INTERNATIONAL WORKSHOP ON TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES SURVEILLANCE (CJD - BSE)

16 - 18 March 1998

Buenos Aires, Argentina

Final Report

With the cooperation of:

• Argentine Ministry of Health and Social Action
• Argentine Neurology Society
• Argentine Pathology Society
• National Service of Agrifood and Quality
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"The Surveillance of Creutzfeldt-Jacob disease (CJD) and other Transmissible Spongiform Encephalopathies (TSEs)"
SECTION I: Background and Agenda
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Considerations. Dr. Jaime Estupiñán
BACKGROUND:

CJD is a rare and fatal disease caused by neurodegenerative changes. Like other transmissible spongiform encephalopathies (TSE), it is experimentally transmissible to animals with the resulting neuropathological changes. Epidemiological studies show that their occurrence is worldwide with an annual incidence of 1 case per million inhabitants. In 85% of the cases, it is a sporadic disease, in 10-15%, it is hereditary, while the remaining cases are iatrogenic.

During 1986 the first case of bovine spongiform encephalitis (BSE) resulting from the ingestion of meat and bone meal contaminated with TSE agents was reported in England and gave rise to an epidemic.

In March 1996, 10 human cases of a new variant of CJD (nvCJD) were also reported in England. It was therefore considered necessary to initiate research on the possible association of such patients and exposure to the agent of BSE. As basis for the studies, the systems for CJD surveillance in Europe were checked and strengthened.

As a result of the increasing scientific knowledge on both human and animal TSE in recent years and there is greater awareness of the need for strengthening TSE surveillance in man, in particular CJD, as a first step towards differentiating this disease from other TSE. It was also found necessary to reinforce and in some instances, to initiate, surveillance of TSE in animals.

OBJECTIVE:

To analyze and discuss the methodology to be applied in order to strengthen surveillance of Creutzfeldt-Jakob disease in the countries of Latin America and the Caribbean.
INTERNATIONAL WORKSHOP ON THE SURVEILLANCE OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (CJD, BSE)
WHO/PAHO - INPPAZ - OIE
16 - 18 March 1998

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LANGUAGE: English/Spanish with simultaneous translation

AGENDA

Monday, 16 March 1998

08:30 - 09:00 Registration
9:00 - 09:30 Introduction and welcome remarks.
Dr. Jaime Estupiñán, INPPAZ-OPS.
09:30 - 11:00 Human TSEs. Overview and epidemiology
Dr. Zeidler, WHO/Geneva
11:00 - 11:30 Coffee break
11:30 - 13:00 Pathology of human TSEs
Dr. Ironside (WHO/Geneva)
13:00 - 14:00 Luncheon
14:00 - 15:00 Safety issues
Dr. Ironside (WHO/Geneva)
15:00 - 15:15 Coffee break
15:15 - 16:45 New Variant CJD
The reasons for global CJD surveillance
Videotape
Dr. Zeidler, WHO/Geneva
16:45 - 17:15 Discussion on Surveillance

Tuesday, 17 March 1998

09:00 - 10:15 Presentations by the countries
(Information on CJD in the participating countries)
10:15 - 10:30 Coffee break
10:30 - 12:30  Presentation (continued)
12:30 - 13:00  Videotape on kuru
13:00 - 14:00  Luncheon
14:00 - 16:15  Further discussion on CJD surveillance and the production of recommendations (working groups)
16:15 - 17:00  All participants

**Wednesday, 18 March 1998**

09:00 - 10:00  Animal TSEs - an overview
Dr W.G.Bradley

10:00 - 10:30  Coffee break

10:30 - 11:30  Bovine spongiform encephalopathy - Surveillance
Dr. W.G.Bradley

11:30 - 13:00  TSE surveillance programs in Latin America and the Caribbean

13:00 - 14:00  Luncheon

14:00 - 15:30  Discussion on TSE surveillance and the production of recommendations
All participants.

15:30 - 16:00  Final discussion on TSE surveillance
All participants

16:00 - 16:30  Closure
INTERNATIONAL WORKSHOP ON THE SURVEILLANCE
OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
(CJD, BSE)
WHO/PAHO - INPPAZ - OIE
Argentina, 16 - 18 March 1998

Conclusions and Recommendations

As regards TSE in man, the Workshop endorsed the following conclusions and recommendations:

For the Countries

1) There was consensus on the need to improve TSE surveillance and on recommending the creation in each country of Surveillance Systems oriented to that end.
   The election of a Coordinating Institution or Focal Point charged with centralizing information in coordination with the national surveillance systems was recommended;

2) The adoption of the WHO definition of case (included in the Training Manual) was recommended for surveillance purposes;

3) In view of the characteristics of this group of diseases in humans (CJD/ nvCJD), Neurologists, Pathologists, Neuroepidemiologists, Psychiatrists, and EEG technicians were identified as primary sources of information;

4) For the notification of suspect cases, forms requiring the minimum necessary clinical information according to the definition of case should be used. For the investigation of cases, the forms designed by WHO should be used;

5) The information should flow from the primary sources toward the Coordinating Institution or Focal Point, and from these toward the local and supranational agencies (PAHO/WHO). Results should be reported to PAHO/WHO at least once a year. Any presumed or confirmed case of new variant of CJD should be reported as soon as possible;

6) The Coordinating National Centers should promote events related to the above-mentioned disciplines for the purpose of strengthening surveillance, to be initiated if possible in 1998;

7) Diagnosis confirmation should be performed by the corresponding National Centers, with the support of the Regional Reference Center when necessary;

8) To confirm the diagnosis of definitive cases, the performance of post mortem cerebral biopsy was recommended.
   In accordance with WHO recommendations, cerebral biopsy in vivo is not recommended, except for the alternative diagnosis of treatable diseases.

9) In cases when it is necessary to inform the public, the guidelines designed by the WHO for that purpose should be used in order to avoid unnecessary alarm;
10) Each country should identify its needs for training human resources and WHO/PAHO shall cooperate in the selection of Training Centers;

11) Intersectorial communication should be encouraged by the integration of the National Commissions with representatives of the disciplines related to the above-mentioned diseases;

1) The National Commissions should disseminate biosecurity measures originating in the WHO;

13) Taking into account the current development of the TSE Surveillance Center in Argentina, it was agreed that it should serve as WHO Regional Collaborating Center;

14) The participation of TSE Surveillance Focal Points in the next Pan American Neurology Congress to be held in Cartagena, Colombia, in 1999 should be encouraged with a view to evaluating the progress made in surveillance activities.

For WHO/PAHO/OIE

1) To facilitate the training of personnel in such countries as may request it;

2) To continue providing technical cooperation for the organization of TSE surveillance;

3) To promote and process the designation of the TSE Surveillance Center in Argentina as Regional WHO Collaborating Center and, if possible, to provide economic resources for its operation;

4) To support cooperation and coordination among the countries for TSE surveillance;

5) To continue providing technical information to the national agencies;

6) To cooperate with the countries in identifying sources of funds and securing economic resources for the strengthening of TSE surveillance.
As regards **TSE in animals**, the Workshop arrived to the following conclusions and recommendations:

**CONCLUSIONS:**

The results of surveillance and prevention actions developed by the countries with respect to BSE showed that the disease was not present in the countries of the American continent.

**RECOMMENDATIONS:**

For the countries:

1. Each country should review its normative and regulatory bases with respect to TSE and harmonize them according to the regulations set forth in the International Zoo-Sanitary Code of the OIE;

2. Each country should reinforce the resources available for the diagnosis and epidemiological surveillance of TSE, standardize techniques and procedures, and incorporate new diagnostic techniques, in accordance with the recommendations made by the OIE;

1. The countries should attempt to harmonize epidemiological surveillance systems by promoting the participation of all the sectors involved, mainly stock farmers, with due account for the recognized bases of surveillance systems in operation in the Latin American Region;

2. Following the recommendations of the OIE, the implementation and updating of risk analysis systems with a multidisciplinary and technically coordinated approach covering the different aspects which characterize TSE epidemiology, should be fostered;

3. The establishment of information channels which give support to the transparent and timely dissemination of data on the surveillance and diagnosis of TSE in animals should be promoted..

For **WHO/PAHO/OIE:**

1. The Workshop recommended that through the Collaborating and Reference Centers, the OIE implement the harmonization of diagnostic techniques by the homologation of systems and reagents;

2. The organization, through PAHO/WHO and OIE, of workshops and seminars on TSE training and information, for the continuous updating of the interested sectors should be promoted.
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WORKING GROUPS

Items to be considered by the working groups during the discussion on Human Spongiform Encephalopathies Surveillance.

Recommendations for the countries:

1- National Surveillance System Organization
   - Case definition (WHO)
   - Identification of primary sources of notification
   - Model form for the collection of information
   - Flow of information
   - Focal points
   - Interdisciplinary coordination

2- Laboratory diagnostic confirmation:
   - National Reference
   - International Reference
   - Autopsy
   - Biopsy

3- Dissemination of information and mass communication
4- Training needs
5- Biosafety measures
6- Intersectorial coordination
7- Coordination between countries

Recommendations for WHO/PAHO-OIE

- Training
- Technical cooperation
- Collaborating centers
- Cooperation between countries
- Promotion of epidemiological surveillance activities

Other matters
Dr. Jaime Estupiñán  
Pan American Institute of Food Protection and Zoonoses. INPPAZ- PAHO/WHO.

INTRODUCTION

Transmissible Spongiform Encephalopathies (TSE) are a group of diseases whose main features are long incubation periods, a progressive course causing degeneration of the central nervous system, as well as spongiform changes and ending always in death.

The encephalopathies affecting animals such as scrapie in sheep and goats, transmissible mink encephalopathy (TME); chronic wasting disease (CWD) of mule deer and elk, bovine spongiform encephalopathy (BSE) and feline spongiform encephalopathy (FSE) belong to this group. Those affecting humans are kuru, Creutzfeld-Jacob Disease (CJD) and the Gersman-Straüssler Syndrome (GSS).

Since BSE was first diagnosed in the United Kingdom in 1986, it has been a source of concern because of its potential effects on public health which led the World Health Organization (WHO) to assemble experts of worldwide standing for a discussion on the problem. To this end, meetings were held in 1991, 1993 and 1995.

Concern increased in March 1996 when the Spongiform Encephalopathies Advisory Committee (SEAC) of the United Kingdom reported on the possible relationship between BSE and a variant of the CJD in humans on the basis of circumstantial evidence, but with no scientific confirmation.

As a result, a further WHO consultation meeting was urgently summoned to consider public health issues related to transmissible spongiform encephalopathies, and took place in Geneva, Switzerland, on 2 -3 April 1996.

Subsequently, another consultation was carried out from 14 through 16 May 1996 with the participation of human and animal neurologists, neuropathologists and scientist to examine in detail the clinical, neurologic and neuropathologic findings associated with the new variant of Creutzfeldt-Jakob disease in comparison with other human and animal TSEs including BSE.

The purpose of this communication is to summarize the conclusions and recommendations of these meetings as regards the potential implications of BSE for public health.
1) OBJECTIVES OF WHO CONSULTATIONS

To examine the available information on transmissible spongiform encephalopathies (TSE) and evaluate the potential risks of these diseases for public health in particular.

- Possible risk for animals and human beings of transmission of TSEs.
- Possible risks arising from the use of products of animal origin as food for human beings.
- Possible risks due to the use of products of animal origin for the manufacture of drugs.
- Possible occupational risks.
- To recommend preventive measures.

2) RISK FACTORS TO BE CONSIDERED IN PUBLIC HEALTH: ROUTES OF TRANSMISSION, DOSES AND SPECIES BARRIERS

- There is evidence of the oral experimental transmission of animal TSEs: this would imply risk for human beings.
- Parenteral transmission of human TSE has been confirmed: risks due to accidents or exposure have been proven (grafts).
- The magnitude of the species barrier is unpredictable with respect to some encephalopathies: genetic factors related with the gene of the PrP protein have been identified.
- The experimental parenteral transmission of animal TSEs has been confirmed: there is evidence of the risk of transmission through the use of drugs of animal origin.

3) REMARKS ON THE POSSIBLE ZOONOTIC EFFECTS OF TSEs.

- There is no experimental evidence of Bovine Spongiform Encephalopathy (BSE) transmission to humans or of the development by humans of the syndrome of Creutzfeldt-Jakob Disease (CJD).
- With respect to the variant of Creutzfeldt-Jakob Disease (V-CJD) exposure of the United Kingdom to BSE has been raised as a probable hypothesis.
- Some observational studies do not show associations between some animal TSEs and CJD. (for example, scrapie).
4) MEASURES AIMED AT MINIMIZING BSE RISKS FOR HUMANS

4.1 With respect to animals:
- To prevent the introduction of the disease in the countries that are free from it.
- To prohibit the use of ruminant tissue meals for animal feed (in the United Kingdom the prohibition dates from 1988).

4.2 With respect to human food:
- In countries affected by the disease the use of "specified offal" for human consumption should be prohibited. Included are nervous tissue, tonsils, thymus, spleen, intestine. (in the United Kingdom the use of "specified offal" for humans was banned in 1989).

4.3 With respect to occupational risks:
- To follow the guidelines for the prevention of zoonoses that have been established for some occupational groups: meat-packing plans personnel, veterinarians and researchers.

4.4 Manufacturing of medicinal products:
- To avoid the use of raw materials of animal origin from countries affected by the disease for the manufacture of medicinal products.
- In the manufacture of medicinal products, additional consideration should be given to the type and source of the tissues, the manufacturing process, the dose and the application route of such products. The classification of tissues adopted by the Pharmaceutical Specialties Committee of the European Community should be followed.

4.5 With respect to the use of some products of animal origin for human consumption:
- Milk: it is considered that it offers no risk.
- Jelly: only if derived from non affected animals and if subjected to a manufacturing process that ensures the elimination of any residual infectivity.
- Tallow: only if derived from non affected animals and if effective extraction processes are used in its preparation.

4.6 With respect to meat:
All the studies carried out by the consultations show that meat offers no risk of transmission for humans. However, as a preventive measure the United Kingdom authorities established that all carcasses of bovines over 30 months old should be boned and subjected to the elimination of nervous and reticuloendothelial tissue.

REFERENCES

SECTION II: REPORTS OF THE EXPERTS
INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare human neurodegenerative condition that occurs worldwide. It is classified as a transmissible spongiform encephalopathy (TSE) because of characteristic spongy degeneration of the brain and its ability to be transmitted to laboratory animals. TSEs also naturally affect a range of animal species including sheep, goats, cows, mink and deer. All human and animal TSEs are fatal and no effective treatment is known that can stop the underlying disease process. Furthermore, at present no reliable presymptomatic test is available.

The nature of the TSE agent is still a matter of debate: according to one theory it is composed largely, if not entirely, of a self-replicating protein (the prion theory) whilst, according to another, the agent is virus-like and possesses nucleic acids. Although strong evidence has become available over the past decade supporting the prion theory, the ability of the TSE agent to form multiple strains is more easily explained by a virus-like agent.

Bovine spongiform encephalopathy (BSE), a TSE affecting cattle, was first reported in England in 1986 and over 170,000 cases have since occurred in the United Kingdom (UK). BSE probably arose through the use of contaminated feed supplements made from the remains of sheep with the TSE scrapie. The feed manufacturing process changed around 1980 in the UK, with the decreased use of solvents and heat being the likely cause of the failure to inactivate the transmissible agent. Relatively small numbers of BSE cases have also been reported in native cattle in France, the Republic of Ireland, the Netherlands, Portugal, Switzerland and Belgium. Small numbers of cases have also been reported in Canada, Denmark, the Falkland Islands, Germany, Italy and Oman, but solely in animals imported from the United Kingdom.

The use in food of those bovine offals considered to pose a potential risk to humans (essentially the brain and spinal cord) was banned in the UK in 1989 and subsequently in other European Union countries where BSE was identified.

In March 1996 the occurrence in the UK of an apparently new clinicopathological variant of Creutzfeldt-Jakob disease (nvCJD) was announced by the British Government. The temporal and geographical association of this disease and the BSE epidemic of cattle raised the possibility of a causal link. Evidence supporting this hypothesis has subsequently accumulated (see below). Because the incubation period of the BSE agent in
human may be long, the possibility of many more cases of nvCJD occurring over the next 10-15 years cannot be dismissed. Furthermore, it is possible that the population exposed to the BSE agent may not be confined to the UK and France: bovine products and by-products sourced from the UK cattle population and meat and bone meal manufactured in the UK were widely exported and the possibility also exists that foreign travellers visiting the UK during the 1980s were exposed to the BSE agent.

DIFFERENT FORMS OF CJD

**Sporadic CJD** (85% of cases), usually affects individuals between the age of 50 and 75. Its cause remains unknown and there is no evidence of a causal link with any animal TSE. Patients usually present (in order of decreasing frequency) with cognitive decline, ataxia or visual disturbance, either alone or in combination. Less common presenting features include behavioral disturbance or a rapid evolution resembling a stroke. Dementia is invariably present during the course of the illness and myoclonus, although a rare presenting feature, is observed in 80% of cases. Visual abnormalities are also common and include non-specific blurring, field defects, perceptual abnormalities and occasionally hallucinations. Seizures virtually never occur at presentation and are only observed later in the clinical course in 10% of patients. As the disease progresses multi-focal central nervous system failure occurs with increasing global cognitive dysfunction, ataxia and dependency, culminating in the patient becoming bedbound, mute and unresponsive. Terminally, the patients are usually rigid, frequently cortical blind and dysphagic - predisposing to aspiration, pneumonia and death. Physical signs correspond with the global central nervous system involvement and include a combination of the cerebellar, pyramidal, and extrapyramidal signs. Primitive reflexes, paratonic (gegenhalten) rigidity, startle myoclonus, cortical blindness and akinetic mutism are also common whereas lower motor neuron signs are rarely observed.

The EEG has traditionally been the most reliable non-invasive diagnostic test. In my experience only about 60% of cases have the characteristic appearance of 1-2Hz generalised triphasic periodic complexes, the remainder usually show non-specific slow wave abnormalities only. However, in published series of repeated recordings the classical appearances were noted in up to 90% of cases. It is therefore recommended that a non-diagnostic tracing should be followed by repeat recording at regular intervals (days or weeks). The typical EEG appearance has not been reported in kuru, nvCJD or typical cases of Gerstmann-Sträussler-Scheinker disease (GSS) and has only rarely been described in growth hormone related iatrogenic disease. A normal EEG does not always exclude the diagnosis of CJD, indeed, there are exceptional reports of such records even in the late stages of the disease. Although the characteristic EEG is virtually diagnostic of CJD there are exceptional reports of similar appearances in other conditions, such as Alzheimer’s disease or metabolic encephalopathies.

Revised diagnostic criteria for a ‘probable’ case of sporadic CJD now includes a positive 14-3-3 CSF assay (if the total duration of the patient’s illness is less than 2 years) – see Annex. The 14-3-3 protein is said to be a marker of neuronal death and studies in the European Union and the USA report that it has a high sensitivity and specificity for the diagnosis of CJD. The assay cannot be used as a screening test and is best reserved for patients suspected of having CJD. The following centres are able to perform this test.
Results from a recent study suggest that the detection of high signal from the basal ganglia on T2 and proton density-weighted MRI supports the diagnosis of sporadic CJD, particularly if a FLAIR sequence or diffusion weighted images are used. However, only limited information is currently available and further studies are required.

**Familial CJD** (10-15% of cases). Fifteen point mutations and 8 different length octorepeat insertions are associated with the various hereditary forms of human TSEs. The clinicopathological phenotype of familial disease is more diverse than sporadic CJD and is largely dependant on the underlying genetic defect. For example GSS and fatal familial insomnia are due to different point mutations and are characterised by presentation with a slowly progressive cerebellar syndrome and severe insomnia with autonomic failure respectively. Distinction between familial CJD and these two conditions is purely semantic as they are all inherited transmissible spongiform encephalopathies. Additionally the illness phenotype in a single kindred of GSS can range from the characteristic slowly progressive cerebellar ataxia to a rapidly progressive dementia indistinguishable from classical CJD. Other patterns of illness associated hereditary disease includes presentation with a spastic paraparesis, an extrapyramidal syndrome or florid psychiatric disturbance. The duration of genetic disease is also very variable, ranging from a few months to over two decades.

**Iatrogenic CJD** (<5% of cases) results from transmission of the causative agent via medical or surgical treatment using accidentally CJD-contaminated materials, e.g. neurosurgical instruments. The phenotype of iatrogenic disease depends on the route of infection. Patients inoculated peripherally (e.g. those cases associated with injected human cadavaric-derived growth hormone) usually develop a progressive cerebellar syndrome reminiscent of kuru. The latter was, and rarely still is, a TSE seen in the Fore-speaking region of Papua New Guinea acquired via inoculation or ingestion of the infective agent during ritualistic cannibalism. Iatrogenic disease following central inoculation (e.g. via the use of contaminated stereotactic EEG electrodes or neurosurgical instruments) takes the form of a rapidly progressive dementia resembling sporadic CJD. Disease resulting from the use of contaminated dura mater grafts can present with either of the above phenotypes.
New variant CJD (nvCJD) is a new disease which was first described in March 1996. It is most likely linked with exposure to the BSE agent. In contrast to typical cases of sporadic CJD, this variant form has affected young patients (average age 27 years vs. 65 years) with a relatively long duration of illness (median 14 months vs. 4.5 months). When viewed under the microscope the brain from the patients with the new variant demonstrates a consistent but previously unseen pattern.

FURTHER INFORMATION ON NEW VARIANT CJD

Clinical features of nvCJD Patients usually experience psychiatric symptoms early in the illness, which most commonly take the form of depression or less often a schizophrenia-like psychosis. Persistent and unpleasant sensory symptoms, such as tingling or burning feelings, have been experienced by half of the cases early in the illness. Neurological signs, including unsteadiness and myoclonus or chorea/dystonia, developed as the illness progressed and, shortly before death, patients become completely immobile and mute.

Diagnosis The characteristic EEG pattern of sporadic CJD did not occur. Blood and spinal fluid tests were normal or unhelpful. Many of the cases had posterior high signal in the thalamus bilaterally on proton density or T2-weighted magnetic resonance imaging and this may become a useful diagnostic sign. At present the diagnosis of nvCJD can only be confirmed following examination of the brain under the microscope. Characteristically, multiple minute protein aggregates surrounded by holes are seen, resulting in a daisy-like appearance and the descriptive term ‘florid plaques’.

The influence of genetic factors is demonstrated by the identification of a particular genetic variant in all 23 cases tested to date. This gene type has been found to occur in about two-fifths of unaffected people tested. It is possible however that nvCJD cases with other genetic types may occur in the future.

Epidemiology The first patient became ill in January 1994 and up to February 1998, 25 cases had been identified, 23 in the UK and a single case in France. There was no preponderance of patients from any particular part of the UK. Information on potential risk factors has been published for ten cases and there is no convincing evidence to indicate that, as a group, these cases had an increased exposure to the BSE agent due to their occupations, diet or medical histories. Nine cases were reported to have eaten beef or beef products since 1986, but none were reported to have eaten brain. One of the cases had been a strict vegetarian since 1991.

Evidence of a link between nvCJD and BSE The hypothesis of a link between nvCJD and BSE was first raised because of the association of these two diseases in time and place. More recent evidence supporting a link includes identification of microscopic features similar to nvCJD in brains of monkeys inoculated with BSE, and the demonstration that nvCJD is associated with a molecular marker that distinguishes it from other forms of CJD and which resembles that seen in BSE transmitted to a number of other species.
The most recent and powerful evidence comes from studies showing that the transmission characteristics of BSE and nvCJD in mice are almost identical, strongly indicating that they are due to the same causative agent. It is also noteworthy that transgenic mice (mice carrying the human prion protein gene) have now been shown to be susceptible to BSE. Furthermore, no other plausible hypothesis for the occurrence of nvCJD has been proposed and intensive CJD surveillance in five European countries, with a low potential exposure to the BSE agent, has failed to identify any additional cases. In conclusion, the most likely cause of nvCJD is exposure to the BSE agent, most plausibly due to dietary contamination by affected cattle brain or spinal cord and with an incubation period of five to ten years.

WHO INVOLVEMENT

Since 1991, WHO has convened seven scientific consultations on issues related to animal and human TSEs. The potential future public health implications of nvCJD were addressed by a WHO consultation in May 1996. As exposure to the BSE agent may extend to populations outside the UK and Western Europe, it was recommended that to detect the number and distribution of any future cases, global surveillance of CJD and its variants would be required. Surveillance has already been established in many European countries, North America, Canada and Australia and WHO’s EMC division is instigating surveillance in other, mainly developing, countries. As part of these activities we have now held three regional TSE surveillance workshops in collaboration with veterinary colleagues from the International Office of Epizootics (who are promoting BSE surveillance), the first was held in Senegal for West African Countries, the second was held in Thailand for southeast Asian countries and the most recent in Cairo for countries of the Eastern Mediterranean region. This is the fourth workshop and further meetings are being planned for later this year in China and southeastern Africa. It is anticipated that with the help of the world’s neurological and epidemiological communities WHO activities for global CJD surveillance will provide information important for enhancing the protection and planning of public health worldwide.
The diagnosis of human TSE depends on neuropathological examination of the brain to confirm a clinically suspected case.

The diagnosis features are:

1. Spongiform change.
2. Neuronal loss
3. Astrocytosis
4. Accumulation of the disease-associated form of PrP in the brain.

In sporadic CJD, these four features are variable from case to case, and are influenced by the PRP genotype at codon 129:

- **mm**: Spongiform change mostly in the cerebral cortex, few plaques.
- **mv**: Kuru-type plaques in the cerebellum spongiform change mostly in the basal ganglia.

The diagnosis of CJD can be made easily in most cases, but additional investigations using immunocytochemistry for PrP are useful for atypical cases and for the diagnosis of new variant CJD.

The neuropathological diagnostic criteria for new variant CJD:

1. Multiple fibrillary PrP plaques in the cerebral and cerebellar cortex often surrounded by spongiform change («Hard» plaques).
2. Multiple small PrP plaques which are only detectable by immunocytochemistry, occurring in cluster within the cerebral and cerebellar cortex.
3. Amorphous PrP deposit around neurons and blood vessels in the cerebral and cerebellar cortex.

Other features of new variant CJD include:

1. Spongiform change not marked in the basal ganglia.
2. Severe thalamic glycos in the posterior nuclei and pulvinar.
3. Massive accumulation of PrP in the cerebellum.
4. Punctate staining for PrP in posterior nuclei.
5. PrP accumulation in lymphoid tissue, usually in follicular dendritic cells.

PrP analysis by Western Blot techniques is also helpful as a research tool, and requires frozen tissue from the brain. A characteristic glycoform pattern is present in new variant CJD and BSE in Western Blot preparation.
SAFETY ISSUES

«Prion» agents are transmissible but prion diseases are not contagious. There is no evidence of an increased incidence of CJD in pathologists, mortuary technicians, laboratory technicians or other health care professionals.

The following principles apply to dealing with tissues from cases of suspected CJD, particularly these with high levels of the infectious agent (brain and spinal cord).

