was first recognised in farmed mink in 1947 and has occurred sporadically since then, but there have been no reports since the 1990s. CWD in Rocky Mountain elk, mule deer and some other deer species is also a TSE. Originally seen only in wild-life facilities in the USA, CWD is now reported in free-ranging and farmed deer and elk in the USA and in Canada. There have been recent reports of CWD in elk exported from Canada to Korea. CWD has not been reported in Europe and TME has not been reported in the UK. TSEs have been recognised in domestic cats and captive, exotic felines and ungulates, most, but not all of which were born in the UK. Strain typing studies have indicated that at least some of these cases and perhaps all are due to exposure to the BSE agent, presumably by the dietary route. These 'mini-epidemics' appear to have subsided to obscurity as a result of the various bans to protect animal species from feed exposure to TSE agents.

Report of a spongiform encephalopathy in primate species in France, and a captive golden cat from Europe that died in Australia, did not involve any residence in the UK.

Reference List:

1. Collinge J (2001) Prion diseases of humans and animals: their causes and molecular basis. Annu Rev Neurosci. 2001; **24**: 519-50.
2. Lasmezas CI (2003) The transmissible spongiform encephalopathies. Rev Sci Tech **22** (1): 22-36.
3. DeArmond SJ, Prusiner SB (2003) Perspectives on prion biology, prion disease pathogenesis, and pharmacologic approaches to treatment. Clin Lab Med 23 (1): 1 -41
4. Transmissible Spongiform Encephalopathies - a summary of present knowledge and research. Spongiform Encephalopathy Advisory Committee. HMSO 1995. ISBN 0 11 242 9874.
5. Control of Substances Hazardous to Health Regulations (Fourth Edition): The Control of Substances Hazardous to Health Regulations 2002. Approved Code of Practice and Guidance. HSE Books. ISBN 0-7176-2534-6
6. BSE (Bovine Spongiform Encephalopathy): Background and General Occupational Guidance. HSE Books. 1996. ISBN 0-7176-1212-0.
7. Guidance for handling meat and bone meal material. MISC 088 1998, (Free supplement to the occupational BSE guidance available from HSE Books.)
8. HSE Agriculture Information Sheet No. 2 (revised) "Common zoonoses in cattle". http://www.hse.gsi.gov.uk/pubns/ais2.pdf.
9. WHO/BCT/QSD/03.01 'WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products. World Health Organisation 2003.
10. Will RG *et al.* (1996) A new variant of Creutzfeldt-Jakob disease in the UK. Lancet **347** (9006): 921-5.
11. National CJD Surveillance Unit (NCJDU) Home page: http://www.cjd.ed.ac.uk/
12. Department for Environment, Food and Rural Affairs. BSE Home Page: http://www.defra.gov.uk/animalh/bse/

Published: 15 December 2003