1- Avoid accidental inoculation by the use of cut-resistant or chain wall gloves.
2- Protect mucus membranes from splashes with contaminated tissue.
3- Minimize contamination of the environment.
4- Use disposable instruments whenever possible.
5- All contaminated waste should be clearly labelled, securely bagged and disposed or by incineration.
6- Risk assessment exercises should be made for all procedures. Published decontamination schedules should be followed.
7- Training of all staff is essential.

TRANSPORT OF SPECIMENS FORM SUSPECTED CJD CASES

1- All specimens should be securely bagged and safety packed.
2- All specimens should carry an appropriate big hard warning.
3- Carriers should be officially approved for the handling of high-risk tissues.
4- The dispatch and arrival of specimens should be recorded.
ANIMAL TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Dr. Bradley

I. HISTORY, CLINICAL SIGNS AND DIAGNOSIS

The group of diseases to which kuru, CJD, scrapie and BSE belong is known as the sub-acute, transmissible spongiform encephalopathies or TSE. The main features of all these diseases include: affection usually of adults, long incubation periods measured in years or even decades, progressive neurological signs ending in death, spongiform change and presence of prion protein (PrP) in the brain (hence prion disease), scrapie associated fibrils (SAF) in brain extracts and experimental transmissibility which is a cardinal feature. With the exception of natural scrapie the diseases are not contagious. In 1985 before the advent of BSE, six TSE were known, three in man (kuru, CJD and GSS disease) and three in animals; scrapie of sheep and goats, transmissible mink encephalopathy (TME) of farmed mink and chronic wasting disease (CWD) of mule deer and elk.

Scrapie is the archetype of these diseases and it was very well known in agricultural circles in the XVIIIth century some 200 years before CJD was identified. Scrapie was responsible for considerable financial loss in some flocks and large epidemics occurred in Europe in the XVIIIth and XIXth centuries. In more recent years it has significantly interfered with trade in live sheep for breeding. Scrapie was well written about from early times when it was already known there was no cure and slaughter was the only option. It has not to this day been regarded as a zoonosis and this is supported by much epidemiological investigation. That it had a wide geographical distribution is indicated by the large number of local names given to the disease such as scrapie in the UK (pruritus and scratching are common features), la tremblante in France (trembling is a clinical feature), rida in Iceland (where pruritus is not a sign) and Traberkrankheit in Germany (trotting is another feature). Australia, New Zealand and some other countries are generally regarded as free of the disease.

It was not until 1898 that the definitive lesion (neuronal vacuolation) was described and in 1936 scrapie was experimentally transmitted. Though principally a disease of sheep, goats can also succumb and much more recently scrapie has been reported in mouflon that had contact with affected sheep. Natural transmission is thought to occur in sheep both maternally and horizontally (probably via the placenta). Once established in a flock it is exceedingly difficult to eradicate. Countries free of the disease have adopted stringent policies in regard to the importation of live sheep and any sheep products that might carry the infection. Recent research on the PrP gene has identified alleles that consistently are associated with scrapie occurrence and others that appear to confer a strong resistance to the development of disease during the commercial lifespan.

Though there is no evidence that scrapie is a zoonosis an American veterinary neuropathologist, Dr William J Hadlow in 1959 first drew attention to the pathological similarity between scrapie and the human disease kuru. He also suggested that transmission studies in a laboratory primate might be attempted using brain from an affected patient. Transmission was subsequently achieved by Gibbs and Gajdusek who also transmitted CJD to chimpanzees and thus opened a new era in human TSE research.

TME is a rare disease of farmed mink but when it strikes, most adults on the farm succumb. It is geographically restricted to North America, Finland, Germany and Russia.

Onset is insidious with behavioural changes, increased aggression, hyperexcitability and hyperaesthesia. In the later stages stupor supervenes and death occurs in a debilitated state. Infected feed appears to be the source perhaps from sheep scrapie (though this has never been successfully transmitted by the oral route despite several attempts) or perhaps another rare source of TSE agent from another unknown species.

CWD is another rare disease of several species of deer and Rocky Mountain elk in North America. It was originally studied in captive animals in wildlife parks but has now been reported in the wild. The origin of infection and mode of transmission are unknown. Weight loss, emaciation, teeth grinding and salivation are
common signs. Deer show polydypsia and polyuria in a high proportion of cases. PrP-positive plaques of a florid type occur in the brains of deer.

Preceding and following the advent of BSE in November 1986 in the UK a number of BOVIDAE and FELIDAE species developed clinical neurological signs and the pathology of a TSE. The species included nyala, gembok, Arabian oryx, scimitar-horned oryx and bison (1 case each), anole (2), greater kudu and eland (6 each); domestic cats 81 (+ 1 each in Norway and Liechtenstein), puma (3), ocelot (2), tiger (1) and cheetah 3, with three more cheetah (exported from the UK, presumably in the incubating phase of disease) that developed clinical signs and succumbed in Ireland, France and Australia. The clinical signs and pathology were briefly described.

The methods for diagnosis were described and included the use of formol-saline fixed brain for microscopic examination and immunohistochemistry to detect PrP, and frozen or unfixed brain for immunoblotting for PrP and for SAF examination. For BSE diagnosis it was often sufficient to examine only the brainstem and particularly the medulla at the obex since in this disease (unlike in scrapie) the sites of lesions are consistent. Protocols for the diagnosis of scrapie and BSE had been published by the EC and have been adopted also by the OIE with a description in the Manual of Standards.

When dealing with TSE-infected tissues it is important to adopt safety protocols to protect workers. The aim should be to reduce risks from exposure by wearing suitable protective clothing and being aware of the important hazards. A method was described in which the brainstem could be removed safely and without damage via the foramen magnum thus reducing risks from saws and sharp instruments or bone fragments.

Experimental transmission of BSE to the following species had been achieved by parenteral routes; cattle, sheep, goats, pigs, marmosets, macaques, squirrel monkeys and mink but not to hamsters or chickens. Oral challenge was successful in cattle, sheep, goats and mink but not pigs or chickens.

II. EPIDEMIOLOGY, PATHOLOGY AND TRANSMISSIBILITY OF BSE

BSE is a new disease with the first clinical cases occurring in April 1985. The first histopathologically confirmed case was examined in November 1986. The mean incubation period is 60 months with a range from 20 months (rare) to perhaps the life span of cattle (also rare if it happens at all). Most cases occur in cattle 3 – 6 years old. The first effective exposure occurred in the period 1981-1982. The cause was an increased exposure to a scrapie-like agent associated with concentrate feeding. The vehicle for the infective agent was meat-and-bone-meal (MBM). The trigger for the start of the epidemic was a commercially and safety-motivated change in rendering of ruminant waste coincident with the time of first exposure. The major change appeared to be the cessation of the hydrocarbon solvent extraction of fat. Abattoir and butcher’s waste that had been treated in this way, having already been cooked and having had some of the tallow extracted, eg by centrifugation or pressing, was subjected to the action of the solvent and then live steam stripping, a second and wet heat process. It was assumed at the time, and now there are data to support it, that the second treatment could have reduced the infectivity titre sufficiently to prevent detectable disease occurrence. Removal of the tallow left a residue of protein rich greaves that is ground to make MBM.

There are still two unproven hypotheses for the origin of BSE. Either from sheep with scrapie or from cattle infected with a scrapie-like agent. Whatever the source, once the epidemic was established it was an inevitable consequence that recycling of infection in incubating or affected cattle via the rendering system and MBM in concentrate feed drove the epidemic ever upwards. This continued until legislation was introduced to protect animal health on the one hand and public health on the other. The initial measures were the prohibition on feeding ruminant protein to ruminant animals, the compulsory slaughter and complete destruction of clinically BSE-suspect animals and, the removal of specified bovine offals, the SBO, (later, specified risk materials).

Subsequently, as a consequence of research results on the effectiveness of rendering processes used in the EU to inactivate the BSE and scrapie agent, some existing ineffective processes were banned from processing ruminant waste in all Member States. However, tallow prepared by these processes was shown to be devoid of detectable infectivity, ie only the MBM retained infectivity in the failed processes. The principle behind these and other subsequent measures was to eliminate or reduce exposure to a level where disease could not occur. It is noted that a zero risk is unprovable.
In regard to the cattle epidemic the feed ban had a dramatic effect in reducing exposures, and thus subsequent disease. However it took several years for the decline in cases to become evident because of the lag time due to the long incubation period. A ruminant feed ban, if completely complied with and enforced would prevent the initiation of an epidemic of feed-borne BSE and, if an epidemic existed, it would be sufficient to eliminate disease gradually over the ensuing years from the date of its effective implementation. In all countries with BSE in native-born cattle (Belgium, France, Ireland, The Netherlands, Luxembourg, Portugal, Switzerland and the UK) cases have occurred in cattle born after the date of implementation of the respective feed bans. In the UK for example the majority of 35,000 animals born after the July 1988 ban are attributed to this cause. In the UK there have been over 170,000 confirmed cases of BSE but other countries have reported from 1 to less than 300 cases.

It is now clear from the results of research that very small amounts (1g, or perhaps less) of infected brain can establish infection in experimentally orally exposed cattle. Such small amounts, especially when dried in the form of MBM produced by inadequate rendering, are easily transferred accidentally to ruminant feed by cross-contamination in feed mills, on farms and during transportation. How could this happen? In many countries (UK is now an exception) pig and poultry feed is permitted to contain mammalian MBM. Whereas this, if infected, is not known to transmit disease to these species, it could cross-contaminate ruminant rations as described unless other steps are taken to prevent this occurrence. To prevent exposure of other species to the BSE agent some form of specified offals ban has been introduced in countries with BSE in native-born cattle. In the UK this was first introduced as a public health protection measure in 1989 and extended to protect all species of animal and bird in 1990. The aim here is to eliminate from all food and feed chains (or for other purposes) those offals that do or are likely to contain infection during the incubation period or during the clinical phase of disease. Complete compliance and enforcement are difficult to achieve initially but with the benefit of experience, adequate resources and education of the industries this can be achieved with a high degree of effectiveness. As a result of the measures and their effective enforcement it is clear that it is possible to effectively eliminate feed-borne exposure of cattle, and other species to BSE. In this regard epidemiological evidence from the UK shows that MBM was the most probable source of TSE in the captive BOVIDAE species and this small epidemic has now declined as a result of the ruminant feed ban. The epidemic in the captive wild FELIDAE species has also declined most probably as a result of the SBO ban. The domestic cat epidemic appears also to be in decline. Other means of perpetuating the epidemic of BSE in cattle, such as maternal or horizontal transmission cannot sustain the epidemic. There is some evidence for a low rate (<1%) of maternal transmission but the mechanism is not known. There is no evidence for transmission via semen or embryos.

The gelatin manufacturing process was described and three principles were identified that could secure a safe end product and reduce risk. These principles could be applied to any bovine product or indeed any product that might use bovine material during manufacture such as some medicinal products. These three principles are sourcing (geographical and by tissue), processing (by methods that inactivate TSE agents effectively) and use (eg technical, medicinal or for consumption). In regard to gelatin it is important to avoid the use of bones that could contain CNS tissues where there was a risk from TSE agents.

Countries at risk from exogenous BSE are those that have imported breeding cattle, SBO or specified risk materials, or MBM from countries with BSE in native-born stock. Endogenous risks could arise in countries that have large sheep and goat populations (relative to the cattle population) and with endemic scrapie and which use ineffective rendering methods to produce MBM and feed it to calves destined for the breeding herd. Analysis of these exogenous and endogenous risk factors must be made in accordance with the recommendations in the OIE International Animal Health Code chapter on BSE. A risk management strategy should be developed and this must include continuous monitoring and surveillance for BSE. In particular brains from targeted populations of higher risk adult cattle must be examined by an approved method as demanded by the Code.

Research has revealed that the tissue distribution of agent in natural cases of BSE is far more restricted than is the scrapie agent in natural cases of Suffolk sheep scrapie, ie it has been found only in the brain, spinal cord and retina. There is no detectable infectivity in any other of about 50 tissues bioassayed in mice, including muscle and milk. In an experimental, pathogenesis study of BSE in cattle orally challenged with BSE-infected brain, infectivity has been detected in the ileum from six months post challenge to 18 months post-challenge and again in the later stages of incubation. Infectivity has been found in CNS tissues and dorsal root ganglia from 3 months before the onset of clinical signs that commenced at 35 months of age. Infectivity was also found in the clinical phase of disease in the cerebral cortex, trigeminal ganglia and, in one experiment only that cannot yet be interpreted, in the bone marrow.
The consequences of the announcement of ten cases of nv-CJD in the UK in March 1996 reported elsewhere in this workshop have been devastating to the UK and to a lesser extent, European beef industry. In regard to the UK there a ban has been imposed by the European Commission (EC) at the behest of Member States on the export of cattle and cattle products (other than milk and semen that are regarded as safe) from the UK. The economic consequences have been serious nationally and especially at the farm level. Despite this the measures now in place in the UK are seen by the UK public and the EC to be effective in providing a very high level of protection against exposure to the BSE agent via food, any other vehicle or occupation. Stringent safety rules have been adopted and enforced by the Health and Safety Executive in the UK in at-risk occupations eg abattoir and laboratory workers, knackermen and veterinarians. In the UK, bovine meat and other organs for consumption must come from cattle under 30 months of age or from cattle in the Beef Assurance Scheme from which the specified risk materials have been removed. All cattle over 30 months of age (around 2 million to date) are destroyed at the end of their commercial lifespan so they can enter no food or feed chain and can be used for no purpose. Selective culls are also in progress as part of the negotiated plan to lift the export ban in due course. The lessons are clear. All countries must take at least the steps recommended by the OIE and so reduce any risk of establishing the disease in the country. Failure to do so could put animal and public health at risk and seriously affect trade in live cattle or cattle products. In this respect the main thrust of a modified draft BSE chapter of the Code was explained. This will not come into force, either in its present or modified form, unless agreed by the International Committee formed of OIE Member Countries in May 1998 at the OIE General Assembly.
SECTION III: REPORTS BY THE COUNTRIES
Argentina
Bolivia
Costa Rica
Chile
Cuba
Ecuador
Guatemala
Panama
Paraguay
Peru
Bovine spongiform encephalopathy (BSE) is a degenerative disease affecting the central nervous system of cattle. It is one of a group of similar animal and human diseases known as transmissible spongiform encephalopathies (TSE).

Described for the first time in the United Kingdom in 1986, BSE has been detected subsequently in other countries of the world in animals imported from the United Kingdom (Oman, Denmark, Germany, Canada, Italy, and Portugal), as well as in native stock (Ireland, Switzerland, France, and Portugal). The disease has become epidemic and is the cause of worldwide alarm not only due to its implications for animal health, but also because of its potential hazards for human health.

The origin of the disease in the United Kingdom is attributed to the presence of a scrapie-like agent in protein concentrates of ruminant origin used as cattle feed. Because of its characteristics (proteins, highly resistant to physical and chemical treatments, capable of crossing species barriers), the etiological agent is considered as a PRION; to date nucleic acid has not been detected in its constitution.

In Argentina, preventive actions initiated in 1988 have made it possible to establish that the country is free from BSE according to the strict international standards on this matter.

Based on the analysis of risk factors for BSE in Argentina (1992 and 1995) it has been established that the main factors associated with the origin and development of the epidemic in the United Kingdom do not exist in the country and for this reason the risk of BSE presence is exceptionally low.

A surveillance program was launched in 1992 for the histological and biochemical examination (detection of PrP) of 1019 brains of predominantly dairy cows classified into three categories: animals suspect of neurological disease, animals detected in poor condition prior to slaughter, and healthy animals selected at random in slaughterhouses. These examinations have continued to date with the analysis during the years 1993 through 1995 of 180 brains from animals in the field suspected of neurological disease; results were negative, both in the histological examination and PrP detection.

Furthermore, since all the relevant normative and regulatory measures aimed at preventing the entry of the disease into the country have been taken, it is concluded that Argentina can be considered free from BSE.

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Spongiform encephalopathies, also known as transmissible amyloidoses or prion diseases, include a group of sporadic, familial, or iatrogenic diseases affecting man and animals.

In animals, these diseases are: scrapie in sheep and goats, transmissible mink encephalopathy (TME), chronic wasting disease (CWD) in cervids, bovine spongiform encephalopathies (BSE), and the disease affecting exotic ungulates such as nyala and greater kudu.

Human forms include:
- Endemic KURU in some tribes of New Guinea between 1957-1982
- CREUTZFELDT-JAKOB disease (CJD)-Sporadic: 1 case /1,000,000 inhabitants/year
- Familial: mutations of the PrP gene codifying the prion protein in codons 178, 200, and 210.
- Iatrogenic: resulting from injection of cadaveric derived human growth hormone or gonadotropin, dura mater or chorneal grafts, use of contaminated stereostaxic electrodes.
- GERSTMANN-STRAUSSLER-SCHNEINKER (GSS) dominant autosomal hereditary form associated with mutations in codons 102, 105, 117, 145, 198, and 217
- FATAL FAMILIAL INSOMNIA (FFI) associated with codon 178 mutation (the combining codon is also involved in a subtype of CJD, but in FFI that mutation is combined with methionine at codon 129.
- Onset of the familial forms often occurs at an earlier age and the disease has a longer duration than in the sporadic forms, as well as a different phenotypical expression for each mutation; however, variations occur, even between members of the same family. Kuru, sporadic and familial CJD and some forms of GSS have been transmitted experimentally.

The pathological substratum is characterized by spongiform changes of the gray matter (cortex and/or gray nuclei, except for IFF), progressive vacuolation and neuronal death as well as hyperplasia and hypertrophy of the astroglia in variable degree. Amyloid plaques are observed in a small percentage of CJD, in the GSS form of the disease, especially in cerebellum, and in the kuru form.

PRION
The etiological agent, unlike bacteria, protozoa, fungi, and viruses, lacks nucleic acid. It corresponds to the infectious isoform of a normal protein cellular form (PrPc) coded by the host. In humans, the PrPc is coded by a gene found in chromosome 20, located essentially on the neuronal surface and bound by a glycolipid anchorage; its function is unknown. It may
be related to communication and synapse. This protein is firmly maintained in each species. The infective form is called PrP CJD or PrP Sc depending on which it is. It differs from the normal protein essentially in its resistance to proteinase K in an abnormal beta folding. The spontaneous transformation of PrPc to PrPSc or PrP CJD would explain the appearance of sporadic forms of this disease, while in the acquired forms, a small amount of the infective form induces or catalyzes the conversion of the normal isoform into infectious. As has already been pointed out, the hereditary forms show well-identified mutations. The PrPc is 33-35 kDa, and is completely degraded by the action of proteinase K, while the PrP CJD or Sc, of equal molecular weight, is resistant to that proteinase and is only partially degraded into a protein of 27-30 kDa, which is added in rod-like structures of characteristics similar to those of amyloids. Prions do not induce an immunological reaction of the host and are very resistant to disinfectant or sterilizing agents.

CREUTZFELDT JAKOB
The first description by Creutzfeldt (2 cases) dates from 1920 and that by Jakob (5 cases) from 1921 and 1923, respectively; of the latter, Jakob's case 3 was subject to neuropathological examination and later confirmed.

The disease was transmitted experimentally for the first time in 1968, after kuru (Gibbs CJ Jr, Gajdusek DC, Asher DM. et al, 1968)

SPORADIC CREUTZFELDT JAKOB
Approximately a third of the cases often presents a prodromic period of weeks or months characterized by mood alterations, loss of memory, confusion, i.e., mental deterioration of variable degree, while another third shows at onset cerebellar or visual involvement and the remaining third, physical and mental symptoms. Exceptionally, evolution after onset is rapid resembling a stroke. In the course of the disease deterioration of the superior cortical functions increases leading to dementia, ataxia, tremors, myoclonus, and/or other startle reactions. Incidence is 1 case/1 000 000/per year and in general duration of illness ranges from months to a year and exceptionally more than 2 years. At presentation, the EEG may be normal or show disorganization at the basis or slow wave activity, later characterized by periodic activity of sharp triphasic waves, of 1 to 2 cycles per second. The computerized tomography is normal or may show light cortical atrophy. Magnetic resonance in addition to atrophy may show non-specific diffuse alterations in cortex and trunk and intensity alteration in T2.

The diagnosis of CJD can only be considered irrefutable when it is neuropathological; clinical diagnosis is indicative of probable or possible disease.

1.1 PROBABLE CJD. progressive dementia and typical EEG and at least 2-4 of the following clinical manifestations:  
a) Myoclonus, b) visual and cerebellar disturbances, c) Pyramidal/extrapyramidal, disfunctions d) Akinetic mutism

1.2 POSSIBLE CJD. Similar to 1.1 but with no EEG or with atypical EEG and less than 2 years' duration.  
Neuropathological verification is essential to support diagnosis and to rule out other differential diagnoses, mainly Alzheimer disease. Biopsy and/or autopsy should be performed in all feasible cases or in cases that do not fulfill all the requirements in order to be considered a possible case of CJD.

FAMILIAR CREUTZFELDT-JAKOB DISEASE
(5-15%), autosomal dominant; the age at onset is similar in the same family and less than in the sporadic form while duration is longer.

**DECONTAMINATION METHOD**

Surgical instruments should be treated with methods that will ensure their decontamination, or discarded. Since conventional sterilization and disinfecting methods do not decontaminate the infectious agent of CJD, hydrolytic autoclaving for 1 hour at 134 °C is recommended. If the material cannot be autoclaved, chemical decontamination by immersion in 2N sodium hydroxide (80g/liter) for 1 hour or 1N for 2 hours, is very effective but non-advisable for aluminum items. (Tissue handling in suspected Creutzfeldt-Jakob disease and other human spongiform encephalopathies, Prion Diseases. Consensus report. Budka et al. Brain Pathology 5:319-322,1995.) Despite this, the current criterion is to discard the surgical materials employed.

Samples of cerebral biopsy or autopsy should be submitted to autoclaving for 1 hour at 132 °C or immersed in formic acid for 1 hour followed by fixation in 4% formaldehyde for 48 hours to reduce the risk of infection. (Budka H. et al. Tissue handling in Suspected Creutzfeldt-Jakob Disease (CJD) and other Human Spongiform Encephalopathies. Brain Pathology 5:319-322 (1995).

Cases of CJD have been observed in health professionals: 6 physicians including 2 neurosurgeons and 2 pathologists, 3 dentists, 1 dental surgeon, 9 nurses, 3 nursing assistants, and 2 histology technicians (Berger J.R. et al Creutzfeldt-Jakob disease in a physician: A review of the disorder in health care workers. Neurology 1993; 43:205-206)

**NEUROPATHOLOGY:**

Macroscopic inspection of the brain may show a variable degree of cortical atrophy and ventricular accentuation. Microscopically, spongiform changes, gliosis, and neuronal depletion affect, in addition to the neopallium, the basal nuclei, cerebellar cortex, and dentate nucleus. The immunohistochemical study with monoclonal antibodies for the prion protein is not essential in typical cases with characteristic changes but is particularly useful for the detection of atypical cases. The resistant proteinase fragment (PrP) of the amiloydogenic protein may present a plaque-like aspect (in approximately 4% of the cases they may be found in brain and/or cerebellum), diffuse synaptic or patchy/perivacuolar. (Budka H. et al. Neuropathological Diagnostic Criteria for Creutzfeldt--Jakob Disease (CJD) and Other Human Spongiform Encephalopathies. Brain Pathology 5:459-466, 1995). The precursor protein or PrPc may be detected in the perikaryon in normal brains; the sections must therefore be pretreated so that only the pathological section is shown. At the ultrastructural level, the vacuoles are detected within the processes and next to the synaptic terminal or in the perikaryon, surrounded by a membrane containing fine partitions and membranous material. Tubular vesicular structures have also been identified in pre and post synaptic terminals.

**IATROGENIC CREUTZFELDT JAKOB DISEASE**

Iatrogenic cases of CJD arising from corneal transplant, dura mater graft, insertion of intracerebral electrodes and, more recently, treatment with cadaveric-derived hypophysis hormone have been reported. It was thus possible to infer that direct infection due to continuity in the brain leads to incubation periods of several months (up to 120) and a demential presentation similar to that of sporadic CJD; in cases originating in the peripheral route, the incubation period may last years or even decades (as with kuru, in which the minimum incubation period has been estimated at 4 to 5 years) with a predominantly
Cerebellar syndrome similar to that previously mentioned. The sporadic and iatrogenic forms of CJD occur especially in homozygous individuals for polymorphism in codon 129 of the gene (PRNP).

**CJD WITH NEUROPATHOLOGIC DIAGNOSIS IN ARGENTINA**

Despite the extensive frontier between Argentina and Chile, where the incidence of Creutzfeldt Jakob disease is high, only 9 cases of sporadic CJD have been published and/or reported at congresses up to 1979.

Dr. C.D. Gajdusek (who was awarded the Nobel Prize in 1976 for his discovery of new mechanisms of infection and pathogenesis in human diseases, particularly the experimental transmission of kuru) visited Argentina in 1983, where he centered his interest in the neuropathological verification of sporadic CJD and its incidence in the Argentine environment. For his purpose, and after our visit to the different departments under his supervision in the NIH (National Institutes of Health, Bethesda, Maryland) we established a reference center for the neuropathological diagnosis of CJD and related pathologies.

In 1989 we published the first 10 cases of biopsy and/or autopsy (Taratuto A.L. et al. Medicina 49:293-303, 1989) completing up to March 1996 a total of 19 cases in Argentina. Two were of Chilean origin and another one visited Chile frequently. Cases ranged from 39 to 74 years, with an average of 54.8. The relationship between male and female cases was 11:8, and the duration ranged between 3.5 and 24 months (average 8.08 months). Signs and prodromic symptoms included personality change lasting from several weeks up to a year in 8 cases, and neurological involvement from onset of disease in the rest. Patients developed pyramidal, extrapyramidal and cerebellar signs, as well as involuntary movements and progressive dementia. Visual dysfunctions were observed in 10 and EEG periodic activity in 13. Two cases had an acute onset similar to a stroke. When performed, CT and MRI only showed mild to moderate variable degrees of cortical atrophy, diffuse in most cases and exceptionally unilateral. The study of 16 biopsies and 4 autopsies showed in all unmistakable signs of spongiform changes, neuronal depletion, and astroglial proliferation at the optic and ultrastructural levels, as well as light overload of neuronal lipofuchsine, with relative preservation of the white matter, but no amyloid plaques. The clinical and neuropathological manifestations in the cases studied were similar to those reported in the literature as classical forms of sporadic CJD.

In addition, we have been informed of the occurrence of 12 cases with neuropathological confirmation in 4 other centers in Argentina during the same period (personal communication), but since CJD is not a pathology of compulsory notification, some isolated cases may have gone unreported.

The incidence of probable or possible cases of CJD (clinical diagnosis) has not been documented because so far CJD incidence in Argentina is not monitored.

No relationship between sporadic CJD cases and transmissible spongiform encephalopathies in animals (v.gr. scrapie) had been reported until March 1996 in the epidemiological studies included in the literature.

In view of the BSE epidemic in the United Kingdom, a National CJD Surveillance Unit was established in 1990 in Edinburgh. In the *Lancet* issue of April 6, 1996 (347: 921-925.1996), the professionals of that Unit reported 10 cases of a new atypical variant of CJD affecting younger people and with a longer average duration than the classical CJD: age at
onset of symptoms 16 - 39 years, mean age at death 29 years, duration of the disease 7.5 - 25 months.

Patients showed behavioral change and psychiatric disorders of prolonged duration, followed by ataxia, with myoclonus and choreoathetosis late in the clinical course, but no typical EEG. Brain biopsy or autopsy showed in addition to spongiform changes, abundant amyloid plaques surrounded by vacuoles, as well as extensive marking with PrP antibody. Although there is still no evidence of the relationship of this new variant with the epidemic of BSE, it cannot be ruled out. Subsequently a similar case was reported in France in a 26-year-old patient (Lancet 347: 1181, 1996)

The World Health Organization held a consultation of experts on clinical and neuropathological characteristics of the new variant of CJD and other human and animal transmissible spongiform encephalopathies (Geneva, May 14-16, 1996).

At the request of WHO, and in relation to the aforementioned meeting, we requested information from prominent neuropathologists from Chile, Brazil, Uruguay, Mexico, and Venezuela. The unofficial data showed that in those countries, as well as in Argentina, no system for the surveillance of Creutzfeldt Jakob disease and related pathologies in humans has as yet been implemented, and that the atypical variant has not been detected in our environment.

Among the most important conclusions of the WHO meeting special mention should be made of the need for establishing a surveillance or monitoring system in order to obtain information on the geographical distribution of the new variant and the real incidence of CJD including all types and subtypes, in addition to carrying out a study on the possible risk factors related to animal TSE following the protocol of the European Community. It was also recommended to promote international cooperation and research on TSE in other species, to evaluate developmental research, as well as to define and suggest some aspects of basic research, and to foster studies on transmission, diagnostic methods for CSF, biosafety and genetics, and possible treatments.
ARGENTINA

Preliminary Document of the National Program for Epidemiological Intensified Surveillance and Prevention of Transmissible Spongiform Encephalopathies in Humans

Summoning institutions:

1. Argentine Neurology Society
2. Argentine Pathology Society
3. Program of Neurological Diseases, Bureau of Community Health, Ministry of Health, Government of the City of Buenos Aires
4. Office of Epidemiology, National Bureau of Sanitary Medicine, Department of Community Care, National Ministry of Health and Social Action

National Program for Intensified Epidemiological Surveillance and Prevention of Transmissible Spongiform Encephalopathies in Humans
Republic of Argentina

1.- INTRODUCTION

During 1996, the possibility that Great Britain could resort to the sanitary slaughter of most of its cattle population as a result of over 158,000 cases of bovine spongiform encephalopathy (BSE) reported since 1986 had a worldwide impact. This situation originated a crisis of confidence with respect to the consumption of beef and threatened to destabilize the trade of this product in Europe.

In the Americas, BSE has not been recognized in livestock, but after its appearance in the United Kingdom, countries such as the USA and Canada have initiated studies aimed at evaluating the risk of the presence or possible entry of the disease.

Since 1990, Argentina has implemented a program for livestock BSE epidemiological surveillance that so far has not shown the presence of the disease. This fact represents an obvious advantage from the sanitary standpoint for the trade of Argentine beef.

Transmissible spongiform encephalopathies (TSE) are a group of diseases characterized by a long incubation period and a progressive course that causes degeneration of the central nervous system (cerebral cortex, cerebellum and gray nuclei), and originates in the CNS spongiform changes leading to a fatal course. The first TSE to be thoroughly studied was...
that affecting sheep, or scrapie of sheep and goats, known in Spanish-speaking countries as "tembladera" and in some regions as «lumbar pruritus» because the animals suffer an apparent pruritus that forces them to scrape and tear out their wool and skin. This disorder has been known in England since the XVIII century from where it spread to the rest of the world. The bovine spongiform encephalopathy (BSE) resembles the ovine form as regards its evolution and pathological anatomy. The disease in bovines is caused by the use of feed supplements containing meat and bone meal from sheep affected by scrapie. The disease has also been described in other animals: mink (TME), mules, deer, and elks (CWD), and cats (FSE).

The transmissible spongiform encephalopathies studied in human beings share clinical and evolutionary features with animal encephalopathies. The pathological anatomy shows neuronal degeneration and death, a proliferation of the glial cells and a vacuolation that causes a spongy aspect in the affected tissues.

The forms of the disease that are best known in humans are sporadic or hereditary Creutzfeld-Jakob disease (CJD), hereditary Gerstman-Straussle-Scheinker disease, fatal familial insomnia, acquired encephalopathies such as kuru, and the exceptional forms of iatrogenic origin (intracranial surgery, recipients of growth hormone and of cornea and dura mater grafts derived from sick donors)

CREUTZFELD-JAKOB DISEASE (CJD) is characterized by rapidly progressive dementia, associated with myoclonus and pyramidal, cerebellar, or extrapyramidal signs. Its evolution is relatively fast leading to death 6 to 12 months after onset. The electroencephalogram may show a characteristic pseudoperiodical sharp wave activity, but the etiology can only be confirmed by cerebral biopsy or necropsy. The disease is distributed throughout the world and affects all ethnic groups. Its incidence is highest in the sixth decade of life. Its frequency is low and is estimated at one case per million inhabitants a year. In addition to the typical cellular injuries, histology sometimes shows amyloid plaques that resist the action of proteases (cellular enzymes)

It has been shown by immunohistochemistry that those plaques are constituted by a protein with no similarity to those found in Alzheimer’s disease. It is currently accepted that this type of protein is the transmitting agent common to all transmissible spongiform encephalopathies.

These protein molecules are called prions in order to distinguish them from viruses, bacteria, fungi and any other known pathogen. The prion contains a single protein which is called PrP (protease resistant protein or prion protein). Prions are therefore defined as small infectious protein particles, which resist inactivation by procedures that modify nucleic acids. Subsequently it was demonstrated that a normal PrP which could be degraded when in contact with proteases was found in healthy brains. Therefore, the pathological PrP is only a variant of a normal protein found in nervous tissue cells. It is codified by a cell gene, i.e., it is the normal product of a gene. The gene producing the human PrP was isolated later on and located in the short arm of chromosome 20. The pathological Prp variant is the infectious, protease resistant form. These encephalopathies develop when a conversion of the normal PrP to the pathological PrP occurs.

The underlying essential fact in the transformation of a normal protein into a pathological protein would be the modification of its molecular structure which, from an alpha-type PrP folding changes to a beta-type protein folding. The abnormal folding has a tendency to form deposits and damage the cells.
Heredity in prion diseases is caused by mutations in some DNA base pairs that induce the abnormal folding of the PrP.

**A NEW VARIANT OF THE CREUTZFELD-JAKOB DISEASE** was described in England with an early age of occurrence, an unusual clinical course, early psychiatric manifestations, and prolonged duration of the disease. Cases of the new variant have also been reported in France.

This new variant and the importance of a possible transmission of the vaccine disease to human beings through consumption of infected meat by-products, were cause of deep concern within the European Community, as well as for the World Health Organization, which convened a meeting of experts on the subject held in Geneva from 14 to 16 May 1996 and in which Dr. Ana Lia Taratuto participated on behalf of Argentina. During the course of the meeting an extensive report on the world situation (see Annex) was prepared and, among other important conclusions, mention was made of the need for establishing a surveillance and control system in order to determine the geographical distribution of this new variant of CJD and its real incidence, as well as for implementing a study on possible risk factors in relation to animal spongiform encephalopathies.

The Ministry of National Economy, through the Secretariat of Agriculture, Fishing, and Food, established by virtue of Resolution 456/96 a **SCIENTIFIC CONSULTING COMMISSION ON BOVINE SPONGIFORM ENCEPHALOPATHY** composed of significant international specialists. The Commission met in Buenos Aires from 7 to 10 April 1997 to carry out an extensive review of the subject. In its final recommendations, the experts pointed out that control measures currently implemented in Argentina to protect animals from TSE were adequate, but suggested some additional actions in order to improve protection and safety even further. In keeping with the recommendations of WHO and the OIE, it was proposed to strengthen TSE surveillance activities in cattle, sheep and humans. The commission will meet again in a year’s time for the purpose of reconsidering the situation of TSE in Argentina and evaluating the progress made by the country in response to the above-mentioned recommendations.

**2. PURPOSE**

*To develop a system for the surveillance and control of neurological pathologies related to transmissible spongiform encephalopathies, establish their possible relation to similar pathologies in animals and, in so doing, to contribute to ensure the quality of livestock production and the health of the population.*
3.- **OBJECTIVES**

1.- To establish the frequency of Creutzfeld-Jakob disease, (sporadic, iatrogenic and familial) and its geographic distribution in the country.

2.- To detect the occurrence of cases of the new variant of CJD and of the other spongiform encephalopathies.

3.- To establish the possible risk factors of the disease in humans.

4. To contribute to the knowledge of the disease in animals.

4.- **SUMMONING INSTITUTIONS**

1. Argentine Neurological Society and Argentine Pathology Society

2. Program of Neurological Diseases, Bureau of Community Health, Ministry of Health, Government of the City of Buenos Aires

3. Office of Epidemiology, National Bureau of Sanitary Medicine, National Ministry of Health and Social Action

5. **METHODOLOGY**

   A surveillance system based on two types of studies is proposed. The first is a retrospective study comprising cases from 1980 to date for the purpose of determining which of them agree with the definitions given below. Letters will be forwarded to the specialist who keep records of such cases.

   The second protocol has been planned to carry out a prospective monitoring of all new cases reported as of the current year (1997) that comply with the definitions stated below. Confirmation of such cases will be based on neuropathological studies and immunohystochemical tests performed at the reference laboratory.

   The NATIONAL CONSULTING COMMISSION, formed by specialists of the summoning institutions and other experts especially invited to participate, should review and advise on the actions carried out under the surveillance system and make the pertinent recommendations.
Cases should be reported to either of the following:

**Programa de Enfermedades Neurológicas**  
Dir. Salud Comunitaria. Sec. Salud. GCBA.  
Dr Raúl H. Forlenza.  
Carlos Pellegrini 313. Piso 9o, Capital Federal (1009).  
Telephone-fax 323-9000 (extension 3029)

**Sociedad Neurológica Argentina**  
Dr. Raúl Domínguez/ Dr. Manuel Somoza  
Combate de los Pozos 59, Piso 1, Depto. 5, Capital Federal  
Telephone-fax: 952-5658

Samples of biopsies or autopsies should be sent for confirmation to:

**Centro de Referencia Neuropatológica de Encefalopatías Espóngiformes Transmisibles**  
Dr. Ana Lía Taratuto.  
Montañeses 2325, Capital Federal  
Telephone-fax 788-3444 (extension 2353)

**CASE DEFINITIONS**

**PROBABLE case of classical Creutzfeldt-Jakob disease (CJD)**  
Progressive dementia and typical EEG (generalized triphasic periodic complexes) and at least two of the following clinical manifestations:

- Myoclonius
- Visual and/or cerebellar disorders
- Pyramidal and/or extrapyramidal dysfunctions
- Akinetic mutism.

**POSSIBLE case of CJD**  
Similar to probable case but with no EEG or atypical EEG and disease duration of less than 2 years.

**CONFIRMED case of CJD**  
A case is considered to be confirmed when diagnosed by standard neuropathological techniques at the reference laboratory, as well as by immunohistochemical tests.

**NEW VARIANT of Creutzfeldt-Jakob disease (nvCJD)**

Clinical features

- Psychiatric presentation with anxiety, depression, seclusion, and other behavioral disturbances followed by neurological disorders
- Development of a cerebellar progressive syndrome in weeks or months after onset of the disease.
- Forgetfulness and other memory impairments, with dementia development in advanced stages
- The EEG does not show the typical changes of the classical CJD.
- Less common features include early presentation of limb and face dysesthesia at the time of onset and of pyramidal signs during the course of the disease
- Neuropathology is mandatory for the diagnosis of a definite nvCJD diagnosis.
Neuropathological features

- Abundant kuru-like amyloid plaques surrounded by vacuoles (clearly visible by H&E and PAS stains).
- Spongiform change most prominent in the basal ganglia.
- Abundant PrP deposits on immunocytochemistry, including prominent pericellular deposition in cerebral and cerebellar cortex (especially in the molecular layer).

BIOSAFETY

Risk of transmission and decontamination method:

- The surgical material should be treated by decontaminating methods or discarded.
- Hydrolytic autoclaving during 1 hour at 134-138 degrees centigrade or in the case of non-autoclavable material, chemical decontamination by immersion in 2N sodium hydroxide (80 g/liter) during 1 hour or 1 N during 2 hours (not advisable for aluminum material).
- In 1995 the FDA determined that all blood products donated by persons who developed CJD should be withdrawn from the market, except stable materials such as albumin. However, recent studies also included this product in the risk of transmission.
- Cerebral biopsy or autopsy material should be submitted to autoclaving for 1 hour at 134-138 degrees C or immersed in formic acid for 1 hour followed by fixation in formaldehyde at 4% for 48 hs in order to diminish the risk of infection.

More information may be obtained from the Neuropathology Reference Center (Centro de Referencia Neuropatológica).
FORM FOR RETROSPECTIVE REPORTING OF CJD

Name and surname of the patient
Place of residence:
Date of birth:
Place of birth:
Date of death:
Months of evolution from onset until death:

Name and surname of the clinical physician:
Telephone and/or fax:
Name and surname of the medical pathologist:
Telephone and/or fax:
Presentation of SYMPTOMS AND SIGNS:
Mark with a cross in: 1= Yes  2=No  3=Describe mental deterioration

Dementia (1) (2)
Behavioral abnormalities (1) (2)
Aphasia (1) (2)
Apraxia (1) (2)
Agnosia (1) (2)
Cerebellar (1) (2)
Visual oculomotor (1) (2) other (3):
Giddiness (1) (2)
Headache (1) (2)
Sensory (1) (2)
Neurovegetative (1) (2)
Pyramidal (1) (2)
Extrapyramidal (1) (2)
Muscular rigidity (1) (2) other (3):

Lower moranta neuron (1) (2)
Generalized convulsions (1) (2)
Myoclonius (1) (2)
CSF (3)
EEG (3)
Cerebral tomography (3)
Cerebral resonance (3):

Pathology
Biopsy (3):
Autopsy (3):

For the notification of new cases (1997 onwards) please request the protocol to the Program of Neurological Diseases Telephone (54)(1) 323-9000 (extension 3029), or to the Argentine Neurology Society (Coordinating Commission) Tel (54)(1) 952-5658

Note: the duly confirmed collected data will be used for epidemiological control and periodic communication to WHO; they will also be disseminated in Argentina. In no case will they be given public use without the participation of the pertinent professionals.
No data are available to evaluate the incidence of possible or probable CJD cases in Argentina. The annual mortality rate due to lack of an epidemiological surveillance program could not be established either.

Only 9 cases have been reported in Argentina from 1945 to 1979.

In 1980 a NRC was establish to provide information to neurologists, neurosurgeons and pathologists on the handling of samples of CJD patients and on the decontamination of surgical instruments in biopsies and autopsies. The first 10 biopsies or autopsies of CJD were published in 1989, and up to December 1996 a total of 22 cases were confirmed at the NRC (Dr. Ana Lía Taratuto, Dr. Gustavo Sevlever, histotechnician M. Schultz), one of them with a family history and all considered as clinically probable or possible CJD cases.

A further 12 cases of CJD (11 sporadic and one originating in dura mater graft) have been confirmed in the same period by neuropathologists of other institutions in Argentina (Dr. C. Caputi: 3 cases/ Dr. H.A. Molina, 6 cases/ Dr. M. Jones: 2 cases; Dr. Theaux, 1 case, personal communication). Therefore, during the period 1980-1996 a total of 34 cases were confirmed by biopsy or autopsy. In March 1997, the Argentine Neurology Society and the Argentine Pathology Society jointly initiated the surveillance of CJD and other transmissible spongiform encephalopathies.

During 1997, 7 new cases were diagnosed and confirmed by neuropathology. In 2 of them, of Chilean origin, it was possible to define the genetic character (codon 200 mutation) through studies on molecular biology carried out in collaboration with the University of Indiana, USA (Dr. P. Piccardo). Case number 7 could correspond to Fatal Family Insomnia and therefore it is necessary to await completion of the molecular genetics study.

The age of the 29 cases reported between 1980 and 1997 at the RNC ranged from 39 to 74 years, with an average of 55.8; of them, 12 were males.
The duration of the disease up to biopsy or autopsy was from 2.5 to 24 months with an average of 7.6 months. Neurological involvement was gradual in 27 cases (weeks or months) and in only 2 cases the presentation was abrupt, similar to a stroke (days). Behavioral and cognition abnormalities were observed at an early stage in 18 patients, while in the 11 remaining cases other neurological symptoms predominated initially. In the final stages of the disease (biopsy or autopsy) the following signs were present: pyramidal in 22, extrapyramidal in 22, cerebellar in 12 and visual in 12. The clinical progression characterized by the triad dementia, myoclonus and periodic EEG was present in 16 cases prior to the neuropathological study. The material for the neuropathological studies came from 20 biopsies and 10 autopsies (in 1 case from both).

All the biopsies and autopsies showed unmistakable spongiform changes, neuronal depletion of variable intensity, astroglial hyperplasia in cerebral cortex, cerebellar cortex and subcortical gray substance, especially in the basal ganglia. No amyloid plaques, precursor protein of amyloid, or immunomarking for TAU in the neocortex were detected. No cases of Gerstman-Straussler-Scheinker disease were found. No atypical cases similar to the new variant of CJD (nv-CJD) described in the United Kingdom and France were reported. The Commission of Epidemiological Surveillance for CJD and other transmissible spongiform encephalopathies (TSE) in humans is formed by: Dr. Ana Lia Taratuto, Dr. Manuel Somoza, Dr. Raúl Domínguez, and Dr. Raúl Forlenza. During this period the commission has directed its effort to disseminating between neurologists, pathologists and public health authorities, the need to carry out surveillance of CJD and its new variant according to the 1996 recommendations of the World Health Organization (WHO).

Activities carried out by the Commission for the surveillance of CJD in Argentina

1- Communications to all the neurologists and pathologists in the country in order to implement the retrospective and prospective reporting of CJD cases in the pertinent forms. Dissemination of safety measures applicable to the handling of biopsies and autopsies, the surgical instruments used and the collected material. Information was also reported in the pages of Neuro-Web.Internet of the Argentine Neurology Society (http://priv.roche.com.ar/neuroweb/)

2- During the World Congress of Neurology, held in September 1997 in the city of Buenos Aires, presentations on the surveillance of CJD and its new variant were made in conferences, symposia and posters. Similar dissemination activities were carried out during the Congress of the Argentine Pathology Society in November 1997.

3- Attendance by invitation at the WHO consultation on CJD and other transmissible spongiform encephalopathies, held in Geneva in May 1996. Attendance at the Special Course on Protein Prion Diseases by the American Neuropathologists Association, in June 1997. Attendance at the meeting of the European Community on Prion Diseases in Humans, held in Vienna in December 1997. Participation in the activities related to bovine spongiform encephalopathy. (Dr. Ana Lia Taratuto) carried out by the Argentine Scientific Consultative Commission of the Secretariat of Agriculture, Livestock, Fishing and Food.

4- Attendance of two members of the Coordinating Commission at the WHO consultation on world surveillance of TSE in humans, carried out in Geneva in February 1998. (Dr. Manuel Somoza, Dr. Raúl Domínguez). During the meeting, the records of the cases reported in Argentina during 1997 were presented and Argentina was proposed for a WHO Collaborating Center.
5- In conjunction with WHO (Dr. Martin Zeidler), the Pan American Health Organization (PAHO) and the Pan American Institute for Food Protection and Zoonoses (INPPAZ), organization of a training course for all South American countries on the diagnosis and epidemiological surveillance of CJD and TSE in humans, held in Buenos Aires from 16 to 18 March 1998. In February 1998, the National Secretariat of Public Health established a Scientific Advisory Commission on CJD and other TSE in humans composed of members of the Epidemiological Surveillance Commission and representatives of the Argentine Neurology Society and the Argentine Pathology Society, among others.

Dr. Ana Lía Taratuto. Fax 54-1-784-7620. E-mail: ataratuto@roche.com.ar
Dr. Manuel Somoza. Fax 54-1-802-9098. E-mail: postmaster@drsomo.sld.ar
BOLIVIA

STATUS OF THE EPIDEMIOLOGICAL SURVEILLANCE
OF CREUTZFELDT-JACOB DISEASE

Dr. Mario E. Barragan

Total Population: 7,000,000 inhabitants

Possible Organization of Health Services for the detection and monitoring of CJD cases

MINISTRY OF PUBLIC HEALTH

NEUROLOGY, NEUROSURGERY,
AND PSYCHIATRIC
HOSPITAL SERVICES

Current status of CJD in Bolivia

1- No official system has been established for the epidemiological surveillance of CJD and its notification is not compulsory
2- However, the Neurology Society has been alert at least since 1968 to its possible presentation in the environment; no suspect cases have been reported so far.
3- In spite of this, the possibility cannot be ruled out entirely and consequently epidemiological surveillance measures should be strengthened.

Recommendations

1- Notification of cases to the Authorities
2- Dissemination of information and communication to the general public.
3- The disease should be declared of compulsory notification
4- Establishment of the terms under which CJD surveillance will be carried out
5- Maintenance of an excellent internal and external level of information of the system.
Brazilian mortality statistics system
■ from death certificates and primary cause of deaths
■ Morbidity statistics.
■ public-assistance program (in-hospital)

any case recorded in the 1987 - 1995 period

Case Reports

Case Reports:

1971 Sanvito et al - Arq. Neurops Sao Paulo
1974 Câmara et al - Brazilian Congress Rio
1977 Guidugli et al - Arq Neurops Sao Paulo
1980 Zukerman et al - Seara Med. NC Sao Paulo
1986 Pinto Jr et al - Arq. Neurops Sao Paulo
1987 Kouyoumdjian Jo et al - Arq Neurops Sao Paulo
1992 Macario ME et al - Rev Br Neurol Rio
(received cadaver pituitary growth h.)
1997 Queiroz & Andrade Fo - Rev Br NP Bahia

Case Series Reports:

Marchiori PE et al - Arq. Neurops Sao Paulo
(1974 - 1995: 7 males x 7 females
from 26 to 76 years of age)
POPULATION COMPOSITION

VITAL STATISTICS
- Population - 147 million (1991)
  (Creutzfeld-Jakob in the world: 1.1 million pop.)

ETHNIC COMPOSITION
- About half, of European origin; ± ⅓ European mixed, Black and/or Indian ancestry; some 10% Black. Some Orientals, mostly of Japanese extraction.
### BRAZIL
MORBIDITY STATISTICS
EPIDEMIOLOGICAL SURVEILLANCE

<table>
<thead>
<tr>
<th><strong>DAILY REPORT</strong></th>
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<tbody>
<tr>
<td>➤ Work Accident (Fatal or Medical Care)</td>
</tr>
<tr>
<td>➤ Cholera</td>
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<tr>
<td>➤ Dengue Haemorrhagic Fever</td>
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<tr>
<td>➤ Diptheria</td>
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<tr>
<td>➤ Meningococal Infection</td>
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<td>➤ Agrotoxic Intoxication</td>
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<tr>
<td>➤ Meningitis</td>
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<td>➤ Other Exogenous Intoxications</td>
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<tr>
<td>➤ Plague</td>
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<td>➤ Rabies</td>
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<tr>
<td>➤ Measles</td>
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<tr>
<td>➤ Dietary Toxiinfections</td>
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<tr>
<th><strong>WEEKLY REPORT</strong></th>
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<tbody>
<tr>
<td>✤ Whooping Cough</td>
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<tr>
<td>✤ Dengue</td>
</tr>
<tr>
<td>✤ Occupational Dermatosis</td>
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<tr>
<td>✤ Acute Diarrhea</td>
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<tr>
<td>✤ Chagas disease</td>
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<tr>
<td>✤ AIDS</td>
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<tr>
<td>✤ Schistosomiasis</td>
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<tr>
<td>✤ Purpuric or Haemorrhagic Fever</td>
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<td>✤ Infectious or Toxic Hepatitis</td>
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<tr>
<td>✤ Rubella</td>
</tr>
<tr>
<td>✤ Occupational Deafness</td>
</tr>
<tr>
<td>✤ Tetanus</td>
</tr>
<tr>
<td>✤ Tuberculosis</td>
</tr>
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CREUTZFELDT-JAKOB DISEASE IN BRAZIL:

ISSUES RAISED:

♦ EPIDEMIOLOGICAL REALITY:
  ♦ real low incidence or
  ♦ underdiagnosis and/or underregistration

♦ IS IT WORTHWHILE (TRANSMISSION POSSIBILITY, BSE)?
  ♦ compulsory notification
  ♦ long-term registration - National CJD Surveillance Unit
  ♦ Educational campaign
    ➔ diagnosis criteria (reliable, valid identification)
BRAZIL

DISEASES ASSOCIATED WITH CLINICAL SIGNS

Dr. Claudio Severo Lombardo Barros
Dr. Sergio Rosenberg

PLANT POISONING

a. PRIMARY

a.1. Tremorgenic toxins (eg.: Claviceps paspali, Phalaris spp.)

a.2 Induced lysosomal storage disease (Solanum fastigiatum)

b. SECONDARY

Semecio spp. Poisoning (hepatic encephalopathy)

VIRAL INFECTIONS

a. Rabies
b. Meningoencephalitis herpesvirus
c. Malignant catarrhal fever

BACTERIAL INFECTIONS

a. Listeria Infection
b. E. coli (young)

METABOLIC (?)

a. Polioencephalomalacia
b. Pregnancy toxemia

MISCELLANEOUS

Brain abscesses
Parasitic cysts (Coenurus)
Trauma
Other
NUMBER OF BRAINS FROM CATTLE SUSPECTED OF NEUROLOGICAL DISEASE
EXAMINED AT VETERINARY DIAGNOSTIC LABORATORIES

<table>
<thead>
<tr>
<th>LABORATORY</th>
<th>1990 - 96</th>
<th>1997</th>
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<tbody>
<tr>
<td>PELOTAS, RS</td>
<td>1,583</td>
<td>226</td>
</tr>
<tr>
<td>MATO GROSSO DO SUL</td>
<td>467</td>
<td>155</td>
</tr>
<tr>
<td>SANTA MARIA, RS</td>
<td>329</td>
<td>32</td>
</tr>
<tr>
<td>UNIV. RURAL, RJ</td>
<td>380</td>
<td>120</td>
</tr>
<tr>
<td>PESAGRO, RJ</td>
<td>76</td>
<td>11</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>2,875</strong></td>
<td><strong>544</strong></td>
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</table>

CATTLE AND SHEEP POPULATION IN BRAZIL

<table>
<thead>
<tr>
<th>REGION</th>
<th>BOVINE</th>
<th>OVINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIDWEST</td>
<td>78,937,818</td>
<td>794,000</td>
</tr>
<tr>
<td>EAST</td>
<td>23,796,110</td>
<td>3,374,000</td>
</tr>
<tr>
<td>NORTH</td>
<td>21,473,115</td>
<td>282,000</td>
</tr>
<tr>
<td>SOUTH</td>
<td>17,555,592</td>
<td>10,848,000</td>
</tr>
<tr>
<td>NORTHEAST</td>
<td>13,691,549</td>
<td>4,652,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>155,454,184</strong></td>
<td><strong>19,950,000</strong></td>
</tr>
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</table>
BOVINE SPONGIFORM ENCEPHALOPATHY

THE BRAZILIAN SITUATION

• Animal TSE are considered exotic diseases in Brazil.
• A surveillance system capable of detecting these diseases is being implemented.

MEASURES TAKEN TO PREVENT THE INTRODUCTION OF BSE and SCRAPIE INTO THE COUNTRY

• Suspension of sheep imports from the UK since 1985.
• Suspension of bovine and other ruminants imports from the UK since 1990.
• Suspension also of the following imports:
  ■ Bovine and ovine embryo
  ■ Bovine semen
  ■ Beef and by-products
  ■ CNS tissue from cattle and sheep
  ■ Hemolympathic organs and gastrointestinal system from cattle and sheep
  ■ Feedstuff containing ruminant protein
  ■ Tissues and fluids from bovine, ovine, caprine and wild ruminants for the manufacturing of pharmaceutical products.

• The prohibition of bovine and bovine derived products were suspended from other BSE countries.
CHILE¹

Epidemiological Surveillance of BSE and Scrapie

Dr. Rubén Moreira Zúñiga

1. GENERAL

Through its official animal health authority, the Agricultural and Livestock Service (SAG), Chile has established preventive measures aimed at maintaining its condition of free from bovine spongiform encephalopathy (BSE) and scrapie.

The minimum risk of BSE introduction into Chile was determined in a study on qualitative risk carried out in 1991 by the SAG Livestock Protection Department, in which all significant factors regarding the appearance of the disease were taken into account. In 1992 the study was submitted for consideration at the Regional Meeting of the International Office of Epizootics (IOE) together with other background documents on the basis of which Chile was included among the countries free from BSE:

As of 1990, importation into Chile of live animals, animal products, by-products, semen, and embryos from countries that could not offer proof of being free from BSE, was prohibited. Importation of feed for ruminants containing proteins of animal origin with the exception of fish and poultry meal was likewise forbidden.

Taking into account that Chile is free from BSE, Resolution Nº 1133 was implemented in 1996 and reported to the World Trade Organization (WTO). The resolution complemented the sanitary requirements for the definitive importation of bovines, semen, embryos and slaughterhouse by-products from countries with BSE.

Moreover, all the standards of the International Zoosanitary Code related to BSE and scrapie have been complied with; the trade of animal products from the affected countries has been restricted; the disease has been declared of compulsory notification, and monitoring studies are under way, in accordance with recent recommendations from international organizations.

In addition, the American hemisphere has been recognized by the World Health Organization (WHO) as free from BSE, and this information has been widely disseminated worldwide. Also, the International Office of Epizootics (IOE), at the 13th Regional Conference for the Americas, held in Havana; Cuba, from 26 to 29 March 1996, set forth in its Recommendation Nº 5 suggestions aimed mainly at keeping the Americas free from the disease.

In Chile, no animals have ever been detected with symptoms compatible with BSE. The disease is of compulsory notification, and an effective and continuous surveillance and monitoring system is applied. This, according to the terms of Chapter 3.2.1 of the Animal Health Code of the IOE, signifies that the country is free from BSE.

¹ Dr. Rubén Moreira Zúñiga, veterinarian, Agriculture and Livestock Service (SAG)
Moreover, the country's stable sheep population amounts to 3,710,459 (Census INE 1997), of which 72% is distributed among the country's regions X, XI and XII. In these areas, sheep production is one of the main livestock economic activities. Its origin goes back to the beginning of the century, and since the 1970s, Chile has been exporting animals and meat to countries in the Americas, Europe, and Asia (an average of over 4 thousand tons of meat in the last 5 years). The sheep products exported to Europe and North America come from the XII Region.

Sheep raising in Chile is carried out in close contact with the animals, and there are several instances in which it is necessary to handle each animal individually, such as the sheering process and the administration of preventive sanitary treatments. In addition, animals of special quality reared in stock farms are handled individually throughout the year. Most sheep-raising farms apply advanced techniques and include veterinary assistance. In addition, official sanitary programs are implemented in the area, including programs for the control of hydatidosis, brucellosis, and ectoparasites.

Since exports began, slaughterhouses are under official inspection and work in accordance with the standards of the European Community (Directive 64/433/EC).

In addition to the above, in the area there are veterinary health care services and centers, including official, private and university diagnostic laboratories specializing in the diagnosis of animal diseases.

As a result of the above measures the sanitary coverage of the sheep population is considerable. From the early days of sheep raising to date, the existence of scrapie has never been reported in Chile nor has there ever been any evidence of its presence. In addition, since the 1970s, a policy for the prevention of scrapie is under implementation and genetic material is only imported from countries with a certified sanitary status regarding the disease.

On the basis of the available facts, it can be concluded that there is sufficient evidence to state that Chile is free from scrapie. Accordingly, the health policy regarding this disease is to implement actions aimed at preventing its entry and to be on the alert regarding possible risks, such as establishing measures in order to certify the status of free from the disease through sanitary surveillance and monitoring of national coverage.

Taking into account health conditions in the country and their impact both in the internal and the export trade, a National Plan for the Prevention of Transmissible Spongiform Encephalopathies was established for the purpose of preventing the entry of the agent by means of regulations and sanitary controls of imported animals and their by-products. In the event of the agent’s entry, the plan foresees activities aimed at its early detection and the establishment of a sanitary emergency scheme that would ensure its eradication.

The main lines of action envisaged in the plan include the training of animal health personnel (public and private), an epidemiological surveillance system, sanitary control, laboratory diagnosis, early detection, sanitary emergency and health education.

On the basis of the afore-mentioned information we are in a position to certify that our country is free from animal transmissible spongiform encephalopathies.
2. - ANIMAL POPULATION

<table>
<thead>
<tr>
<th>REGION</th>
<th>CATTLE</th>
<th>SHEEP</th>
<th>GOATS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>females&gt; 30 months*</td>
<td>total</td>
</tr>
<tr>
<td>I</td>
<td>4618</td>
<td>1616</td>
<td>46005</td>
</tr>
<tr>
<td>II</td>
<td>524</td>
<td>183</td>
<td>14984</td>
</tr>
<tr>
<td>III</td>
<td>6606</td>
<td>2312</td>
<td>8640</td>
</tr>
<tr>
<td>IV</td>
<td>38795</td>
<td>13578</td>
<td>71936</td>
</tr>
<tr>
<td>V</td>
<td>136065</td>
<td>47623</td>
<td>56574</td>
</tr>
<tr>
<td>R.M.</td>
<td>165106</td>
<td>57787</td>
<td>30241</td>
</tr>
<tr>
<td>VI</td>
<td>157034</td>
<td>54962</td>
<td>184690</td>
</tr>
<tr>
<td>VII</td>
<td>373270</td>
<td>130645</td>
<td>206120</td>
</tr>
<tr>
<td>VIII</td>
<td>561040</td>
<td>196364</td>
<td>186251</td>
</tr>
<tr>
<td>IX</td>
<td>790451</td>
<td>276658</td>
<td>247166</td>
</tr>
<tr>
<td>X</td>
<td>1601592</td>
<td>560557</td>
<td>396593</td>
</tr>
<tr>
<td>XI</td>
<td>168770</td>
<td>59069</td>
<td>337565</td>
</tr>
<tr>
<td>XII</td>
<td>137674</td>
<td>48186</td>
<td>1923694</td>
</tr>
<tr>
<td>TOTAL</td>
<td>4141545</td>
<td>1449540</td>
<td>3710459</td>
</tr>
</tbody>
</table>

(*) Estimated

3. - SURVEILLANCE OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES (TSE)

For the purpose of accumulating evidence ratifying Chile´s status of free from BSE and scrapie, a population study at the national level was initiated in 1996 in order to detect the possible presence of both diseases. The study envisaged the systematic sampling of cattle and sheep of ages at risk (old animals) within the framework of a statistical design that provides a high confidence level in the estimate (99%) for p = 0.5%.

For the purpose of processing the samples, the following criteria for numbers of cuts per sample were defined, depending on the disease under investigation and the type of sample obtained.

**BSE:**
animal brain samples with neurological disease: 8 cuts per sample
animal brain samples with no nervous system symptoms: 4 cuts per sample

**Scrapie:**
animal brain samples with neurological disease: 14 cuts per sample
animal brain samples with no nervous system symptoms: 7 cuts per sample

The study is carried out in animals slaughtered at slaughterhouses and from areas with a greater number of animals of both species.

Nº OF SAMPLES PROGRAMMED FOR MONITORING
BSE - SCRAPIE, CHILE
<table>
<thead>
<tr>
<th>REGION</th>
<th>Nº BOVINE SAMPLES</th>
<th>Nº SHEEP SAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>VII</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>VIII</td>
<td>110</td>
<td>50</td>
</tr>
<tr>
<td>IX</td>
<td>120</td>
<td>80</td>
</tr>
<tr>
<td>X</td>
<td>160</td>
<td>90</td>
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<tr>
<td>XI</td>
<td></td>
<td>130</td>
</tr>
<tr>
<td>XII</td>
<td></td>
<td>520</td>
</tr>
<tr>
<td>RM</td>
<td>530</td>
<td>10</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

STATISTICAL DESIGN:

Monitoring scrapie (sheep)  \( p = 0.5\% \), level of confidence 99\%, \( n = 1000 \)

Monitoring BSE (cattle)  \( p = 0.5\% \); level of confidence 99\%; \( n = 1000 \)

The guidelines for the diagnosis criterion used, as well as for processing the samples are those recommended by international experts:

- Confirmation of bovine encephalopathy and scrapie by microscopic examination of the brain (18 June 1993).

No transmissible spongiform encephalopathies (TSE) have been diagnosed in any of the species of economic or zoological interest, recreation (pets) or wild animals.
<table>
<thead>
<tr>
<th>Species</th>
<th>Nº of samples processed</th>
<th>Nº of cuts examined</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>342</td>
<td>1368</td>
<td>negative</td>
</tr>
<tr>
<td>Sheep</td>
<td>53</td>
<td>371</td>
<td>negative</td>
</tr>
<tr>
<td>Goats</td>
<td>6</td>
<td>42</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>401</td>
<td>1781</td>
<td></td>
</tr>
</tbody>
</table>

In the case of cattle brain cuts were made at the following levels:

Cut A: obex  
Cut B: posterior cerebellar peduncles  
Cut C: colliculus or anterior quadrigeminal tubercle  
Cut D: colliculus and anterior quadrigeminal tubercle.

In the case of sheep brain cuts were made at the following level:

Cut A: obex  
Cut B: caudal medulla to posterior cerebellar peduncles  
Cut C: midpons  
Cut D: midbrain through the rostral culliculus and medial geniculate  
Cut E: cerebellum (sagital cut)  
Cut F: caudal diencephalon to the internal capsule through the mamillary body  
Cut G: thalamus optic tract, hypothalamus.

FOOTNOTES/ENDNOTES
FootNote 1. Dr. Rubén Moreira Zúñiga, veterinarian, Agricultural and Livestock Service (SAG)
COSTA RICA

EPIDEMIOLOGICAL SURVEILLANCE
OF CREUTZFELDT-JACOB DISEASE

Dr. Gerardo del Valle Carazo

Area: 51,100 Kms $^2$
Population: approximately 3,000,000 inhabitants

Human spongiform encephalopathy is not included in the list of transmissible diseases of compulsory notification and for this reason there is no official report. Neurologists of Costa Rica have made comments concerning some clinically suspect cases.

Agencies that can participate in the Epidemiological Surveillance (Human and Animal)

- Office of control of communicable diseases of the Ministry of Health
- Animal Health Department of the Ministry of Agriculture and Livestock
- Neurological Science Society
- Neurophysiology Society
- Pathology Society
- Psychiatric Society
- Pathology Services of the Principal Hospitals in Costa Rica.
- Services of Hospital Neurology
- Psychiatric Hospital and Psychiatric Services in other hospitals.

Costa Rican Fund of Social Security

- Office of drug control of the Ministry of Health
- Zoonosis Department of the School of Veterinary Medicine, National University
- National Institute of Research in Health (INISA) (University of Costa Rica)
- Costa Rican Research and Teaching in Health Institute (INCIENSA)
- Office of Food Protection of the Ministry of Health, Chamber of Livestock Owners
- In the country there are 36 neurologists and a similar number of neurosurgeons and psychiatrists.
- Electron microscopy is available: 8 computerized axial tomography scanners, three of them of the social security system, 12 electroencephalography services, 7 of which belong to the social security system, as well as 2 private centers for magnetic nuclear resonance imagining that provide services to the social security system.
- The vast majority of the population of Costa Rica belongs to the national social security system.
CUBA

EPIDEMIOLOGICAL SURVEILLANCE OF CREUTZFELDT-JACOB DISEASE

Dr. Ricardo Santiago Luis González

No statistical control data are available to estimate the annual incidence of Creutzfeldt-Jacob disease.

In 1990 two women, 69 and 40 years’ old respectively, with clinical and electroencephalographic diagnosis died at the Institute of Neurology in Havana; the diagnosis was subsequently confirmed at autopsy. The diagnosis of a 59 year-old man who died in 1985 was also confirmed by autopsy.

In the last 10 years and according to the mortality data compiled from death certificates at the Ministry of Public Health Statistics Department, there were 7 cases of the disease, 5 women and 2 men whose ages ranged between 51 and 73 years, average 62 years. All cases were diagnosed clinically and electroencephalographically by neurologists. All were sporadic cases; none had originated in grafts. The diagnosis of one of these cases was confirmed by autopsy. No cases of spongiform encephalopathies have been reported.

In the country there are approximately 120 neurologists and neurology and neurophysiology services are available in all the provinces.

The disease is of compulsory notification and surveillance is adequately guaranteed through the National Bureau of Epidemiology which has Units of Analysis and Trends in Health distributed throughout the country.

Cuba's population amounts to a little over 11,000,000 inhabitants. Life expectancy at birth is 75 years, and there are 55 physicians per every 10,000 inhabitants. Around 30,000 people are included directly in primary health care through the family doctor plan.

The leading causes of death are:

1- Cardiac diseases
2- Malignant neoplasms
3- Cerebrovascular diseases.
ECUADOR

AN APPROXIMATION TO THE DIAGNOSTIC INCIDENCE OF CREUTZFELDT JAKOB DISEASE

Dr. Marcelo Placencia

INTRODUCTION

In Ecuador, no programs have been implemented either in the specialized neurological services or through neurologists societies for the epidemiological surveillance of Creutzfeldt-Jakob disease (CJD) or of human transmissible spongiform encephalopathies (TSE). For this reason no national systematic data are available.

Due to several observational biases, the automatic inclusion of CJD in the national disease registries is not feasible. In order to illustrate this assertion, we checked the Hospital Statistics Yearbooks published by the National Institute of Statistics and Censuses; the information appearing therein is based on the diagnoses of patients when discharged from hospital coded in accordance with the three-digit list of the PAHO/WHO International Disease Classification, 9th edition. Between 1983 and 1992, discharges from both public and private centers in the entire country amounted to 4,700,000, 26 of which were classified as Infections of the central nervous system due to slow viruses and 3,058 as other cerebral degeneration (c/d. 331).

After making the necessary adjustments, these figures represent a national annual rate per 1,000,000 inhabitants of 0.23 and 27.8, respectively. CJD is concealed within those figures in a proportion difficult to establish automatically. In addition, identification is not verified when discharge diagnoses are made, so that the same person may be included more than once in the discharge registration of each year.

As regards death certificates, diagnoses have been classified in codes that include several groups according to an abbreviated list of causes of death. This constitutes a repetition to an even greater extent of the difficulty mentioned above with respect to hospital discharges. In addition, frequently the leading cause of death which appears in the certificate is one among the last complications suffered by a dying patient (pneumonia, myocardial infarction, etc.), instead of the causal disease, so that the latter may be excluded from the registries.

The pathologies seen in the out-patient services are not reflected in the national epidemiological figures because they are not registered systematically. There is some epidemiological surveillance through samplings carried out at sentinel posts under the Ministry of Public Health, mostly based on diagnoses made by the primary health care services. This procedure furnishes very useful estimates with which to provide feedback for programs on pathologies of high or medium prevalence (diarrhea, respiratory infection, etc.) or high-risk groups (children, mothers, etc.), where CJD is not likely to occur.

The fact that Ecuador has a 12,000,000 population included in several health subsystems and no definite geographical limits as to health care coverage and the inhabitants who are entitled to receive it, increases even further the methodological complexity. Thus, hospitals with advanced technological means, where normally CJD patients would go, receive patients
from dissimilar and overlapped areas, whose epidemiological denominator is difficult to establish. Computerized registries of case histories have only recently been introduced in Ecuador and have been installed in small centers that are not an adequate source of epidemiological information for the study of CJD.

The health subsystem with a more realistic definition of areas and users is that of the Ecuadorian Institute of Social Security (IESS). Data on one of its areas are presented below.

OBJECTIVES

To describe the probable incidence of the specialized clinical diagnosis of CJD per 1,000,000 inhabitants per year, in the population covered by the IESS, as a sample for Ecuador.

MATERIAL AND METHODS

The IESS has approximately 1,900,000 members, of whom 1,000,000 are economically active or retired adults and the rest, rural families. Approximately 800,000 of the total members (population of IESS Regions N1 1,4,5,8) have been assigned to use as a higher technology reference hospital the ´´Carlos Andrade Marin´´ (HCAM) in Quito, where patients discharged annually average 20,000 and outpatient consultations, 320,000.

The neurology and neurosurgery services of the HCAM have an average of 800 admissions and 12,000 outpatient consultations per year for whose registration the author developed the NeuroSys database. The database provides the complete diagnosis, as well as the demographic and other type of data on patients admitted and discharged since 1987 and on outpatient consultations since 1994. A search for CJD was made among 12,500 patients included in the data base. In order to confirm and provide more information on the outcome of the search, the EEG tracings and the case history of those positive for CJD in the hospital’s general file were reviewed.

For the purposes of this report, we consider as cases those with CJD clinical diagnosis, as established by the attending specialized physicians.

In order to calculate the annual incidence, our numerator was the number of cases during each year and the denominator, the IESS members in that same year whose reference hospital for specialized attention was in theory the HCAM (IESS regions N1 1,4,5,8). This segment comprises 800,000 inhabitants.

RESULTS

Of the 12,500 patients registered in the NeuroSys database since 1987, 9 had CJD clinical diagnosis and were admitted to hospital between 1992 and 1996. Seven of them were males and two were women, with an average age of 54.5 years. 23.4 cases (range 37 to 82). In 3 the case history was not available for review.

The evolution period prior to diagnosis was between 1 and 10 months in 6 cases and in 3, data were not available. Three died while confined at hospital and the remaining cases were discharged but the final outcome is not known.
Dementia was present in all cases; in 3 it was exclusive and in the rest it occurred in combination with myoclonus (4), ataxia (1), parkinsonism (1), supranuclear paralysis (1), sudden focal deficiency (1). In one there was, in addition, non-hypertensive cerebral parenchymous hemorrhage in the months previous to the onset of dementia.

The EEG was abnormal in 8 cases and in 1 it was not available. Three showed periodic activity and in 2 it was accompanied by diffuse effects. In e was intermittent rhythmic frontal activity (FIRDA), and in 1, also diffuse effects. One showed signs of frontal injury and the remaining 2, of diffuse effects.

Brain imaging was normal in 3 cases; cortical atrophy was observed in 1, parenchymous calcification also in 1 (a case with periodic suppression outbreaks in the EEG) and in 4 it was not available.

The annual incidence of CJD per 1,000,000, for cases in 1992, 1993, 1994, 1995 and 1996, was: 1.25, 3.75, 2.50, 2.50 and 1.25, respectively.

**DISCUSSION**

The most important problem posed by these data is related to the reliability of diagnosis, which could not be confirmed at autopsy, follow-up until death, or repeated EEGs. Despite this, all cases except one (that with a previous cerebral hemorrhage), had presentations compatible with CJD, and can therefore be used as referential information for an approximate calculation of the incidence of this diagnosis based on the country’s specialized services.

The availability of population data on disease cases and on the general population is essential for estimating the incidence rate. Our calculation may therefore be considered unorthodox to a certain extent. However, it is reasonable to think that the seriousness of CJD, the fact that it is not an acute disease and that its treatment in the home is expensive, would induce the family of the patient affiliated to the IESS, to resort to the reference hospital, where no payment would be required. On the basis of these assumptions, we believe that the data reported above represent the most probable local reality; in addition, they fall within the scope of what is expected worldwide.

**ACKNOWLEDGMENTS**

To the neurology and neurosurgery services and to the Clinical Archives of the CAM Hospital of the IESS in Quito. To the Ministry of Public Health of Ecuador. To the PAHO/WHO Representation in Ecuador. To the Pan American Institute for Food Protection and Zoonoses.
INTRODUCTION

In the profile of health problems in Guatemala, communicable and non-communicable diseases are predominant, according to the terms of what is now known as the epidemiological transition. This implies that the Guatemalan population is subject simultaneously to many risk factors which are interrelated to the response provided by the health services, to each person’s biology and to a particular lifestyle. Consequently, the quality of life of the Guatemalan people is experiencing a crisis.

GEOGRAPHY AND POPULATION

Guatemala has an area of 108,889 sq. km and is located in the northern part of Central America; it is bounded to the north and west by Mexico, to the east by Belize, Honduras and El Salvador, and to the south by the Pacific Ocean. According to the last census, its population amounts to 10 million. Politically and administratively it is divided into 330 municipalities, 22 departments and 8 regions. The average temperature is 15 degrees centigrade, and annual rainfall ranges between 1,200 and 2,500 mm, with a rainy season from May to October and a dry season from November to April.

As much as 65% of the population lives in the rural area and 43% considers itself indigenous. Distribution by sex shows that 49% are men and 51%, women. The country’s population pyramid is predominantly young. Illiteracy at the national level amounts to 36% in those over 15 years old, and is higher in women and in people who live in rural areas. Approximately one million people migrate annually from the plateau toward the southwestern region in order to sell their labor force for the coffee and sugar harvests. The infant mortality rate is 48 per 1,000 live births and maternal mortality, 13.88 per 10,000 live births. The health service coverage is estimated to be 40%.

HEALTH SECTOR

The health sector comprises the Ministry of Public Health and Social Welfare (the institution that provides most services in the country and regulates the activities carried out within the sector), the Guatemalan Social Security Institute, an autonomous agency that covers rightful claimants and their families through their inclusion in specific programs, Municipalities, the private sector (with a low
MORBIDITY AND MORTALITY PROFILE

The leading causes of morbidity registered in the country, are:

1. Acute Diarrheal Disease
2. Acute Respiratory Infection
3. Malnutrition
4. Malaria
5. Chagas’ disease

The leading causes of reported mortality are:

1. Acute Respiratory Infection
2. Acute Diarrheal Disease
3. Malnutrition
4. Tuberculosis
5. Malaria

ORGANIZATION OF THE HEALTH SERVICES

The Ministry of Public Health and Social Welfare provides services throughout the country in such places as:

- Health units located in villages and hamlets and served by nursing assistants and a technician in rural health, who are responsible for preventive and health care programs and health promotion.
- Health centers located in county seats and served by medical personnel, nurses, nursing assistants, environmental sanitation inspectors, technicians in rural health, and a secretary.
- National and regional hospitals, usually located in departmental seats and large cities. At present there are 36 hospitals under the responsibility of a Director who is a physician and is assisted by administrative personnel and medical staff of the different specialties, nurses, laboratory and X-rays technicians, and the personnel of 106 supporting services. There are 7 hospitals with a pathologist in their staff and 5, also have a neurologist. Technically and administratively these hospitals are under the management of the different health divisions.
- Health Divisions, whose management is responsible for supervising health promotion, health problems prevention and care; usually located in departmental seats and large cities. They currently number 27 and include a health sector chief, an epidemiologist, a registered nurse, a supervisor of environmental sanitation inspectors and a supervisor of rural health technicians.
- Health Services General Bureau, in charge of coordinating the different technical and policy-making levels responsible for the supervision, monitoring, evaluation, and training of the operational levels (posts up to health sector divisions) in the management of health programs.
From the point of view of the zoonoses, it is important to draw attention to the coordination that exists at all levels (operative and technical-regulatory) with other institutions such as the Ministry of Agriculture, a state agency that provides support through 4 diagnostic confirmation laboratories, and the University of San Carlos (autonomous), with one laboratory.

**ORGANIZATION OF THE EPIDEMIOLOGICAL SURVEILLANCE SYSTEM**

The epidemiological surveillance system is organized so that the information is generated at the community level and reaches the health unit where it is consolidated (in general a unit serves several communities). From here it is reported to the health center, which follows the same consolidation procedure (since the health center is responsible for several units). It is then reported to the health sector division which, after consolidating once again the information received from all its centers, transmits it to the Data Processing Unit. This unit is responsible for processing the information and transmitting it to the Disease Surveillance and Control Division (EPIDEMIOLOGY) and to other national sections and offices (local, departmental, regional) and international agencies that are users of the system.

This reporting system operates on a weekly basis and usually with no delay depending on the type of disease, in accordance with the EPIDEMIOLOGICAL SURVEILLANCE REGULATIONS in force. The laboratories (both official and private, etc.) also play an important role in this system and are under the obligation of reporting to their corresponding administrative level.

**STATUS OF THE CREUTZFELDT-JAKOB DISEASE**

In accordance with the review of mortality data and the reports of neurologists and pathologists of the reference hospitals (San Juan de Dios General Hospital and Roosevelt Hospital) NO CASES OF CREUTZFELDT-JAKOB DISEASE OR OF ITS NEW VARIANT HAVE BEEN RECORDED OR BEEN REFERRED FOR CLINICAL OR PATHOLOGICAL CONFIRMATION in the last 15 years. However, there have been cases of dementia with no definitive diagnosis because of the custom of the patients’ family to take them out of the hospital when confronted with complications or for fear of the final outcome, thus eluding the system of these centers regarding necropsies.

The Creutzfeldt-Jakob disease is not included among the diseases of compulsory notification specified in the respective Manual.

**STATUS OF THE BOVINE SPONGIFORM ENCEPHALOPATHY**

In accordance with the reports of the Ministry of Agriculture, Livestock, and Food, no suspected or confirmed cases of bovine spongiform encephalitis have occurred in the country, and the level of risk is perceived as very low since the great majority of livestock breeders (98%) have small and medium-sized farms where herds are raised in the field and no meals or concentrates are used for feeding.

In addition, since 1996 the entry into the country of live animals, beef, mutton, and goat meat, flesh and bone meal, medicinal by-products, biologicals prepared with
bovine materials from European Union countries where cases or outbreaks of bovine spongiform encephalopathy had occurred has been banned. The measure was adopted on the basis of Article 31 of the Animal Health Regulations. The same prohibition was applied to the importation of medicinal products and by-products, reagents and biologicals prepared with bovine items from the same origin.

As part of the same activities, supervision in customhouses has been reinforced. At the same time, close coordination has been maintained with APHIS, PAHO/WHO, and OIRSA.

The laboratories were strengthened and BSE differential diagnosis will be performed on brains sent for rabies diagnosis confirmation.

**STATUS OF TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES**

On the basis of the above statements, it may be affirmed that in Guatemala no human cases of Creutzfeldt-Jakob disease and its new variant, or of bovine spongiform encephalopathy have been reported. Preventive and control activities within which surveillance plays an essential role, have also been strengthened.
Panama has a population of 2,500,000 inhabitants. There are 10 neurologists, 1 neurophysiologist, 1 neuroradiologist, several epidemiologists, no neuropathologist.

The Ministry of Health has 1 electrocardiograph and 2 more for the Social Security Service. There is no institutional MRT.

Social Security has 1 tomography scanner and it is hoped that another one will be installed at the Ministry of Health in the coming months.

Pathology currently does not apply biosafety measures for potentially communicable diseases. There is an epidemiological surveillance system for infectious-contagious diseases, but it does not include CJD, whose notification is not compulsory.
PARAGUAY

VIGILANCIA EPIDEMIOLOGICA
DE LA ENFERMEDAD DE CREUTZFELDT-JACOB

Dr. José Corti
Dr. Pedro Rolón

Superficie: 406.000 Km²
Población 5.000.000 de habitantes
Regiones: Oriental
          Occidental

Densidad Mayor de Población (Oriental)

16 Neurólogos / 15 Neurocirujanos / 30 Psiquiatras

[*] Programas de Salud/Ministerio de Salud Pública
[*] Departamento de Patología del Ministerio de Salud Pública y B.S.
    Departamento de Vigilancia Epidemiológica
[*] 2 equipos de R.M.N.
[*] 12 Tomógrafos - (2) Helicoidal
[*] 1 spectograma
[*] Electroencefalograma 15-20 maquinas
[*] Programa de Vigilancia
    Puesto de Salud - Centro de Salud - Hospital
    Lógicamente - en la cadena un neurólogo o neurocirujano verá al paciente
[*] 10.000.000 ganado vacuno
[*] 300.000 a 500.000 ovejas
[*] 1980 - 1998
[*] 2 pacientes con encefalopatías espongiformes (CJD):
    1 caso varón 49 años - clínica - EEG - autopsia
    1 caso mujer 58 años - clínica - EEG - biopsia (CT de cráneo/RMN Vivió en Holanda 25-30 años)

Promedio: 7 meses (fallecidos ambos)
Subsecretaria de Estado de Ganadería
Servicio Nacional de Salud Animal (SENACSA)

• 18 Oficinas zonales
• 64 Oficinas regionales
• 2 laboratorios histopatológicos con técnicos que trabajan en forma conjunta con la Facultad de Ciencias Veterinarias
• Población bovina ≅ 8.700.000
• Población ovina alrededor 2.000.000
• Sistemas de información bien estructurados, tanto a nivel nacional como internacional
• Cuenta con normativas legales bien específicas: enfermedad de declaración obligatoria
• El sistema de vigilancia epidemiológica se realiza a partir de muestras que llegan al laboratorio para diagnóstico de rabia. Todas aquéllas que arrojan resultado (-) Neg. a rabia. Además rastreo a nivel de mataderos, especialmente con animales mayores de 48 meses.
• Según recomendación de la OIE se procesaron en el año 1997, 200 muestras arrojando todas resultado negativo
  Elaboración de Informe a ser presentado a la OIE para la certificación de país libre de encefalopatía espongiforme bovina (BSE)
PERU

CREUTZFELDT-JAKOB DISEASE

Dr. Alfredo Villalobos

1998:

January - February

60,000 consultations; only 28 cases of dementia according to classification FO2 and A81 (ICD - 10), but no case of CJD (FO2.1 and A81.0)

1997

370,000 consultations; no cases

1992 - 1996

In 150,000 hospitalizations in the IPSS:

Only 1 case of Creutzfeldt-Jakob disease, a 58 year-old woman with clinical diagnosis and EEG, but no autopsy.

No case described as the new variant of CJD disease.

Subsequently 2 further cases (sporadic) were identified), with positive episodic EEG.

1986 - 1990

Two cases: one, sporadic in a 67 year-old man from Chile; the other had a relevant family history.
SECTION IV: GENERAL INFORMATION

"Transmissible Spongiform Encephalopathies. Training manual".
"WHO Consultation on the Global Surveillance, Diagnosis and Therapy of Human.
Transmissible Spongiform Encephalopathies".

"The Surveillance of Creutzfeldt-Jacob disease (CJD) and other Transmissible Spongiform Encephalopathies (TSEs)"
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*Dr. M. Zeidler* 1

## INTRODUCTION

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1. To provide information important for enhancing the protection and planning of public health worldwide.
2. To provide information that would be helpful in establishing more accurate diagnosis of all forms of CJD.
3. To prevent iatrogenic spread of disease (e.g. through the use of contaminated neurosurgical instruments or via human-derived tissue/material).
4. To increase global scientific knowledge of the human and animal TSEs.
5. To help to identify underlying occult risk factors.
6. To establish a baseline that would allow any relevant change to be detected (e.g. in clinical features, pathology and incidence).

Participants should disseminate information relevant to national CJD surveillance to the appropriate professional groups in their countries, particularly neurologists, neurophysiologists and epidemiologists, using established networks, such as neurological societies, and printed material.

In each country, the health care professionals most likely to be in a position to diagnose cases of CJD should be contacted on at least an annual basis reminding them to report cases of definite or probable CJD.

Each of the countries represented would identify a national focal point, most probably one of their delegates attending the workshop, who would be responsible for organising a national CJD surveillance meeting in their own country.

The national focal point would collect data on the number of probable and definite cases of CJD in their country and forward this (even if zero) on an annual basis to WHO.

WHO will financially support the national workshops and help provide training material.

WHO, through its CJD collaborating centres, will provide short periods of training in diagnostic techniques, including neuropathology, molecular genetics and the emerging CSF assays, for key personnel.

The usefulness of the retro-orbital post-mortem cerebral biopsy will be ascertained by assessing its use in a number of suspect CJD autopsies performed in WHO collaborating centres and the Prasat Neurological Hospital and Institute in Thailand. The results of this study will be published.

WHO, through its collaborating centres, will make slides available to interested pathologists of various forms of CJD, using both conventional and immunocytochemical stains.
Workshops should be set up to enable the OIE Code recommendations on BSE to be implemented. Training at the bench should be included.
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Section 1: Introduction

1.1 The transmissible spongiform encephalopathies and rationale for global Creutzfeldt-Jakob disease surveillance

Creutzfeldt-Jakob disease (CJD) is a rare and fatal human neurodegenerative condition. It is termed a ‘transmissible spongiform encephalopathy’ (TSE) because of experimental transmissibility to animals and its characteristic neuropathological spongiform change. The human TSEs, of which CJD is by far the most common, appear to occur sporadically in about 85% of cases, 10-15% are inherited and the remaining cases are iatrogenic. Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI) are rare human transmissible neurodegenerative disorders and are best considered as familial variants of CJD. The cause of sporadic CJD remains unknown despite extensive study, and, in particular, there is no evidence of an epidemiological link with scrapie, a naturally occurring TSE of sheep and goats. Iatrogenic CJD has arisen following transmission of the infectious agent during the use of contaminated human pituitary-derived growth hormone or gonadotropin, dura mater grafts, neurosurgical instruments and corneal transplantation. Although our understanding of the TSEs has increased dramatically over the past decade the exact nature of the transmissible agent remains elusive, with some scientists arguing that it is virus-like and contains nucleic acid, and others that it is composed of an abnormal and infectious isoform of a normal membrane protein - the ‘prion hypothesis’.

CJD is thought to occur worldwide, but as systematic surveillance has only been undertaken in a minority of countries the incidence in most of the world is unknown. A recent large study of CJD in the European Union suggested an incidence of between 0.5-1.5 cases/million per year. However, in certain populations human TSEs have been found to be much more common. The annual incidence of CJD in Libyan-born Israelis is over 30 cases/million. This was once thought to reflect the consumption of scrapie-contaminated sheep brain or eyes but is now recognised to result from the high prevalence of a gene associated with familial CJD in this population. In the 1950s another human TSE, kuru, was found to be endemic in the Fore region of Papua New Guinea with a prevalence as high as 2% in some tribes. The cause of kuru was initially far from clear but detailed anthropological studies concluded that the condition was due to the transmission of the infective agent through ritualistic cannibalism. Since these practices stopped the disease has become almost extinct.

Other than scrapie of sheep and goats, naturally occurring animal TSEs have historically been rare, with only relatively small numbers of cases documented in mink, elk and mule-deer. There is no evidence that any of these animal TSEs have ever been transmitted to man. In 1986 a novel TSE of cattle, bovine spongiform encephalopathy (BSE), was first recognised in the UK and over the subsequent decade an epidemic of more than 168,000 cases has occurred. Current evidence suggests that BSE originated from the use of cattle feed containing meat and bone meal (MBM) contaminated by a scrapie-like agent derived from either sheep or cattle. The processes used for the rendering of waste animal materials to produce MBM changed in the 1970s.
and early 1980s, from mainly batch to more energy-efficient continuous methods. Of particular importance was a sudden decreased use of hydrocarbon solvents for tallow extraction, especially in the period 1981/2, which was thought to have lead to insufficient inactivation of the infective agent. Since reaching a peak in 1992, the incidence of BSE has dropped rapidly in the UK, almost certainly due to statutory measures banning potentially infective material entering cattle feed.

In March 1996, 10 cases of a new variant of CJD (nvCJD) were reported in the UK. These patients exhibited an apparently novel and distinct clinicopathological phenotype and, although unproven, an aetiological link with the BSE agent, given the temporo-spatial association, was considered likely. In April 1996 the recent death of a young man from nvCJD was reported in France and by July 1997 a further eleven cases had been confirmed in the UK. If indeed nvCJD is linked with exposure to the BSE agent, and because the incubation period may be long, the possibility of many more cases occurring over the next 30 years cannot be dismissed. Furthermore, it is possible that the population exposed to the BSE agent, and therefore hypothetically at risk of developing nvCJD, may not be confined to the UK and France. Cases of BSE have been identified in relatively small numbers of native-born cattle from Switzerland, the Republic of Ireland, France, Portugal, Belgium and the Netherlands. Cases have also been reported in Germany, Italy, Oman, Canada, Denmark, and the Falkland Islands, although only rarely, and solely in animals imported from the UK. However, British cattle have been exported in the past even further afield including to countries in Asia, North and South America, Africa and Australasia. Bovine products sourced from the UK cattle population and MBM manufactured in the UK were also widely exported and the possibility also exists that foreign travellers visiting the UK during the 1980s were exposed to the BSE agent.

The future public health threat of nvCJD in the UK, Europe and potentially the rest of the World, is of concern and currently unquantifiable. In order to ascertain the number and distribution of any future cases global CJD surveillance, as recommended by the WHO Consultation on TSEs in May 1996, is required. Programmes have already been established in many European countries, North America, Canada and Australia. Throughout 1997 and 1998, WHO will be running a series of training courses worldwide with the intention of helping individual countries to set up national surveillance of all forms of CJD. Key members of a country’s neurological and epidemiological communities will be invited to participate in these courses and subsequently report numbers of cases on an annual basis. Four WHO collaborating centres, located in Scotland, Austria, USA and Japan, will help by providing epidemiological expertise and laboratory technical support. It is anticipated that the WHO global CJD surveillance activities will lead to a greater understanding of CJD and its variants, including the potential causes of iatrogenic CJD and the distribution of the various hereditary forms, and will provide information important for enhancing the protection and planning of public health worldwide.
1.2 A brief word on nomenclature

Unfortunately much confusion surrounds the term used to describe CJD-related disorders of humans and the comparable diseases of animals, largely reflecting disagreements over the nature of the causative agent. These conditions have commonly been referred to as: transmissible spongiform encephalopathies, prion diseases, transmissible cerebral amyloidoses or slow-virus diseases. No term is perfect, but for reasons of clarity this text will mainly refer to these disorders as ‘transmissible spongiform encephalopathies’. The terms ‘slow-virus disease’ and ‘prion disease’ are avoided as it is still not known if the transmissible agent is viral-like, containing DNA, or composed of abnormal prion protein. And, although it has certain advantages, the term ‘transmissible cerebral amyloidoses’ has traditionally been much less widely used than ‘TSEs’. It is widely accepted that the group of human and animal neurodegenerative disorders in Table 1 belong to the same group of conditions and although we will call these transmissible spongiform encephalopathies we accept that this term is also imperfect as some of the human hereditary forms may lack spongiform change neuropathologically or have yet to be transmitted.

Table 1: Human and animal transmissible spongiform encephalopathies

<table>
<thead>
<tr>
<th>Human TSE</th>
<th>First reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creutzfeldt-Jakob disease:</td>
<td></td>
</tr>
<tr>
<td>Sporadic</td>
<td>1921</td>
</tr>
<tr>
<td>Familial</td>
<td>1924</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>1974</td>
</tr>
<tr>
<td>New variant</td>
<td>1996</td>
</tr>
<tr>
<td>Gerstmann-Sträussler-Scheinker disease</td>
<td>1928</td>
</tr>
<tr>
<td>Kuru</td>
<td>1955</td>
</tr>
<tr>
<td>Fatal familial insomnia</td>
<td>1986</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Animal TSE</th>
<th>First reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrapie</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>1730</td>
</tr>
<tr>
<td>Goat</td>
<td>1872</td>
</tr>
<tr>
<td>Mouflon</td>
<td>1992</td>
</tr>
<tr>
<td>Transmissible mink encephalopathy</td>
<td>1965</td>
</tr>
<tr>
<td>Chronic wasting disease of mule and elk deer</td>
<td>1967</td>
</tr>
<tr>
<td>Bovine spongiform encephalopathy</td>
<td>1986</td>
</tr>
<tr>
<td>Feline spongiform encephalopathy</td>
<td></td>
</tr>
<tr>
<td>Domestic cat</td>
<td>1990</td>
</tr>
<tr>
<td>Puma</td>
<td>1992</td>
</tr>
<tr>
<td>Cheetah</td>
<td>1992</td>
</tr>
<tr>
<td>Ocelot</td>
<td>1994</td>
</tr>
<tr>
<td>Tiger</td>
<td>1996</td>
</tr>
<tr>
<td>Spongiform encephalopathy of captive wild ruminants</td>
<td></td>
</tr>
<tr>
<td>Nyala</td>
<td>1987</td>
</tr>
<tr>
<td>Gemsbok</td>
<td>1988</td>
</tr>
<tr>
<td>Arabian oryx</td>
<td>1989</td>
</tr>
<tr>
<td>Eland</td>
<td>1989</td>
</tr>
<tr>
<td>Kudu</td>
<td>1989</td>
</tr>
<tr>
<td>Scimitar-horn oryx</td>
<td>1993</td>
</tr>
<tr>
<td>Ankole</td>
<td>1995</td>
</tr>
<tr>
<td>Bison</td>
<td>1996</td>
</tr>
</tbody>
</table>
Section 2: Human transmissible spongiform encephalopathies

2.1 Creutzfeldt-Jakob disease: an introduction

In 1920 Hans Gerhard Creutzfeldt, a German neuroscientist, reported the case of a 22-year-old women with a six year history of progressive cerebral dysfunction. A year later another German neuroscientist, Alfons Jakob, described further cases and in 1922 the term ‘Creutzfeldt-Jakob disease’ was first introduced. Although some of these first cases would not have met modern neuropathological criteria, a retrospective analysis suggests at least half were the condition we now know as CJD. The disease remained an obscure and poorly understood condition over the ensuing four decades, a situation not helped by the use of the multiple synonyms (listed below).

- Disseminated encephalopathy
- Spastic pseudosclerosis
- Cortico-pallido-spinal degeneration
- Cortico-striato-spinal degeneration
- Jakob’s syndrome
- Presenile dementia with cortical blindness
- Heidenhain’s syndrome
- Subacute vascular encephalopathy with mental disorder
- Subacute presenile spongiosus atrophy
- Nevin-Jones disease
- Brownell-Oppenheimer syndrome.

Following the identification of transmissibility of CJD to primates in 1968, epidemiological surveys, including case-control studies, have been undertaken in France, the USA, Israel, Japan, the UK and more recently collaboratively in the European Union. Our current understanding of CJD epidemiology is indebted to these studies which have led to a greater insight of the clinical and pathological features of CJD in addition to addressing the difficult question, given the rarity of disease, of aetiological risk factors.

The incidence of CJD is approximately 0.5-1.5 cases per million persons per year. The female to male ratio is representative of the general population and no distinct pattern of socio-economic incidence prevails.

2.2 Sporadic Creutzfeldt-Jakob disease

The majority of CJD cases occur sporadically, and in this group there is no evidence of geographical clustering or case to case transmission. The mean age at onset of disease is approximately 65 years but is known to range from 14-92 years of age (see graph p56). Case-control studies have yielded controversial results, suggesting an association of CJD with various factors including surgery to the head, surgery requiring sutures, herpes zoster infection, trauma to the head or body, tonometry, consumption of various meats, farming, and exposure to a range of animals including fish and squirrels. However, none of these associations
have consistently been found and therefore they may simply reflect the difficulty of obtaining reliable associations from small studies. A recent meta-analysis, comprising 178 cases and 333 control patients, found no statistical evidence for an association between the development of sporadic CJD and diet (including consumption of brain), previous surgery, blood transfusion, occupation or animal exposure. However, even this relatively large analysis may lack the statistical power to detect minor, but relevant, risk factors. In the near future data from over 400 case-control pairs identified as part of recent European Union Collaborative Study Group of CJD will be available, with a greater power to detect potentially relevant risk factors than the previous smaller national studies.

**Clinical features**

The classical diagnostic triad of CJD is a rapidly progressive dementia, myoclonus and a characteristic electroencephalogram (EEG). The median and mean duration of illness are 4.5 and 8 months respectively, and only 4% of cases survive longer than two years (see survival curve p56). Patients usually present (in order of decreasing frequency) with cognitive decline, ataxia or visual disturbance, either alone or in combination. Less common presenting features include behavioural disturbance or a rapid evolution resembling a stroke. There is sometimes a history obtained of non-specific symptoms, such as headache, fatigue, sleeping difficulties, weight loss, malaise or anxiety, in the illness prodrome. Dementia is invariably present during the course of the illness and myoclonus, although a rare presenting feature, is observed at some stage in 80% of cases. Visual abnormalities are also common and include non-specific blurring, visual field defects, perceptual abnormalities and occasionally hallucinations. Seizures virtually never occur at presentation and are only observed later in the clinical course in 10% of patients. As the disease progresses multi-focal central nervous system failure occurs with increasing global cognitive dysfunction, urinary incontinence, ataxia and dependency, culminating in the patient becoming bedbound, mute and unresponsive. Physical pain is an uncommon feature at any stage of the illness and, due to the rapid progression of cognitive impairment, any retained insight is usually soon lost. Terminally, the patients are usually rigid, frequently cortical blind, dysphagic (predisposing to aspiration and pneumonia, the commonest cause of death) and may develop Cheyne-Stokes respiration.

Physical signs correspond with the global central nervous system involvement and may include a combination of cerebellar, pyramidal, and extrapyramidal signs. Primitive reflexes, paratonic (gegenhalten) rigidity, cortical blindness and akinetic mutism are also common whereas lower motor neuron signs are rarely observed. Myoclonus is probably the most important clinical sign. It usually shows some asymmetry; is typically arrhythmic, asynchronous and stimulus sensitive; and noted most frequently in the limbs, but also commonly affects the body and/or face. Stimulus sensitive myoclonus or a startle reaction can occur in response to sudden noise, visual threat, touch, noise, or muscle stretch, but usually myoclonus can also be noted at rest. Attempted movement may induce the jerks as may a maintained posture such as holding the arms outstretched.
**Differential diagnosis**

The characteristic clinical features of CJD - rapidly progressive dementia and myoclonus - can rarely occur in patients with Alzheimer’s disease, the most common condition mimicking CJD. Reports exist of the characteristic EEG appearances of CJD occurring in Alzheimer’s disease but these are exceptional. Other conditions that are important in the differential diagnosis are listed below.

- Vascular dementia (e.g. multi-infarct dementia and subcortical arteriosclerotic encephalopathy)
- Diffuse Lewy body disease
- Brain tumours (both primary and secondary)
- Cerebellar degeneration
- Frontotemporal dementia (e.g. Pick’s disease type and motor neuron disease type)
- Progressive supranuclear palsy
- Multiple system atrophy
- Corticobasal degeneration
- Metabolic encephalopathies
- Drug-induced encephalopathies (e.g. Bismuth, amitriptyline, mianserin, lithium, baclofen)
- Viral encephalitis

**Pathology**

As with animal TSEs, no specific macroscopic abnormalities are detected outside the central nervous system (CNS) at autopsy in CJD. Although macroscopic examination of the brain may be unremarkable, cortical atrophy is often found, although this may vary greatly from case to case and within the various regions of the cortex in each individual. Sometimes the pattern of atrophy may correspond with the clinical syndrome, such as involvement of the occipital lobes in cases with relevant visual symptoms, or may occasionally extend to involve the basal ganglia, thalamus and hypothalamus.

The microscopic hallmarks of sporadic CJD are spongiform change, neuronal loss and astrocytosis (see illustration p55). Amyloid plaques, similar to those of Alzheimer’s disease, but composed of prion protein (PrP – see below and Section 5) rather than β-amyloid, are seen in about 10% of sporadic CJD cases, but are much more common in kuru, iatrogenic CJD and the familial forms of disease. Spongiform change consists of a fine vacuolation of the grey matter neuropil in which vacuoles vary from 2 μm to 20 μm in size, with larger vacuoles becoming confluent to form irregular cavities. In longstanding cases severe spongiform change, neuronal loss and astrocytosis may occur, leading to status spongiosus with collapse of the cytoarchitecture. Neuronal loss and reactive astrocytosis generally tend to be most apparent in the grey matter areas with spongiform change.

An adjunct to the neuropathological investigation of CJD and related disorders has come from advances in PrP immunocytochemistry. In this technique tissue sections are stained using monoclonal or polyclonal antibodies directed against PrP. Because tissues may normally express PrP<sup>C</sup> (the normal cellular PrP isoform), pre-treatment is required with proteinase K to ensure that only the pathological PrP<sup>Sc</sup> (the abnormal isoform,
Sc = scrapie form) is detected. Although the pattern of PrP positivity may be as variable as standard pathology, certain generalities can be made. PrP immunostaining patterns appear to be of two main types: perivacuolar deposits and discrete plaques. In the presence of severe spongiform change in the neocortical grey matter, irregular strongly positive PrP deposits are present within coalescing vacuoles and around the periphery of these lesions. The second type of distinctive abnormality, PrP positive plaques, may be more conspicuous with immunocytochemistry compared to routine hematoxylin and eosin staining. The most frequent sites of plaque formation include the granular layer and, to a lesser extent, the central white matter and molecular layers of the cerebellum. Well defined plaques may also be seen in the basal ganglia, thalamus, brainstem and cerebral cortex. More subtle staining patterns are often seen, in particular some neurons may be outlines by granular PrP depositions, and in addition to this perineuronal pattern, sometimes intra-neuronal staining may be detected.

2.3 Familial disease

The entire open reading frame of all known mammalian and avian PrP genes resides within a single exon. In humans this encodes a product of 253 amino acids, which includes 4 octapeptides contiguous with a preceding nonapeptide of similar sequence. To date 12 point mutations and eight different length octarepeat insertions have been associated with genetic disease. Familial disease, inherited as an autosomal dominant trait, accounts for approximately 10-15% of all cases of CJD and is associated with greater clinicopathological diversity than sporadic disease. The most common disease-associated mutations are codon 102 (Pro→Leu) and codon 200 (Gln→Lys). Tables 2 & 3 list the clinical and pathological features of the conditions that result from the various known octarepeat inserts (Table 2) and point mutations (Table 3). Also listed are the country of origin of the known cases and a general description of the condition, such as ‘spastic paraparetic GSS’ or ‘familial CJD’. The condition is described as ‘sporadic’ when none of the cases with the particular genetic defect are known to have a relevant family history. Such cases could arise, for instance, if other relatives had been asymptomatic carriers or were unrecognised as having the condition; the genetic abnormality had occurred de novo in the affected individual; or if the mutation was an incidental finding, not related to the development of disease. To date, no instance of a case with a genetic defect shown to have arisen de novo has been identified. However, detecting such a case requires the exclusion of the genetic abnormality in both parents, information which is frequently difficult to obtain. Deletions have been identified in the PrP gene of asymptomatic controls as well as patients with CJD (and are therefore probably only an incidental finding). An octarepeat insert has been identified in only a single control patient, who had no relevant personal or family history to suggest CJD. The failure to identify insert or point mutations in a large number of further control subjects implies that a PrP gene mutation in a case of CJD is likely to be causative.

Gerstmann-Sträussler-Scheinker disease and FFI can be considered as variants of familial CJD as they are all transmissible neurodegenerative conditions associated with mutations of the PrP gene. Gerstmann-Sträussler-Scheinker disease has traditionally been described as an autosomal dominant disorder that presents with a progressive cerebellar ataxia and leads characteristically to multicentric amyloid plaques seen on
neuropathology. However, the illness phenotype in a single kindred of GSS can vary considerably, with some affected individuals having a disease characterised by a rapidly progressive myoclonic dementia indistinguishable from classical CJD. Gerstmann-Sträussler-Scheinker disease can more simply be used to refer to the forms of hereditary disease in which a characteristic pathological phenotype predominates, in particular the presence of numerous cerebellar multicentric PrP positive amyloid plaques (see histology p55).

The first report of FFI was made in 1986 and relates to an Italian kindred. The disease is characterised clinically by severe insomnia and autonomic failure, and pathologically by marked thalamic gliosis and little or no spongiform change. The genetics of FFI are particularly interesting: although a mutation at codon 178 is necessary for the development of disease, it is the presence of a polymorphism coding for methionine ‘downstream’ at codon 129 on the abnormal allele that appears to determine the FFI phenotype. The same 178 mutation but coding for valine at codon 129 of the affected allele is associated with a clinicopathological phenotype clearly distinct from FFI, thus illustrating the dramatic effect on disease that can result from a subtle change in prion protein structure.

Approximately 50% of hereditary cases lack a clear family history of a similar disorder. This is probably due largely to incomplete penetrance and the mis-diagnosis of other affected family members (e.g. with conditions such as ‘Huntington’s chorea’, ‘Alzheimer’s disease’ or ‘multiple sclerosis’) Genetic penetrance appears to vary somewhat between the various genetic forms, e.g. individuals carrying the codon 102 mutation almost invariably develop disease, unless they succumb to another condition, whereas carriers of the codon 200 mutation are relatively more likely to remain disease-free.

Approximately 2% of apparently sporadic cases of CJD, with no relevant family history, are found to carry a mutation. This percentage increases further if there is a family history of ‘dementia’ or other neurological or psychiatric disorder. Prion protein gene analysis should only be performed after a full explanation of the possible implications of the test and obtaining informed consent from the patient or, more usually, their relatives. Genetic material is commonly extracted from a small sample of EDTA-preserved blood (10-20ml) but can also be obtained from other tissues e.g. brain obtained at autopsy.

The human PrP gene plays a central role in conferring susceptibility to disease by means of a methionine/valine polymorphism at codon 129; iatrogenic cases of CJD have a high frequency of homozygosity (either methionine or valine), whilst in sporadic CJD 79% of cases are methionine homozygotes (compared with 37% of controls – see pie diagrams p55). Furthermore, it has been observed that the codon 129 polymorphism influences the age of onset and clinical presentation in some cases of hereditary CJD by interaction with pathogenic mutations in other parts of the PrP gene. It also influences the nature and distribution of neuropathological lesions in sporadic CJD, in particular PrP plaques are more common in valine homozygotes (VV) or heterozygotes (MV) than in methionine homozygotes (MM). Evidence also suggests that the EEG of cases with valine homozygosity is much less likely to show the classical periodic complexes compared with other genotypes. The duration of illness is slightly prolonged in those carrying at least one valine allele.
It is noteworthy that the association with codon 129 status and susceptibility to sporadic CJD has not been seen in Japan where the population has a different distribution of codon 129 genotype (MM = 92%, MV = 8% and VV=0%). However there appears to be no difference in the incidence between sporadic CJD in Japanese and Caucasians. Similarly the distribution of PrP genotypes in cases of kuru (MM = 30%, MV = 50% and VV=20%) does not differ significantly from a group of controls of the same ethnic background (MM = 30%, MV = 48% and VV=22%).

Table 2: Characteristics of genetic disease with insert mutations

<table>
<thead>
<tr>
<th>Insert size (one extra repeat)</th>
<th>Condition</th>
<th>Epidemiology</th>
<th>Clinical findings</th>
<th>Neuropathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 base pairs</td>
<td>Familial</td>
<td>French Single case.</td>
<td>Age 73, diziness, visual agnosia, ataxia, dementia, cortical blindness and akinetic mutism. Death occurred 4 months from onset.</td>
<td>Nil available</td>
</tr>
<tr>
<td>48 base pairs (two extra repeats)</td>
<td>Familial</td>
<td>North America. Single family.</td>
<td>Patient aged 58 with typical CJD-like phenotype including PCs. Patient’s mother had a slowly progressive dementia over many years and also carried the insert mutation.</td>
<td>Typical of CJD</td>
</tr>
<tr>
<td>72 base pairs (three extra repeats)</td>
<td>No case reported</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>96 base pairs (four extra repeats)</td>
<td>Sporadic</td>
<td>Single French, Japanese &amp; British cases.</td>
<td>Ranges from classical CJD to a slower dementia with myoclonus. Ages 56, 62, 82</td>
<td>One case had cerebellar plaques, another had classical pathological &amp; PrP staining of molecular layer of the cerebellum.</td>
</tr>
<tr>
<td>120 base pairs (Five extra repeats)</td>
<td>Familial</td>
<td>North America</td>
<td>Age onset between 31 and 45. Duration 5 to 15 years. Progressive dementia, extrapyramidal, pyramidal cerebellar signs, and myoclonus</td>
<td>Classical with no plaques. One case had minimal pathological abnormalities.</td>
</tr>
<tr>
<td>144 base pairs (Six extra repeats)</td>
<td>Familial</td>
<td>British and Japanese families.</td>
<td>Age of onset 22-53. Duration 2-18 years. Progressive dementia +/- cerebellar, extrapyramidal and pyramidal signs; myoclonus, chorea, seizures. A long psychiatric prodrome is sometimes noted. EEG may show PCs.</td>
<td>Very variable from classical changes +/- plaques to cases without any specific features to suggest CJD.</td>
</tr>
<tr>
<td>168 base pairs (Seven extra repeats)</td>
<td>Familial</td>
<td>Single Japanese case and North American family.</td>
<td>Age at onset 23-35. Duration 7 to &gt;13 yrs. Slowly progressive dementia, rigidity and cerebellar signs +/- myoclonus</td>
<td>Varying degree of spongiform change, neuronal loss, glosis +/- plaques.</td>
</tr>
<tr>
<td>216 base pairs (Nine extra repeats)</td>
<td>Familial</td>
<td>British and German</td>
<td>Reported cases aged 54 and 32 at onset. FH of dementia in both cases. Slowly progressive dementia in one case &gt;6 years. No PCs. One case had myoclonus.</td>
<td>Available in one case. Marked PrP positive amyloid plaques in cerebellum and basal ganglia. No spongiform change. A few neurofibrillary tangles.</td>
</tr>
</tbody>
</table>
### Table 3: Characteristics of genetic disease

<table>
<thead>
<tr>
<th>Codon/mutation</th>
<th>Condition</th>
<th>Epidemiology</th>
<th>Clinical findings</th>
<th>Neuropathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>102 (Pro→Leu)</td>
<td>Usually ataxic GSS</td>
<td>Most common GSS mutation. France, USA, Germany, Italy, UK, Israel, Austria and Japan.</td>
<td>Early cerebellar ataxia, myoclonus, dystroglycan, aphasia, pyramidal tract and lower motor neuron signs. Later: dementia.</td>
<td>P/P plaques †+++, ker+ multi-centic type; slight spongiform change; system atrophies of the spinocerebellar tracts, posterior columns, atrophy of brain stem, subcortical nuclei &amp; fibre systems.</td>
</tr>
<tr>
<td>105 (Pro→Leu)</td>
<td>Spastic paraparetic GSS</td>
<td>Japan</td>
<td>Spastic gait disturbance and progressive dementia without either cerebellar signs, myoclonus, or periodic complexes (PCs) on the EEG. Onset in the fourth or fifth decades and duration &gt;7 years.</td>
<td>Numerous amyloid plaques in the cerebral cortex, severe gliosis but no spongiform changes. Cerebellar histologically preserved except for scant P/P plaques.</td>
</tr>
<tr>
<td>117 (Ala→Val)</td>
<td>Dementing GSS</td>
<td>Alsatian family; American family of German descent; and a British family.</td>
<td>The clinical picture became more severe over the generations, and consisted of dementia, pyramidal and extrapyramidal signs, pseudobulbar features, and cerebellar signs in some family members.</td>
<td>P/P positive uni- &amp; multi-centic plaques, neuronal degeneration, moderate spongiform change.</td>
</tr>
<tr>
<td>145 (Tyr→Stop)</td>
<td>Familial CJD</td>
<td>Japan</td>
<td>Single case reported. Twenty-one year duration of a progressive dementia starting at age 38.</td>
<td>Many P/P-positive amyloid plaques and neurofibrillary tangles.</td>
</tr>
<tr>
<td>178 (Asp→Asn)</td>
<td>Fatal familial insomnia</td>
<td>Italian, Italian-American, German, French, Australian and British families.</td>
<td>Average age at onset is ~50. Onset is with progressive insomnia, autonomic failure, endocrine and memory disturbances. Later dementia, cerebellar ataxia &amp; myoclonus. Duration 7-36 months</td>
<td>Atrophy of the anterior ventral &amp; mediodorsal thalamic nuclei, olivary atrophy, varying degree of cerebral and cerebellar cortical gliosis. No plaques. Spongiform change rare.</td>
</tr>
<tr>
<td>178 (Asp→Asn)</td>
<td>Familial CJD</td>
<td>Finnish, French, Hungarian, Dutch, Canadian and British families</td>
<td>Average age at onset is ~47, and relatively long average duration of ~15 months. Patients usual present with memory impairment, behaviour and mood changes, and although myoclonus was usual PCs, were reported in only one of over 40 cases.</td>
<td>Considerable diversity, cerebral cortex and basal ganglia most severely involved, prominent spongiform change and gliosis. Less prominent neuronal loss, no plaques.</td>
</tr>
<tr>
<td>180 (Val→Ile)</td>
<td>‘Sporadic’ CJD</td>
<td>Japan</td>
<td>66 and 79 year old women. Older case had an extrapyramidal syndrome, dementia, myoclonus and akinetic mutism. Duration 1-2 years. No PCs seen in either case.</td>
<td>Cortical spongiform change. No plaques. Weak synaptic P/P staining.</td>
</tr>
<tr>
<td>180 (Val→Ile)</td>
<td>on one allele &amp; 232 (Met→Arg) on other allele</td>
<td>‘Sporadic’ CJD</td>
<td>85 year old man. No PCs.</td>
<td>‘Sporadic-type’</td>
</tr>
<tr>
<td>198 (Phe→Ser)</td>
<td>GSS with neurofibrillary tangles</td>
<td>Indiana kindred</td>
<td>Characteristically the disease leads to dementia, ataxia and an extrapyramidal syndrome with an average duration of illness around 6 years.</td>
<td>P/P positive amyloid plaques widespread, neurofibrillary tangles numerous in the cerebral cortex, hippocampus, and substantia innominata. Spongiform change is occasional and mild.</td>
</tr>
<tr>
<td>200 (Gln→Lys)</td>
<td>Familial CJD</td>
<td>Commonest mutation causing familial CJD. Slovakia, Chile, Japan, USA, Sephardic Jews, and families of Greek, British, French, Tunisian and Polish, origin.</td>
<td>Very similar to sporadic CJD, but with slightly earlier average age at onset (56 vs. 65yrs)</td>
<td>As in sporadic CJD with spongiform change, gliosis, neuronal loss, very rarely amyloid plaques</td>
</tr>
<tr>
<td>208 (Arg→Hist)</td>
<td>Sporadic CJD</td>
<td>USA</td>
<td>Single case, aged 62, progressive dementia, hallucinations, ataxia myoclonus and a characteristic EEG. Died 7 months after the onset of dementia.</td>
<td>Astrocytosis, extensive spongiform change without plaques or neurofibrillary tangles.</td>
</tr>
<tr>
<td>210 (Val→Ile)</td>
<td>Familial CJD</td>
<td>Italian, French, Japanese and Chinese families.</td>
<td>Phenotype similar to sporadic CJD Asymptomatic 81 &amp; 82 year old relatives carried mutation.</td>
<td>‘Sporadic-type’</td>
</tr>
<tr>
<td>217 (Gln→Arg)</td>
<td>GSS with neurofibrillary tangles</td>
<td>Swedish family.</td>
<td>Patients present with dementia and later developed gait ataxia and dysphagia.</td>
<td>Numerous neurofibrillary tangles in the neocortex. P/P positive plaques in cerebral and cerebellar cortex.</td>
</tr>
<tr>
<td>232 (Met→Arg)</td>
<td>‘Sporadic’ CJD</td>
<td>Japan</td>
<td>Patients presented with rapidly progressive dementia, myoclonus, became akinetic mute and had PCs. Illness duration 4 to 24 months.</td>
<td>Spongiform changes, neuronal loss and severe astrocytosis. No plaques</td>
</tr>
</tbody>
</table>
2.4 Iatrogenic Creutzfeldt-Jakob disease

In 1974 a CJD case suspected to have arisen from an environmental source was reported in the USA. The patient had received a corneal transplant when aged 55 because of a corneal dystrophy. Eighteen months later she developed lethargy and ataxia, followed by myoclonus, spasticity and akinetic mutism. She died eight months after the onset of her symptoms. The donor of the graft had died after a two month history that included ataxia, memory loss and myoclonus. Both the recipient and donor had typical neuropathological features of CJD at autopsy. Studies have subsequently demonstrated infectivity in corneas of animals inoculated with the CJD agent. Corneal donation from patients dying with dementia is now prohibited.

Further cases of iatrogenic CJD were reported in 1977. Two young patients from North America had undergone electrocorticography in 1974 for intractable epilepsy. During the procedure the same two previously used and sterilised silver electrodes had been inserted into their cerebral cortices for several hours. The patients developed progressive neurological disease, after a delay of 16 and 20 months, and subsequently died from histologically confirmed, and transmitted, CJD. The electrode probes used in both cases had previously been implanted for two days into the brain of a 70-year-old women with a four month history of mood disturbance, ataxia, mental deterioration and involuntary movements. She died three months later of histologically confirmed CJD. The electrodes had been cleaned with benzene, disinfected with 70% ethanol and sterilised in formaldehyde between each use. Twenty-eight months after their implantation in the original CJD case, the electrodes were inserted into the frontal lobes of a chimpanzee, who, after a period of 18 months, developed an encephalopathy histologically confirmed as CJD.

Although the above were the first iatrogenic cases reported, it seems likely that four other instances of contaminated neurosurgical instruments transmitting CJD had occurred in the UK and France in the 1950s and 60s. It is presumed that in these cases routine sterilisation procedures were insufficient to abolish infectivity and it is now strongly recommended that instruments used for neurosurgical and invasive ophthalmological procedures on patients with CJD (or at risk of developing CJD, such as individuals with a family history of CJD, human dural homograft recipients and human cadaveric-derived pituitary hormone recipients) should be destroyed.

In 1987 the first case of CJD linked with the use of a cadaveric-derived dural homograft during a neurosurgical procedure was reported. Subsequently a further 68 similar cases have been identified, including cases from the UK, Canada, the USA, Italy, Spain, Germany, Australia, New Zealand, and Japan. The majority of the implicated grafts were ‘Lyodura’, produced by a single manufacture between 1982 and 1986 (when Lyodura was often pooled), and most, if not all, of the patients received dura produced prior to the introduction of a decontamination procedure involving treatment with 1 N sodium hydroxide for 1 hour and rigorous donor selection. However, experimental evidence suggests that sodium hydroxide is not always a reliable disinfectant for TSE agents. Furthermore, even the most stringent donor screening may not detect pre-
symptomatic, but potentially infective, carriers of the TSE agent. The use of commercial cadaveric-derived dural homografts has therefore been largely discontinued in New Zealand, Australia, and the United Kingdom and the use of *dura mater* replaced with suitable synthetic or autologous alternatives.

Table 4: Summary of all proven or highly probable cases of iatrogenic Creutzfeldt-Jakob disease

<table>
<thead>
<tr>
<th>Mode of infection</th>
<th>Number of patients</th>
<th>Agent entry into brain</th>
<th>Mean incubation period, range</th>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotactic EEG</td>
<td>2</td>
<td>Intracerebral</td>
<td>18 mo (16,20)</td>
<td>Dem/cereb*</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>4</td>
<td>Intracerebral</td>
<td>20 mo (15-28)</td>
<td>Vis/dem/cereb</td>
</tr>
<tr>
<td>Corneal transplant</td>
<td>3</td>
<td>Optic nerve</td>
<td>17 mo (16, 18)*</td>
<td>Dem/cereb*</td>
</tr>
<tr>
<td><em>Dura mater</em> graft</td>
<td>69</td>
<td>Cerebral surface</td>
<td>5.5 yr (1.5-12)*</td>
<td>Cereb (vis/dem)*</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td>4</td>
<td>Haematogenous</td>
<td>13 yr* (12-16)</td>
<td>Cerebellar</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>94</td>
<td>Haematogenous</td>
<td>12 yr* (5-30)*</td>
<td>Cerebellar*</td>
</tr>
</tbody>
</table>

*Calculated from the midpoint of hormone therapy to the onset of CJD symptoms

*Dem, dementia; Cereb, cerebellar.

*Although clinical information not available for all cases

Cadaveric derived human growth hormone (hGH) has been used since 1958, mainly for the medical treatment of children with growth hormone deficiency. The hormone had been manufactured in batches, each produced from a large number of pituitary glands (up to 2000), and was administered by intramuscular or subcutaneous injection. In 1985, the first case of CJD in a patient who had received hGH occurred; and subsequently a further 93 cases have been reported, mainly in France, the UK and the USA; but cases have also been identified in Brazil and New Zealand in patients who received hGH manufactured in the USA, and in Australia in patients who had received locally produced hGH. Four cases of CJD were also recorded in Australian women treated with cadaveric derived pituitary gonadotropin. It is thought that the incriminating batches used to treat these hGH and gonadatropin related CJD cases had been contaminated by donors with CJD and that sterilisation methods employed were not sufficient to inactivate the infectious agent. It is of note that a sample of one such batch transmitted CJD to primates and that experiments have shown that the infectious agent can survive methods of «inactivation» used in commercial production. The use of cadaver-derived growth hormone has now been replaced by recombinant growth hormone, but due to the long incubation period of CJD, it is likely that some further cases will appear in years to come.

The clinical phenotype of iatrogenic CJD is largely dependant on the route of agent inoculation: patients inoculated peripherally (*e.g.* hGH recipients) usually develop of progressive cerebellar syndrome reminiscent of kuru, whilst those inoculated centrally (*e.g.* through the use of stereotactic EEG probes or neurosurgical instruments) typically develop a rapidly progressive dementia similar to sporadic CJD. The illness resulting from the use of contaminated dural homografts can resemble either of these phenotypes. Incubation period is also largely determined by the route of infection, with central inoculation leading to the onset of disease more rapidly than peripheral inoculation (Table 4).
The main neuropathological characteristics of sporadic CJD: spongiform change, neuronal loss and astrocytosis occur in iatrogenic disease, although the distribution of lesions varies from case to case. However, the neuropathology of hGH related cases is noteworthy as there is usually pronounced cerebellar atrophy associated with neuronal loss, widespread spongiform change and PrP amyloid plaque formation. Immunocytochemistry also shows a more widespread distribution of PrP in a diffuse pattern within the cerebellar granular layer in many of these cases. Furthermore, neuropathological changes in the spinal cord, particularly the presence of PrP amyloid plaques, are more frequent in hGH related iatrogenic cases than in sporadic CJD.

Possible occupational risks from TSEs

Although CJD has been documented in a neurosurgeon, two neuropathology technicians, an orthopaedic surgeon and a pathologist, it is reassuring to note that in none of these individuals was there a history of a definite infective event. The orthopaedic surgeon had however worked with human and ovine dura mater 20 years prior to his illness. Case-control studies do not suggest that individuals potentially exposed to the TSE agent in the health care setting are at an increased risk of developing CJD. However, the possibility that cases of CJD have rarely occurred in such circumstances cannot be confidently dismissed. It is noteworthy, and of some further reassurance, that no case of CJD has been documented in any person working in a research laboratory studying human or animal prion TSEs.

A statistically significant excess of cases of CJD in cattle farmers has been reported in the UK since 1990. Of concern, four of these six cases were known to have had BSE-affected animals in their herds. However, analysis of the clinical and pathological features of these cases shows that none had the nvCJD phenotype. This observation has been strengthened by recent molecular biological data that demonstrates that the PrP glycosylation pattern characteristic of both BSE and nvCJD was not present in any of these cases. Furthermore analysis of the incidence of CJD in dairy farmers from other European countries, in which BSE is rare or absent, reveals a similar excess of cases. This observation suggests that dairy farmers may be at increased risk of CJD for reasons other than exposure to the BSE agent. One possible explanation for the apparent excess of cases in dairy farmers, particularly in the UK, is that case ascertainment in this group has been better than in other groups because of concern of a possible link between the bovine and human diseases.

Possible risk of CJD from blood products

Though there is no proven or even probable instance of transmission of CJD by blood, blood components or plasma derivatives, increased awareness has recently raised concern about such a possibility. Numerous attempts have been made to detect the infective agent in the blood of experimentally infected animals. Although some results have been negative, several laboratories have reported the irregular presence of small amounts of infectivity in blood and particularly in buffy coat during both the preclinical incubation period and clinical phase of the disease. A recent experiment has demonstrated a low level of infectivity in the plasma and cryoprecipitate fraction from mice experimentally infected with CJD. A few attempts have also been made to detect the infectious agent in the blood of humans with CJD, four of which were successful (one from serum
and three from buffy coat). It is important to emphasize that the presence of the infectious agent in the blood of either experimentally infected animals or naturally infected humans has been determined by transmission of disease to laboratory rodents only by intracerebral inoculation, and that the single experiment using an intravenous route of inoculation failed to transmit disease (units of blood from three CJD patients transfused into three chimpanzees). Taken together, these data suggest that blood components from patients with CJD may contain low levels of infectivity. However, it is considered difficult to extrapolate from experimental data to the situation in a medical setting. Furthermore, epidemiological studies have yet to identify a single instance in which disease was actually transmitted by blood. It is reassuring that in a population highly exposed to specific blood products, as is the case of haemophiliacs, there are no reports of CJD to date.

The appearance of a nvCJD raises new concerns. Because of a possible oral route of infection and a novel strain of infectious agent, the distribution of tissue infectivity in nvCJD may differ from that of other forms of CJD. This is supported by evidence that suggests that at least one part of the lymphoreticular system, the palatine tonsil, may harbour the abnormal PrP isoform in nvCJD but not in sporadic disease. However, the weight of evidence suggests that the risk of parenteral transmission of any TSE by blood is remote, if not nil, and there is currently little evidence to suggest that nvCJD will necessarily be any different in this respect. Transmission studies using blood from cases of nvCJD are currently ongoing.

In view of the theoretical possibility that blood from patients incubating a TSE may harbour the infective TSE agent the World Health Organization recommends that the following groups should be excluded as blood donors:

1. recipients of extracts derived from human pituitary glands (growth hormone and gonadotropin).
2. those with a family history of CJD, GSS or FFI.
3. those who have received a human dura mater graft.

2.5 Kuru

Kuru is a TSE that was confined to highland New Guineans living in a number of adjacent valleys in the mountainous interior of Papua New Guinea. It was first described in 1955, although cases had probably been occurring for several decades before this. The term ‘kuru’ means ‘shivering or trembling’ in the language of the Fore, the cultural and linguistic group in which more than 80% of cases occurred. The point prevalence of the disease in this population was about 1%, which was also the yearly incidence. Women and children were much more commonly affected than adult males, leading to a male/female ratio of more than 3:1 in some villages, and suggesting (incorrectly) that sex-linked genetic factors were important in disease aetiology. Although the cause of kuru was initially unclear, intensive study concluded that the disease resulted from the practice of ritualistic cannibalism, a rite of mourning and respect for dead kinsmen, with resulting conjunctival, nasal, skin, mucosal and gastrointestinal contamination with highly infectious brain tissue. For cultural reasons men were only infrequently exposed to infectious tissues during these funeral rituals, thus
explaining the relative scarcity of the disease in adult males. The recognition that other tribes remained free of kuru despite cannibalistic practices similar to the Fore, led to the suggestion that kuru may have initially arisen following the ritualistic cannibalism of a sporadic or familial CJD victim in the Fore region, and it is of note that CJD has been reported in Papua New Guinea. Kuru has gradually been disappearing since cannibalistic rituals ceased toward the end of the 1950’s, and with the passage of time progressively older age groups have become free of kuru. Between four to eight cases still occur annually, thus demonstrating that the incubation period can range from $\leq 4.5$ years (the age of the youngest victim) to $> 35$ years. It is noteworthy that no child born after the cessation of cannibalism, from a mother affected with kuru, is known to have developed the disease, suggesting that direct maternal transmission rarely, if ever, occurs.

In 1959 an American veterinary pathologist, Dr William Hadlow, drew attention to the similarity between the neuropathology of kuru and scrapie. It was known at this time that scrapie was transmissible and subsequently Drs Clarence Gibbs Jr. and Carleton Gajdusek demonstrated transmission of kuru to a chimpanzee in 1965.

The clinical course of kuru is remarkably uniform, with cerebellar symptoms progressing to total incapacitation and death, usually within 3 to 9 months. The disease has been divided into three clinical phases. The first, or ambulant, stage starts with unsteadiness of stance or gait and often of the hands. This is preceded in some cases by symptoms of headache and limb pains. Dysarthria starts early, and speech progressively deteriorates as the disease advances. Convergent strabismus often appears early too, and persists. Shivering tremors are also noted during this phase. In the latter part of the first stage the patient usually takes a stick for support when walking. The second, or sedentary stage, is reached when the sufferer can no longer walk without complete support. Tremors and ataxia become more severe, rigidity of the limbs often develops, associated with widespread involuntary movements, particularly myoclonus $\pm$ choreoathetosis, and a startle reaction may be seen. Emotional lability, leading to outbursts of pathological laughter, frequently occurs and although most patients show a resignation to, and a light-hearted attitude toward their illness, some patients become depressed. Mental slowing is apparent, but severe dementia is conspicuously absent. The third, or terminal, stage is reached when the patient is unable to sit up without support; ataxia, tremor, and dysarthria become progressively more severe and incapacitating. Pyramidal, extrapyramidal and frontal release signs may be seen at this stage and in time plasticity, inanition, and signs of bulbar involvement develop. The patient becomes mute and unresponsive, deep decubitus ulceration and hypostatic pneumonia often occur, and the patient finally succumbs, usually, but not always, in a state of emaciation.

In keeping with the prominent cerebellar clinical features of kuru, neuropathology demonstrates macroscopic atrophy of the cerebellar vermis in most cases. Microscopically changes are more widespread in the CNS and are characterised by marked astrocytosis throughout the brain; mild spongiform change of the grey matter; diffuse neuronal degeneration that is most severe in the cerebellum and its afferent and efferent connections; and minimal demyelination. Typical intracytoplasmic vacuolation is usually observed in the large neurons of the striatum. The most striking histological abnormality however is the presence of PrP-positive amyloid plaques, most conspicuous in the cerebellum, and occurring in about 80% of cases.
2.6 New variant Creutzfeldt-Jakob disease

Background to the identification of new variant CJD

In 1990 surveillance of CJD was reinstituted in the UK because of concern that the agent responsible for the epidemic of BSE in British cattle might transmit to humans. The rare occurrence of two teenage patients with CJD in the second half of 1995 was followed over the next few months by the identification of eight further young cases (see line diagram p57). All ten patients shared a distinct and previously unseen clinicopathological phenotype. A review of the literature and consultation with experts in CJD pathology and epidemiology from Europe and the rest of the World failed to reveal any further cases. It was therefore concluded, in light of the temporo-spatial association with the occurrence of BSE, that this apparently new variant of CJD was most likely causally linked with exposure to the BSE agent. A further twelve cases have been diagnosed between March 1996 and July 1997, eleven in the UK and a single case in France. During this period further scientific evidence in support of a link with the BSE agent has become available: the identification of pathological features similar to nvCJD in macaque monkeys following intracerebral inoculation with BSE, and the demonstration that nvCJD is associated with a pattern of PrP glycosylation that distinguishes it from other forms of CJD and which resembles that seen in BSE transmitted to a number of other species. Furthermore, no additional cases of nvCJD were identified in other countries over this time period or retrospectively. However, proof of an association between nvCJD and BSE has not been established, and is likely to depend on the results of experiments to determine if the diseases share the same ‘strain type’ and continued epidemiological vigilance in the UK, Europe, and the rest of the world.

Epidemiology of nvCJD

Twelve of the 22 cases are female and ten male. Their age at onset of symptoms ranges from 16 to 48 years (mean 27 years – see graph p57). All the patients lived in the UK, apart from the single French case (who had never travelled to Britain). Some of the patients had been longstanding residents in Wales, Scotland or Northern Ireland, and spatial analysis fails to shows clustering of cases to any particular part of the UK. Information on potential risk factors has been published for ten cases. Four had no history of any operation, four had undergone minor surgery (two tonsillectomy in 1975 and 1991, one a foot operation in 1984, one a uterine dilatation and curettage in 1989), one had surgery for congenital glaucoma twice around 1970, and another had had a caesarean section (1974), colonoscopy (1992, 1994), and laparoscopy (1986). One patient had worked as a butcher from 1985 to 1987 and another had visited an abattoir for two days in 1987, but was not know to have had contact with animals or animal products. None had ever worked on farms with livestock, although one patient had spent one week’s holiday a year on a dairy farm between 1976 and 1986. There was no record of BSE in this herd. Dietary histories are available for nine cases, all were reported to have eaten beef or beef products since 1986, but none were reported to have eaten brain. One of the cases had been a strict vegetarian since 1991.
New Variant CJD - Clinical features

There follows a detailed description of the features of the first 14 histologically confirmed cases of nvCJD identified in the UK.

Early features

The two striking early features of nvCJD are sensory disturbance and behavioural change, both of which are unusual in sporadic CJD. Four of the fourteen cases initially complained of sensory symptoms. One case developed foot pain severe enough to warrant referral to a rheumatologist; another presented with foot pain followed within a fortnight by hand and face dysesthesia; two further patients initially complained of sensory changes (dysesthesia +/- paraesthesia) in the legs. Four of the other ten patients, although not initially complaining of sensory symptoms, developed these during an early stage of their illness - two had persistently cold feet, one hemi-dysesthesia and another pain below both knees. The sensory symptoms were continuous and persistent throughout most of the illness in all these cases. Another patient, without overt sensory symptoms, was noted to have hyperesthesia. Five patients underwent electromyography and/or nerve conduction studies. These were normal in four cases and abnormal in one, which showed minor changes of uncertain significance.

All but one patient saw a psychiatrist during their illness, six as the initial referral. Most cases were depressed, apathetic and withdrawn early in the clinical course, often accompanied by weight loss and mild insomnia. Fleeting delusions were common, e.g. microscopic people living in the body, a new-born baby was dead, and two patients developed a schizophrenia-like psychosis. One of these, following treatment with neuroleptic medication, made an almost complete recovery for about a month before becoming withdrawn, developing sensory symptoms and a progressive dementia.

Clinical course

Although a minority of cases suffered from forgetfulness or mild unsteadiness of gait from an early stage, frank neurological signs were not apparent for many months (median 6.25, range 4 to 24.5 months) after disease onset (see Table 5). During this period the most prominent clinical features were psychiatric disturbance and/or sensory symptoms. After the onset of frank neurological dysfunction, mainly in the form of ataxia, the illness rapidly progressed with global cognitive impairment, involuntary movements, incontinence of urine and progressive immobility leading to increasing dependency, unresponsiveness and mutism. Pre-terminally the patients were usually akinetic mute and at least three developed cortical blindness. Dysphagia usually developed, predisposing to aspiration and pneumonia, the most frequent terminal event. The mean delay from developing unsteadiness to becoming bedbound was 6 months (range 2.5 to 12.5 months), and from bedbound to death 1.5 months (range 1 week to 6 months) although two patients remain alive 6.5 and 18 months after
becoming bedbound. Most patients had minor fluctuations in their clinical course with cognitive or neurological dysfunction varying over a few hours or days, often related to a change of medication or infective episode.

Three cases were noted to have transient seizure-like episodes during their clinical course (3, 7.5 and 10.5 months from onset). All three patients were in hospital, cognitively impaired and were taking chlorpromazine at the time of the seizures. The episodes took the form of ‘absence attacks’ in one case (who had been commenced on sodium valproate a month previously in view of cognitive impairment, an abnormal EEG and a past history of primary generalised epilepsy); hypertonia and unresponsiveness in another patient; and loss of consciousness, twitching and cyanosis in a third.

The terminal stages of the 14 cases of nvCJD, after the development of progressive cognitive impairment and involuntary movements, were similar to the late stages of classical CJD. The median total clinical duration of illness was 14 months (range 9.5->35 months – see survival curve p56)

**Clinical signs**

The neurological signs were cerebellar: limb or gait ataxia, in nine cases. These occurred in isolation in three, or in combination with either involuntary movements, pyramidal signs, primitive reflexes, or sensory signs, in the others. The remaining cases first developed either pyramidal signs (+/- dysphasia), dysarthria or involuntary movements, although unsteadiness of gait was noted within weeks even in these cases. Those with the longest delay to the development of neurological signs had a long prodrome with mild personality change or forgetfulness followed by sensory disturbance. The majority of cases developed primitive reflexes, cerebellar and pyramidal signs. All patients developed persistent involuntary movements, initially chorea (7 cases) or myoclonus (7 cases), and five of the seven patients who initially had chorea were later noted to also have myoclonus. Although seven cases were not formally noted to have chorea four of these were described as ‘fidgety’. Seven cases were noted to have upgaze paresis, an uncommon feature of classical CJD, after the development of other focal neurological signs.

Formal neuropsychometry was performed in six cases after their routine clinical examination had suggested cognitive impairment. All assessments revealed evidence of global cognitive dysfunction.
Table 5: Clinical features and months to clinical milestones of the first 14 cases of nvCJD in the UK

<table>
<thead>
<tr>
<th>Presenting features</th>
<th>Sensory symptoms</th>
<th>Forgetful</th>
<th>Unsteady</th>
<th>Neurological signs</th>
<th>Involuntary movements†</th>
<th>Mute</th>
<th>Bedbound</th>
<th>Abnormal EEG</th>
<th>Normal EEG</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Withdrawn</td>
<td>No</td>
<td>5</td>
<td>6</td>
<td>6.5</td>
<td>8³</td>
<td>10</td>
<td>11</td>
<td>6</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Dysaesthesia</td>
<td>Yes</td>
<td>5.5</td>
<td>4.5</td>
<td>5.5</td>
<td>5.5</td>
<td>13</td>
<td>17</td>
<td>-</td>
<td>5.5 &amp; 8.5</td>
<td>&gt;35</td>
</tr>
<tr>
<td>Foot pain</td>
<td>Yes</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>8.5³</td>
<td>9.5</td>
<td>8.5</td>
<td>6</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Yes</td>
<td>6.5</td>
<td>6.5</td>
<td>8.5</td>
<td>9⁶</td>
<td>15</td>
<td>16</td>
<td>9.5</td>
<td>8.5</td>
<td>18</td>
</tr>
<tr>
<td>Forgetful</td>
<td>No</td>
<td>0</td>
<td>2.5</td>
<td>4.5</td>
<td>7³</td>
<td>6</td>
<td>5</td>
<td>1.5</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Aggression &amp; apathy</td>
<td>No</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td>9⁴</td>
<td>10.5</td>
<td>10</td>
<td>10</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Panaesthesia</td>
<td>Yes</td>
<td>9</td>
<td>10</td>
<td>3.5</td>
<td>11⁵</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>11.5 &amp; 14.5</td>
<td>22.5</td>
</tr>
<tr>
<td>Dysaesthesia</td>
<td>Yes</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>16.5⁶</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td></td>
<td>17.5</td>
</tr>
<tr>
<td>Personality change</td>
<td>Yes</td>
<td>1</td>
<td>4.5</td>
<td>5.5</td>
<td>5.5</td>
<td>8</td>
<td>9</td>
<td>5</td>
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<td>9.5</td>
</tr>
<tr>
<td>Depression</td>
<td>No</td>
<td>3.5</td>
<td>3.5</td>
<td>4</td>
<td>5⁵</td>
<td>7.5</td>
<td>11</td>
<td>12.5</td>
<td>4.5 &amp; 6.5</td>
<td>13</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>Yes</td>
<td>0</td>
<td>23.5</td>
<td>24.5</td>
<td>23⁶</td>
<td>28.5</td>
<td>28.5</td>
<td>25</td>
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<td>28.5</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>Yes</td>
<td>10.5</td>
<td>12</td>
<td>14</td>
<td>14⁷</td>
<td>17</td>
<td>16.5</td>
<td>14</td>
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<td>17</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>No</td>
<td>5.5</td>
<td>9.5</td>
<td>11</td>
<td>13.5⁸</td>
<td>13.5</td>
<td>13</td>
<td>12</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Agitation, weight loss &amp; insomnia</td>
<td>No</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>4⁹</td>
<td>7.5</td>
<td>7</td>
<td>6.5</td>
<td></td>
<td>&gt;15.5</td>
</tr>
</tbody>
</table>

| Median | 4.5 | 5.5 | 6.25 | 8.75 | 11.75 | 12 | 9.75 | 14 |

† First involuntary movements either chorea (C) or myoclonus (M). ‡ alive.

Table 6: Psychiatric features of the first 14 cases of nvCJD in the UK

<table>
<thead>
<tr>
<th>Initial psychiatric diagnosis</th>
<th>Emotional lability</th>
<th>Anxiety</th>
<th>Apathic/withdrawn</th>
<th>Aggression</th>
<th>Depression</th>
<th>Delusions</th>
<th>Auditory hallucinations</th>
<th>Visual hallucinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive illness</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nil</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Organic rather than functional*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Paranoid illness with possible first rank symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Thought that amnesia may well be hysterical rather than organic*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Severe agitated depression</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuro-degenerative disorder*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Depressive illness with significant anxiety symptoms*</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Both organic and functional symptoms - thought to be developing a psychosis*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Major depressive illness</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>No evidence of depression or any other psychiatric disorder</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Schizophreniform psychosis*</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anxiety, hyperventilation - possible underlying depression</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Severe depression without psychotic features. Marked agitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Total | 9 | 12 | 13 | 11 | 9 | 12 | 5 | 8 |

* Possibility of an organic cause raised.
Table 7: Neurological signs noted during the clinical of the first 14 cases of nvCJD in the UK

<table>
<thead>
<tr>
<th>Myoclonus</th>
<th>Chorea</th>
<th>Pyramidal signs</th>
<th>Cerebellar signs</th>
<th>Rigidity</th>
<th>Primitive reflexes</th>
<th>Upgaze paresis</th>
<th>Akinetic mutism</th>
<th>Cortical blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>+</td>
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</tr>
<tr>
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<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Total 12 7 13 11 12 11 7 11 3

New variant CJD - Investigations

The laboratory investigation of CJD, including the new variant, is discussed in Section 4. Below is a summary of the neurophysiological, biochemical, neuroradiological and other investigations performed on the cases described above.

EEG

Each case underwent electroencephalography on multiple occasions (two to five times). The characteristic EEG pattern of classical CJD was not seen, even though four patients had recordings in the final month of illness. Initial tracings were normal in four cases and in three of these the subsequent recording was also unremarkable (See Table). These three patients had a normal EEG even though they had documented cognitive impairment, cerebellar signs and involuntary movements prior to the recording. Abnormal recordings were noted in twelve patients and all showed pathological slow wave activity (see nvCJD EEG p58). This tended to deteriorate as the illness progressed.

CSF analysis

All patients had CSF analysis. A leucocyte response was not seen in any case. Four patients had slightly raised CSF protein (0.5-0.9g/l) but in nine the level was normal. The results of CSF electrophoresis are available for
11 cases and in none were oligoclonal bands detected. Analysis of 14-3-3 protein - see section 4.5

**Neuroimaging**

Ten cases underwent brain computed tomography (CT), eight patients were reported to have normal scans and two non-specific abnormalities: dural calcification in one case and a slightly enlarged lateral ventricle and cerebellar interhemispheric cistern in another. Cranial magnetic resonance imaging (MRI) showed no significant abnormalities in eight cases, three of whom had normal repeat studies. Four patients were reported to have mild generalised atrophy; one case as having slightly prominent ventricles with one or two small areas of high signal in the left frontal white matter; and two others had posterior thalamic high signal on T2-weighted (and one case also proton density-weighted – see p58) images. A retrospective analysis of MRI from these cases is ongoing, and provisional information (without comparison with controls) suggests that most, if not all, cases show abnormal high signal from the posterior thalamic on T2-weighted or proton density weighted images.

Abnormal areas of cerebral perfusion were detected in both cases that had single-photon emission computed tomography (SPECT) studies. A single patient underwent positron emission tomography (PET) which was normal.

**Genetic analysis**

Sequencing of the open reading frame of the PrP gene identified no mutations in the cases screened so far. All 21 cases tested to date have the methionine-methionine genotype (MM) at codon 129 which differs significantly from Caucasian controls (37%, p<0.0001) and sporadic CJD (79%, p=0.02). It is interesting to postulate why this might be. It is thought that the ability to transmit a prion disease between species is determined by the homology of the central residues of their prion protein structures (which includes residue 129). Recent evidence suggests that, unlike humans, bovines only code for methionine at the equivalent site to the human codon 129 polymorphism. Therefore, if nvCJD is due to infection with the BSE agent, and bovine PrP is usually, if not always, homozygous for methionine at codon 129, the MM genotype in humans may confer an increased susceptibility to bovine prions.

**Differential diagnosis**

A number of cases of suspect nvCJD have subsequently been shown to have an alternative diagnosis. The commonest condition that may closely resemble nvCJD appears to be sporadic CJD in young persons. Even in retrospect the clinical features of one case of sporadic CJD in a 46-year-old man were not readily distinguishable from those of nvCJD and illustrate the importance of neuropathological examination. Furthermore genetic/familial CJD tends to present at a younger age than typical cases of sporadic CJD, may
present with a prolonged psychiatric prodrome and run a relatively protracted clinical course. Approximately one-third to one-half of genetic cases half no clear family history of CJD emphasising the importance of analysis of the PrP gene in all suspect cases of nvCJD. Other conditions that were referred to the UK National CJD Surveillance Unit initially as suspect nvCJD are listed below.

- Transient encephalopathy of unknown cause with complete recovery (three cases)
- Encephalitis with inflammatory CSF but no definite diagnosis (three cases)
- Hashimoto encephalitis (one case)
- Multiple system atrophy (one case)
- ‘Vascular encephalopathy’ (one case)

Pathology

Neuropathological examination in nvCJD shows spongiform change and PrP plaques confirming the diagnosis of CJD. Spongiform change, neuronal loss, and astrocytosis is most evident in the basal ganglia and thalamus, and is present focally in the cerebrum and cerebellum, most evidently in areas with confluent spongiform change.

The most striking and consistent neuropathological abnormality is PrP plaques. These are were extensively distributed throughout the cerebrum and cerebellum, with smaller numbers in the basal ganglia, thalamus, and hypothalamus. Many of these plaques resembled kuru-type plaques with a dense eosinophilic centre and pale periphery and, unusually for this type of lesion, were surrounded by a zone of spongiform change (see figures p59). Other extremely rare in other forms of CJD, similar lesions have been described in scrapie, where they have been referred to as "florid" plaques.’ Immunocytochemistry for PrP shows strong staining of these plaque-like lesions, but also shows many other smaller plaques, which appeared both as single and multicentric deposits. PrP deposition was also seen in a pericellular distribution in the cerebral cortex and in the molecular layer of the cerebellum, the pattern of which suggests deposition around small neurones (figure 3). Plaque and pericellular PrP deposits occur throughout the cerebrum and cerebellum, and are clearly visible in the absence of confluent spongiform change in the surrounding neuropil. In the basal ganglia and thalamus, a perivacuolar pattern of PrP staining is also seen, with linear tract-like deposits within the grey matter. PrP plaques are also noted in these regions although are fewer than in the cerebrum and cerebellum (figure 4).

Predicting the future number of cases of nvCJD

Statistical modelling of the size of a potential nvCJD epidemic has been performed. This was based on the dates of onset of the first 14 cases identified in the UK and the assumption of a causal link between nvCJD and BSE. The estimate for the total number of infections occurring in the UK ranged from less than 100 to greater than 80,000 cases. This large variability reflects the difficulty of modelling based on a relatively small number of cases and uncertainties relating to incubation period. It was concluded that even though only 14
cases had been identified at that time it would be premature to assume that any subsequent epidemic would be small. Furthermore, it was noted that although the number of cases over the next few years might provide a better indication of how large any potential epidemic might eventually be, much uncertainty could remain even after four years.

Section 3: Animal transmissible spongiform encephalopathies

3.1 Scrapie

Scrapie is the prototype transmissible spongiform encephalopathy. It is an insidious degenerative disease affecting the CNS of sheep and goats. Natural scrapie has also been reported in moufflon, a primitive relative of sheep, but only in Great Britain. The term ‘scrapie’ describes the tendency for affected sheep to scrape themselves against trees or bushes (see photograph p60) and the disease was known as la tremblante (trembling disease) in France, as Gnubberkrankheit (itching disease) or Traberkrankheit (trotting disease) in Germany, ridia in Iceland, súrlókór (brushing disease) in Hungary and by multiple other names in Britain. As a clinical entity it was recognised in sheep in England as early as 1730 and has subsequently been reported in many countries including Austria, Belarus, Belgium, Colombia, the Czech Republic, Slovakia, France, Germany, Ghana, Ireland, the Isle of Man, Israel, Japan, the Netherlands, Northern Ireland, Somalia, Spain, Switzerland, the United Arab Emirates and the United States of America. Although scrapie occurred due to importation of sheep to Australia and New Zealand, the disease was successfully eradicated through stringent and immediate efforts to depopulate the imported sheep as well as their animal contacts.

Scrapie was first experimentally transmitted by inoculation of a ewe in the 1930s. Demonstration of transmission of mice in the early 1960s permitted the disease to be intensively studied but in spite of this the exact mechanism(s) of scrapie spread in nature remains obscure. It is commonly accepted that the disease is infectious and contagious but that genetic factors are also important. Infection is most commonly transmitted from ewe to lamb, both up to the time of parturition and afterwards when the ewe and lamb run together. There is also horizontal spread of infection between unrelated adults and this may account for some of the scrapie cases in older sheep. Placental tissue is known to be infectious and this is commonly postulated as a possible source of transmission both to the lamb and unrelated animals sharing the same pasture. The exact routes of infection are unresolved but possibilities include transplacental, oral, nasal, optic or cutaneous. Complex genetic factors involving the \( PrP \) gene, and potentially other genes, are known to affect incubation period and thus the apparent susceptibility of sheep to scrapie, the possibility of genetically engineering animals resistant to disease has been raised.

In natural scrapie the onset of disease is often insidious. Early signs of disease are apprehension, restlessness, hyperexcitability and aggressiveness, and some animals even manifest apparent dementia. Fine tremors of the head and neck are observed, and as the disease progresses these become more generalised, involving the whole
body and producing a shivering effect. Fasciculations of superficial skeletal muscles may occur, and signs of cutaneous irritation, self-induced by rubbing and scratching, constitute one of the most characteristic clinical features, though do not occur in all cases e.g. Icelandic scrapie (rida). As the disease evolves the gait becomes ataxic with severely affected animals unable to stand or walk without falling. In the advanced stages of the disease, animals become stuporous and manifest visual impairment, excessive salivation and wasting. The duration of natural clinical disease is usually less than four months.

In keeping with other TSEs the neuropathological triad of spongiform change, neuronal loss and astroglial proliferation occur in scrapie. Vacuolation of the neuronal cytoplasm is a marked and pathognomonic feature, being particularly evident in the brainstem and the ventral and lateral horns of the spinal cord. Cerebral amyloidosis is seen in just over half of natural cases of scrapie. Another characteristic feature of scrapie and other TSEs is the presence of rod-shaped structures seen on electron-microscopy and known as scrapie-associated fibrils (SAFs - see electron micrograph p60). The SAFs are fibrillar forms of amyloid – the same amyloid which is contained in PrP plaques. Although there is no currently available clinical diagnostic test for the disease, a recent study has identified the presence of abnormal prion protein in tonsillar tissue from sheep presumed to be infected with scrapie, long before the occurrence of clinical signs. When validated this would raise the possibility of tonsillar biopsy as a clinical diagnostic, and possibly presymptomatic, test.

3.2 Bovine spongiform encephalopathy

Bovine spongiform encephalopathy was first reported in British cattle in November 1986. Most cases were infected as calves; the modal age of disease occurrence is five years (range 29 months to 18 years) and the average incubation period 60 months. Current evidence suggests that the disease originated from the use of feed supplements containing meat and bone meal (MBM) contaminated by a TSE agent. The stringency of the rendering procedure, by which animal materials were processed to produce MBM, changed during the 1970s and early 1980s and decreased use of hydrocarbon solvents and the adoption of lower temperatures may have resulted in increased survival of the infective agent. These changes were adopted in response to a fall in the value of tallow (the fat-rich fraction of the process whose yield is increased by using solvent), a rise in the cost of energy and a need to replace old plant with safer systems not using potentially explosive and carcinogenic solvents. Epidemiological evidence suggests that sheep scrapie, endemic in Great Britain, was the likely source of the infective agent that initiated the BSE epidemic. However, experiments indicate that BSE is associated with a single major strain of infective agent and although over 20 different scrapie strains are recognised, to date, none appear to match that seen in BSE. This has led to the further hypothesis that BSE may have been an uncommon sporadic and/or hereditary disease of cattle that was dramatically amplified as a result of infected bovine material entering the modified rendering process. Whatever the origin of the agent responsible for BSE it is likely that the recycling of infected cattle through the rendering process in the 1980s was largely responsible for fuelling the large and explosive epidemic. It is of note that BSE has been experimentally transmitted via the oral route to cattle by as little as 1g of BSE-infected bovine brain.
The British Government made BSE notifiable in June 1988 and shortly afterwards a statutory ban on the feeding of ruminant-derived protein to ruminants was introduced. In November 1989 a ban was introduced on the use of certain specified ‘high risk’ bovine offals (SBO) for human consumption (brain, spinal cord, tonsils, thymus, spleen and intestines from animals >6 months old). The selection of which offals should be included in the SBO ban was based on the evidence of infectivity of tissues from scrapie-infected sheep. BSE infectivity has now been demonstrated in the brain, spinal cord and retina of naturally affected cattle and the distal ileum of those infected experimentally. However, a wide range of tissues from clinically affected cases of BSE have shown no detectable infectivity using the mouse bioassay (which has potential limitations, in particular its sensitivity due to the ‘species barrier’ - see later), and these include muscle, milk and a range of lymphoreticular tissues. In September 1990 the use of SBO was further restricted, being prohibited for use in feed for all animals and birds. At the end of 1992 BSE reached its peak incidence in the UK but thereafter declined rapidly, almost certainly in response to the statutory measures. However, new cases of BSE were being observed in cattle that were born after the implementation of the feed ban. It has been suggested that most of these cases occurred because of the continued use of feed rations produced before the ban; cross-contamination of cattle feed by feed containing MBM intended only for pigs or poultry; and an incomplete compliance with the SBO ban. Further measures were instituted to address these particular issues and following the announcement of a possible link between BSE and a nvCJD in March 1996, cattle >30 months old and heads from all bovines over 6 months old were excluded from all food or feed chains.

Although the pattern of the epidemic remains consistent with the hypothesis that the vast majority of cases arose through infection with contaminated feed, it remains possible that other routes of transmission may occur infrequently, in particular maternal transmission from dam to calf. A study to assess maternal transmission suggests that this may occur at a low rate (estimated to be responsible for only about 1% of cattle expressing disease) but also tentatively suggests that genetic factors may influence susceptibility.

The appearance of a number of novel TSEs, causally linked with BSE, in domestic and captive animals raises the question of whether BSE occurs, or will occur, in further animal species. Particular concern has been expressed regarding the possibility of BSE in sheep, pigs and poultry. BSE has been experimentally transmitted to sheep by feeding as little as 0.5g of infected bovine brain and it is known that some sheep were fed MBM until this practice was banned in 1988. In this regard the lack of evidence of a BSE-related epidemic of sheep scrapie is reassuring, but concern was sufficient to led to the ban of ovine brain from sheep over 6 months of age for human consumption in the UK and France as part of a risk reduction strategy.

Pigs, but not chickens, have been shown to be susceptible to BSE by parenteral inoculation of infected bovine brain homogenate. However, challenging pigs with a very large oral dose of BSE-infected brain failed to produce disease, at least up to 6.5 years post-challenge.

By the end of 1996, over 168 000 confirmed cases of BSE had been reported in UK (see bar graph p61). Relatively small numbers of cases have also been reported in native-born cattle in Switzerland, the Republic of
Ireland, France, Portugal and the Netherlands. Small number of cases have also been reported in Germany, Italy, Oman, Canada, Denmark, and the Falkland Islands, but solely in animals imported from the UK (source: cases reported to the Office International des Epizooties by member countries).

The duration of the clinical course of BSE is typically one or two months, but ranges from seven days to 14 months. The most commonly observed signs are apprehension, hyperaesthesia and ataxia, but affected animals may also show a decreased milk yield and loss of condition. There is no effective treatment and the disease always progresses to death in the affected animal. A number of other bovine conditions can mimic the illness phenotype of BSE e.g. magnesium deficiency (‘staggers’), and currently no practical and reliable laboratory diagnostic disease marker has been reported, emphasising the importance of pathological diagnosis. Research is in progress to identify disease markers in CSF and urine.

Pathological changes (see illustration p61) are similar to scrapie in many respects with vacuolar lesions largely confined to the brainstem and accompanied by neuronal degeneration and an astrocytic reaction. Sparse cerebral amyloid plaques are seen in a small proportion of cases. In contrast to scrapie greater diagnostic importance is attributed to the neuropil vacuolation than neuronal vacuolation.

3.3 Chronic wasting disease of mule and elk deer

Chronic wasting disease (CWD) is a TSE of deer and elk that has only occurred in limited areas in the western United States. It was first recognised as a clinical syndrome in 1967 and is typified by chronic weight loss leading to death. There is no known or suspected relationship between CWD and any other animal TSE.

CWD has occurred in four captive wildlife research facilities in northern Colorado and one in south-eastern Wyoming. Although cases of CWD have been seen in two zoological parks, the affected animals all originated from the above-mentioned research facilities. Soon after recognition of the disease, animal movement from these facilities was stopped. CWD has also been confirmed in fewer than 70 free-ranging deer and elk in a limited number of counties in northern Colorado and south-eastern Wyoming. Animals born in captivity and those born in the wild have been affected with the disease.

Species that have been affected with CWD are Rocky Mountain elk, mule deer, white tailed deer, and black-tailed deer. Other ruminant species, including wildlife and domestic cattle, sheep and goats, have been housed in wildlife facilities in direct and indirect contact with CWD-affected deer and elk. No cases of CWD in these ruminant species have been detected. The origin and mode of transmission of disease is unknown. Based on the epidemiology of CWD, transmission is thought to be lateral, and possibly maternal. Transmission via feed is not believed to occur as affected animals have been fed a variety of foodstuffs with no common animal link being established. It is of note that painstaking attempts to eradicate CWD from captive facilities, including thorough decontamination and a 12-month period free of elk or deer, failed to prevent disease recurrence.
3.4 Transmissible mink encephalopathy.

Transmissible mink encephalopathy (TME) was first described in 1967 but had occurred on mink farms in Minnesota and Wisconsin as early as 1947. The disease occurs as outbreaks and in farmed mink only and has been recognised in Idaho, Russia, Finland, Canada and Germany. Although a rare condition, mortality is high, with nearly all adult mink on an affected ranch succumbing to the disease during an outbreak. Evidence points to infected feed as the cause of TME and it has been suggested that scrapie is the likely contaminant. However, experimental transmission of scrapie to mink via the oral route has not been successful to date, although this may be because TME is caused by a different scrapie strain that those used experimentally. The possibility of a bovine origin of TME has also been raised. Products from fallen or sick cattle (‘downer cows’) were said to have been fed to a colony of affected mink in the USA and that these animals had been fed a diet free of any ovine material. However, surveillance of cattle in the USA has not revealed a single case of BSE, thus arguing against a bovine origin of TME infection. Furthermore, although BSE has been experimentally transmitted to mink the incubation period, clinical signs and neuropathology showed significant differences from natural TME. No convincing evidence for maternal or horizontal transmission of natural disease exists.

3.5 Feline spongiform encephalopathy

In 1990 the first case of feline spongiform encephalopathy (FSE) in a domestic cat was reported. The 6-year-old animal had been referred to the Bristol Veterinary School, in England, with a progressive neurological condition. It failed to respond to treatment and subsequent neuropathological examination revealed a scrapie-like spongiform encephalopathy. Although no previous naturally occurring TSE had been documented in a feline, CJD had been experimentally transmitted to a cat in 1972 and several times thereafter. Since 1990 cats with FSE have been reported from most regions of the UK (total 77 up to June 1997) and a single case each has been documented in indigenous cats from Norway and Liechtenstein. FSE has also been documented in captive large cats: three puma, four cheetahs, one tiger and two ocelots. Experimental evidence supports the hypothesis that these novel feline diseases are causally related to BSE (see end of section on animal encephalopathies). It is probable that the domestic cats have been infected through the consumption of infected feed, but the precise ingredient is not known, and it is of note that no case has been reported in a cat born after the potentially infective bovine offals were banned from use in feed or food for any species in September 1990. It is assumed that disease in the captive large cats arose though the consumption of uncooked infected bovine material, such as heads and necks containing central nervous tissue.
3.6 Spongiform encephalopathies of captive wild ruminants

In a British zoo in 1986 a nyala (which belongs, like cattle, to the family ‘Bovidae’) died of a spongiform encephalopathy, signalling the first case of a ‘BSE-like’ condition in British livestock to the British veterinary community. Subsequently, additional cases of spongiform encephalopathy occurred in other captive wild Bovidae in Britain: gemsbok, Arabian oryx, greater kudu, eland, and scimitar-horned oryx. As with FSE, the temporo-spatial clustering of these novel spongiform encephalopathies would be consistent with a causative link to BSE. Although it would seem likely that dietary exposure was of most importance, it is noteworthy that one of the kudu was the offspring from an affected mother. This raised the additional possibility of maternal transmission in this species, though subsequent epidemiological investigation suggested that a feed source was possible.

3.7 Strain typing studies of the TSE agents in animals

The ‘strain’ of a TSE has been defined by characteristic features when transmitted to mice. For example, when inoculated into genetically similar mice a particular scrapie strain leads to a consistent incubation period and pattern of neuropathology. Using a range of genetically distinct mice allows a strain profile based on incubation period and neuropathological distribution of lesions (the ‘lesion profile’) to be produced (see figure p62). Such experiments have suggested that scrapie exists as over twenty separate strains, whereas BSE is due only to a single major strain of agent, which is distinct from those of scrapie. Furthermore the transmission characteristics of FSE, the novel spongiform encephalopathies of kudu and nyala, and experimental transmissions of the BSE agent to sheep, goats and pigs resemble those of the BSE agent, and thus provide supportive evidence for a causative association. Similar strain typing experiments for conventional sporadic CJD and nvCJD are currently in progress.

Section 4: Diagnostic tests for Creutzfeldt-Jakob disease

4.1 Routine blood tests

Routine haematological and biochemical investigations, including inflammatory markers, are usually normal in CJD and other TSEs. In about one-third of cases the liver function tests are deranged, usually in the form of mildly elevated transaminases - the reason for this is not known.
4.2 Electroencephalography

The EEG was first recognised as an important aid to the diagnosis of CJD in 1954 and was included as a component of the first published diagnostic criteria in 1979. The EEG has traditionally been considered the most reliable non-invasive diagnostic of CJD. Approximately 60-70% of cases are reported to develop the diagnostic ‘classical’ appearance of 1-2Hz generalised bi/triphasic periodic complexes, the remainder usually show non-specific slow wave abnormalities only. As the possibility of a characteristic tracing increases with time, it is recommended that following a non-diagnostic recording further tracings should be repeated at regular intervals (days or weeks) in suspected cases. The response to diazepam is unpredictable with the classical appearances being either abolished or unaltered by its administration. The typical EEG appearance has not been reported in kuru, nCJD or ‘classical’ GSS and has only rarely been described in growth hormone related iatrogenic disease. A normal EEG does not exclude the diagnosis of CJD, indeed, there are exceptional reports of such records, even in the late stages of the disease. Although the characteristic EEG is virtually diagnostic of CJD in the correct clinical context, similar appearances have very rarely been described in other conditions, such as Alzheimer’s disease or metabolic encephalopathies. (Table 8).

<table>
<thead>
<tr>
<th>Table 8: Differential diagnosis of CJD-like EEG</th>
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<tbody>
<tr>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Lewy body disease</td>
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<tr>
<td>MELAS syndrome</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Anoxic encephalopathy</td>
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<tr>
<td>Binswanger's disease</td>
</tr>
<tr>
<td>Baclofen, mianserin, metrizamide &amp; lithium toxicity</td>
</tr>
<tr>
<td>Hyperammonemia</td>
</tr>
<tr>
<td>Hypo and hypernatraemia</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
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<tr>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>AIDS dementia</td>
</tr>
</tbody>
</table>

Difficulties in EEG interpretation

EEG interpretation is often subjective, and no standardised criteria for a ‘diagnostic’ tracing have been widely agreed. We have included a selection of EEG records at the end of this document (p63-5) illustrating recordings that we feel are typical, classical traces (i.e. diagnostic) and others that we would classify as ‘suggestive’ but not diagnostic.
4.3 Brain biopsy

This procedure is unlikely to significantly benefit the patient unless a potentially treatable condition is also considered a possibility. Therefore, although diagnostic in most cases, brain biopsy cannot be recommended as a procedure to confirm the clinical suspicion of CJD. It is potentially hazardous, not only to the patient (who may develop a surgical complication such as infection or haemorrhage) but also to hospital staff. It is mandatory that the neurosurgical instruments are stored and destroyed if the diagnosis of CJD is confirmed, as adequate sterilisation cannot be guaranteed. Approximately 5% of biopsies from definite cases are not confirmed using this method, reflecting the potentially uneven distribution of pathology in CJD.

4.4 Neuroimaging

The main role of neuroimaging is to exclude other conditions. Computerised tomography is usually normal in CJD (80% of cases), but sometimes atrophy is found, especially in patients with a protracted illness. Magnetic resonance imaging abnormalities have been reported, particularly abnormal high signal from the basal ganglia on T2-weighted images (noted in only 4% of MRI reports in one series but 79% of retrospectively reviewed scans in another). However, most MRI scans are reported as being normal or showing generalised atrophy only. High T2-weighted signal abnormalities largely confined to the posterior thalami have been reported in two cases of nvCJD, a pattern not previously reported in other forms of CJD and therefore possibly specific for the new variant.

Magnetic resonance spectroscopy (for N-acetylaspartate) has been disappointing as an early diagnostic tool in CJD.

Positron emission tomography has been reported in only a few cases and the clinical usefulness of this technique remains to be established. Using $[^{18}F]$ 2-fluoro-2-deoxy-D-glucose, regional hypometabolism of glucose has been shown to correlate in general with neuropathological lesions in familial and sporadic cases. The hypometabolism is thought to reflect loss of neuronal function.

Single photon emission computed tomography scanning has also been reported in only a few cases of CJD and frequently showed abnormal perfusion when contemporaneous imaging by MRI or CT was unremarkable. However, the specificity of SPECT abnormalities, and hence its use as a diagnostic tool, also remains to be established.
4.5 Cerebrospinal fluid

In CJD the cerebrospinal fluid (CSF) usually contains no inflammatory cells but a slightly elevated protein (0.5-1g/l) occurs in about one-third of cases. The presence of oligoclonal bands confined to the CSF has only rarely been described. Recent reports have suggested that the detection of a ‘marker of neuronal death’ in the CSF, the 14-3-3 protein, is both a highly sensitive and specific test for CJD (this immunoassay is derived from on an older and more complex technique using 2D-gel electrophoresis to detect two proteins designated p130 and 131). The results of a small number of blinded samples from the UK has been promising, in particular positive results from two confirmed cases of nvCJD. However, three further nvCJD samples were falsely negative, although suboptimal storage may have contributed to this result (it is recommended that samples should be stored frozen as soon as possible after collection). The detection of another CSF marker, neuron-specific enolase, is said to be a more rapid and simple, although less accurate, test than the detection of 14-3-3 protein. The diagnosis of CJD is usually straightforward. Therefore, the clinical usefulness of these or other diagnostic tests is likely to depend on their ability to correctly detect those cases in which diagnostic difficulty occurs. This group largely consists of those in which the typical EEG appearance is not seen: the minority of sporadic cases, nvCJD and most iatrogenic cases. Although results to date have been promising, too little information is currently available to reliably predict how clinically useful these CSF tests will be. At present the above-mentioned CSF assays are only available in a few centres in Europe and the USA, but it is hoped that the WHO collaborating centres will be able to help with training in the use of any of these techniques if they prove to be diagnostically useful.

4.6 Future diagnostic tests

Recent studies have demonstrated that the abnormal form of human PrP may exist as at least four distinct molecular ‘strains’ determined, in part, by sites and degree of glycosylation within the protein structure. The strain appears to be associated with the clinical phenotype and may reflect disease aetiology, for example, the ‘type 4’ strain pattern is associated with nvCJD. Another report describes the presence of abnormal PrP in palatine tonsillar tissue obtained at autopsy from a patient with nvCJD (see histology p59). Furthermore, it was possible to demonstrate the molecular ‘strain type’ from this tissue. This raises the possibility that palatine tonsillar biopsy may be a useful test for nvCJD. However, it is not known when in the clinical course tonsillar biopsy would be diagnostic, whether tonsillar tissue is always affected in nvCJD and if similar changes would be detectable in other forms of CJD. Indeed, a recent study from Japan failed to identify abnormal PrP in tonsillar tissue from a group of 11 sporadic CJD or GSS patients. The relationship of biological strain type to molecular strain type has not been established.

Prion protein is normally expressed on white blood cells and platelets but there is currently no convincing evidence that they carry the abnormal PrP isoform. However, the possibility that small amounts may be detectable, leading in a blood test for CJD, cannot be dismissed.
Section 5: The nature of the infectious agent

The infectious nature of scrapie was discovered in 1935 when a previously healthy ewe developed the disease following intraocular inoculation with spinal cord from an affected sheep. Transmissibility of the human diseases kuru (1966), CJD (1968), GSS (1981) and FFI (1995) followed but the exact nature of the infectious agent remained elusive. In 1954 the concept of ‘slow-virus disease’ was first introduced. However, exhaustive, but unfruitful, efforts to find the ‘TSE virus’, and a conspicuous lack of inflammatory response, argued against a viral aetiology. Furthermore the infectious pathogen shows a remarkable resistance to treatments that would normally be expected to inactivate viruses, such as ultra-violent and ionising radiation. In 1967 a radical theory was put forward suggesting that the infectious agent could be a self-replicating protein. Subsequent experiments showed that scrapie infectivity was associated with a partially protease resistant protein, and in 1982 the term ‘prion’ was introduced for this hypothetical proteinaceous infectious particle. Advances in molecular biology have subsequently contributed greatly to our knowledge of the TSE agent, often supporting the protein-only hypothesis. Prion protein is now known to be a normal outer cellular membrane glycoprotein, expressed on most cell types, but predominantly in the CNS. This normal protease sensitive cellular form is transformed into the abnormal protease resistant isoform in the disease state. The difference between the normal and pathological isoforms appears to be solely conformational and is achieved post-translationally. The prion hypothesis states that once produced the abnormal isoform, PrPSc, acts as a template for the conversion of more PrPC to PrPSc, thus, a chain reaction is set in motion with more and more PrPC being transformed into the pathological PrPSc isoform. The prion theory may help explain the central paradox of the TSEs: how a disease can develop as an inherited, sporadic, and infective disorder. It is suggested that the mutations associated with these hereditary disorders renders the mutant PrPC inherently unstable, with a high tendency to fold into the disease-causing PrPSc isoform. In sporadic disease the initial pathogenic prion protein needed to seed the production of PrPSc occurs as a rare spontaneous event, perhaps due to a somatic mutation of the prion protein gene in one or more cells. Finally in infective disease the inoculated PrPSc initiates the chain reaction of host PrPC conversion to PrPSc.

Although the prion theory has gained increasing popularity over the past 15 years, many scientists still believe the transmissible agent is viral-like, containing DNA. Some have argued that perhaps the infectious DNA is associated with and protected by host protein – the ‘virino hypothesis’. In support of these ‘viral’ hypotheses is the demonstration that different ‘strains’ of agent can be detected in hosts with identical PrP genotypes, thus suggesting the presence of a strain specific informational molecule independent of the prion protein. The obvious candidate for such a particle would be nucleic acid, and it is difficult to explain strain variation in the context of the prion hypothesis. Although recent evidence suggests that the prion protein may be able to retain strain information by adopting different conformations, the large number of scrapie strains would require ovine PrP to form an extraordinary range of different conformations.
5.2 Properties of the infectious agent

The efficiency of TSE transmission from donor to host is dependent on several factors, including route of entry. Experimental evidence suggest that ease of transmissibility decreases in the following order.

- Intracerebral: most efficient
- Intravenous
- Intraperitoneal
- Subcutaneous
- Intragastric: least efficient

It is of note that the intragastric route has the lowest efficiency requiring in mice about $10^5$ times more LD$_{50}$ than the highly efficient intracerebral route. Animal studies based on experimental scrapie show that when peripheral routes of infection are used replication of the TSE agent occurs early in the spleen and lymph nodes. The agent reaches the brain from the spleen probably via the visceral sympathetic fibres of the splanchnic nerves which facilitate the agent entering the mid thoracic spinal cord, from where it appears to pass caudally at a maximum rate of about 1mm/day. It is interesting to note that splenectomy in the early stages of the disease delays neuroinvasion, showing the importance of the lymphoreticular system in the initial stages of infection.

Once infection has passed to the brain and spinal cord it can pass centrifugally to the peripheral tissues and this may account for the low and inconsistent infectivity at these sites.

Another important factor determining the transmissibility of the TSE agent is this ‘species barrier’. This refers to the greater difficulty that exist when trying to transfer infection across species compared to within the same species. This was discovered in the 1960s when it was found to be difficult to transmit scrapie from sheep to rodents. Evidence suggests that the prion protein structure may play an important role in the determination of the species barrier: the greater the homology between the PrP gene sequence and the PrP structure of the donor and the host it seems the more likely that the host will acquire prion disease. This may have particular relevance when considering the susceptibility of humans and other animals to the BSE agent. The bovine/human species barrier is not known but it is reassuring to note that transgenic mice expressing human, rather than murine, PrP have not developed disease over 500 days post inoculation with BSE. However, the human gene inserted into these mice is homozygous for valine at residue 129 in contrast with all the cases of nvCJD screened to date which are homozygous for methionine. Furthermore, recent in vitro studies of the efficiency of human PrP conversion by bovine prions has suggested a more efficient reaction if the human PrP has methionine rather than valine at polymorphic residue 129. The results of further studies with transgenic mice homozygous for methionine at codon 129 of their human transgene are awaited.
Section 6: Treatment

Good nursing care to prevent the complications of immobility, such as pressure sores, is likely to be the most important treatment for a patient with CJD. Therapies aimed at palliation of any distressing symptoms, such as clonazepam or sodium valproate for myoclonus, are frequently successfully administered. Sedatives may be required for agitation, but such symptoms, if present, often abate at the illness progresses.

No treatment has been proven to halt the course of the CJD, although a number of specific therapies have been tried including magnesium, amantidine, interferon and other antiviral agents. Patients are frequently administered steroids, acyclovir or thiamine in the hope that they may have an occult, treatable condition such as a cerebral vasculitis, viral infection or Wernicke’s encephalopathy. None of these therapies have an appreciable effect in CJD. Amphotericin, doxorubicin and several other compounds have been found to delay death in hamsters or mice experimentally infected with scrapie. However, both these drugs are toxic and need to be injected directly into the brain and at the time of, or before inoculation. Amphotericin has been tried, but without success in human CJD. Prophylactic administration of Congo red, a sulphonated amyloid-binding dye commonly used as a diagnostic stain for amyloids, before or shortly after experimental scrapie infection, may significantly delay the onset of clinical disease.

It has been shown that transgenic mice in which the PrP gene for has been removed (and therefore do not produce PrP naturally or following inoculation with prions) appear clinically well. This has led to the suggestion that ablative gene therapy, or the use of anti-sense oligonucleotides to ‘turn off’ the production of PrP, may be a useful treatment strategy. It is possible that increasing understanding of the three dimensional structure of PrP could lead to therapies. Evidence suggests that PrP$^c$ contains four central $\alpha$-helices whereas the pathological form, PrP$^{Sc}$, has a greater $\beta$-sheeted structure. If a molecule could be found that was able to bind and stabilise the central $\alpha$-helices this may in turn prevent the conversion of PrP$^c$ to the putative disease-causing moiety. However, such therapies are purely theoretical at present.
Section 7: Case definitions

Recommended case definition of CJD subtypes.

1. Sporadic CJD.

a. Definite:
   i) Neuropathologically confirmed; and/or
   ii) Immunocytochemically confirmed prion protein (PrP) positive (Western blot); and/or
   iii) Presence of scrapie associated fibrils.

b. Probable:
   i) Progressive dementia; and
   ii) Typical EEG (1-2 Hz generalised repetitive triphasic periodic complexes); and
   iii) At least two out of the following four clinical features:
       Myoclonus; visual or cerebellar, pyramidal/extrapyramidal, akinetic mutism.

c. Possible:
   i) Progressive dementia; and
   ii) No EEG or atypical EEG; and
   iii) Duration <2 years; and
   iv) At least two out of the following four clinical features:
       v) Myoclonus; visual or cerebellar, pyramidal/extrapyramidal, akinetic mutism.

2. Iatrogenic CJD

i) Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or
ii) Sporadic CJD with a recognised exposure risk.

3. Familial CJD.

NB. For the purpose of surveillance this includes Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI).

i) Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or
ii) Neuropsychiatric disorder plus disease-specific PrP mutation.
4. New variant CJD

Neuropathology is mandatory for the diagnosis of a definite nvCJD which is based on the following features:-

i) Abundant kuru-like amyloid plaques surrounded by vacuoles (clearly visible on H&E and PAS stains);
ii) Abundant PrP deposits on immunocytochemistry, including prominent ‘pericellular’ deposition in cerebral and cerebellar cortex (especially in the molecular layer).
iii) Spongiform change most prominent in the basal ganglia;
iv) Marked thalamic astrocytosis;

The following features are characteristic of nvCJD, although not sufficient for a definite diagnosis. Other forms of CJD may share some of these features and not every case of nvCJD cases demonstrates all these characteristics. Validated diagnostic criteria for a clinically ‘probable’ or ‘possible’ case are not yet available.

i) A psychiatric presentation with depression and/or psychosis lasting weeks or months
ii) Onset of progressive unsteadiness within weeks or months of presentation
iii) Early and persistent paraesthesia/dysaesthesia
iv) Chorea and/or myoclonus
v) Late illness progression similar to classical CJD, with dementia and multifocal neurological signs
vi) EEG does not show ‘typical’ appearance and may be normal
vii) MRI scan showing posterior thalamic high signal on T2- and/or proton density-weighted images
viii) Prolonged illness duration
ix) Young age

Genetic analysis to exclude familial CJD is important and patients should have no history of exposure to a known risk factor for iatrogenic disease.
Section 8: Tissue handling and safety precautions

Although the TSE agent is known to be infectious it is not contagious in the usual sense. Individuals exposed to patients with CJD: their spouses, nurses and doctors, do not appear to have an increased risk of developing the disease. Furthermore, professionals who might be considered 'high risk' in relation to exposure to TSE agents: e.g. pathologists, neurosurgeons, butchers etc. also do not appear to be at an increased risk of developing CJD.

No proven instance of CJD contracted occupationally has been identified. However, the over 170 cases for iatrogenic CJD contracted through inoculation of contaminated CNS tissue or corneal transplantation serve to remind those of us involved in the management of CJD patients of the importance of safety procedures in relation to the TSE agents. The table shows the comparative frequency of infectivity in organs of human or animals with TSEs and it is apparent that the greatest infectivity is found in the CNS lower levels may be found in other tissues. However, there is no proven instance of iatrogenic CJD arising from any tissues other than brain, dura mater, and cornea.

Table 9: Distribution of comparative frequency of infectivity in organs of human or animals with spongiform encephalopathy

<table>
<thead>
<tr>
<th>Host tissue</th>
<th>Human/kuru(^a)</th>
<th>Sheep/goat scrapie</th>
<th>Cattle BSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>++</td>
<td>+++</td>
<td>(++)</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>++</td>
<td>+++</td>
<td>(0)</td>
</tr>
<tr>
<td>Eyeball</td>
<td>+++</td>
<td>+++</td>
<td>(0)</td>
</tr>
<tr>
<td>Peripheral nerve</td>
<td>(0)</td>
<td>+++</td>
<td>(0)</td>
</tr>
<tr>
<td>Pituitary gland</td>
<td>NT(^c)</td>
<td>+++</td>
<td>NT</td>
</tr>
<tr>
<td>Spleen</td>
<td>+</td>
<td>+++</td>
<td>(0)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>+</td>
<td>+++</td>
<td>(0)</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>+</td>
<td>NT</td>
<td>(0)</td>
</tr>
<tr>
<td>Serum</td>
<td>(0)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Whole or clotted blood</td>
<td>0</td>
<td>±</td>
<td>(0)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>(0)</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Lung</td>
<td>+</td>
<td>±</td>
<td>(0)</td>
</tr>
<tr>
<td>Liver</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Kidney</td>
<td>+</td>
<td>0</td>
<td>(0)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>NT</td>
<td>0</td>
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<tr>
<td>Thymus</td>
<td>NT</td>
<td>±</td>
<td>NT</td>
</tr>
<tr>
<td>Intestine</td>
<td>(0)</td>
<td>+++</td>
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</tr>
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<td>Heart</td>
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<td>0</td>
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<td>Skeletal muscle</td>
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<td>Testis</td>
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<td>Ovary</td>
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<td>Placenta</td>
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<td>0</td>
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<tr>
<td>Amniotic fluid</td>
<td>(0)</td>
<td>(±)</td>
<td>(0)</td>
</tr>
<tr>
<td>Cord blood</td>
<td>(+)</td>
<td>NT</td>
<td>(0)</td>
</tr>
<tr>
<td>Colostrum</td>
<td>(+)</td>
<td>0</td>
<td>NT</td>
</tr>
<tr>
<td>Milk</td>
<td>(0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Based on isolations of the infectious agent from the natural hosts of each disease.
\(^b\)Dem. Infectivity: +++ almost always present, ++ frequent, + irregular, ± rare, 0 undetectable. Parentheses indicate very few tested specimens.
\(^c\)NT: not tested.
The resistance of the TSE agent to standard medical sterilisation procedures is noteworthy. Experimental evidence demonstrates that the agent shows resistance to the following: exposure to boiling, freezing, ethanol, H2O2, permanganate, iodine, ethylene oxide vapour, detergents, organic solvents, formaldehyde, UV and gamma irradiation, and standard autoclaving. Below are guidelines that have been produced for the European union Biomed-1 Concerted Action 'the human prion diseases: from neuropathology to pathology and molecular genetics'. It is envisaged that these will be helpful to those involved the management of patients with TSEs.

The autopsy

What specific precautions should be made for an autopsy performed on a patient with suspected transmissible TSE?. Since procedures given below can be followed without imposing disproportionate hardship, there is no reason to refuse an autopsy on a patient with suspected TSE. The risk of infection for the personnel can be considered lower than that in autopsies on patients with viral hepatitis or HIV infection, so that the general precautions taken for such autopsies are more than adequate on patients with CJD. Decontamination of the autopsy material, however, requires specific measures. The following protocol is kept as simple as possible and more detailed instructions may be found elsewhere. The most important objective of the autopsy is to enable a definite diagnosis by neuropathology. It is thus sufficient, in most cases, to restrict the autopsy to removal of the brain. This can safely be done in an autopsy room, does not require specific safety or containment facilities, and does not expose the involved personnel, including morticians etc., to an increased risk, provided that the following procedures are correctly performed.

1. The autopsy personnel should avoid accidental penetrating wounds by wearing protective gear as in other infectious autopsies (hepatitis, HIV infection, etc.), including safety gloves (e.g. Teflon-made from 'Spectra', or metallic gloves) beneath rubber gloves, a disposable apron, and eye and moth protection.
2. Contamination of the autopsy table should be avoided by a non-permeable disposable plastic sheet or similar material.
3. Removal of the brain: The head is positioned in the usual way, with a thick layer of cellulose sheets underneath. The skull should be with a mechanical (non-electrical) hand saw which is easier to decontaminate than an electrical saw. Before removal of the brain from the skull, it is strongly recommended to take some parts of the brain (recommended: apricot-sized pieces of cerebrum, preferentially from one pole, and of cerebellum) for freezing, to enable eventual further diagnostic procedures and research if appropriate. This tissue must be put into two layers of small plastic bags and put into, and frozen within, a tightly closing plastic container clearly marked. The brain is then removed from the skull in the usual way and put in a tightly closing plastic container with buffered 4% processing. Both the fixed brain and the fixative solution are still infectious and should be appropriately labelled.
4. If wished, internal organs may be inspected and sampled in situ without removal from the body cavities.
5. After the autopsy is completed, the plastic and cellulose sheets are folded together and put with other disposable material into a container for infectious hospital waste and incinerated.
6. All instruments (saw, knife, etc.) and eventually contaminated surfaces must be decontaminated by the procedures given below.

7. Accidents involving parenteral exposure to material or contaminated wastes from TSEs should be recorded.

Neuropathology service

1. The personnel should wear safety gloves; special care should be taken to avoid accidental penetrating wounds.

2. The formaldehyde-fixed brain is processed on a table covered by a disposable plastic sheet and cut on layers of cellulose sheets (to be discarded by burning with infectious hospital waste).

3. To deactivate CJD infectivity, it is recommended to soak the tissue blocks for histology (not more than 5mm in thickness) in concentrated (95-100%) formic acid for one hour, followed by fresh 45 formaldehyde solution for at least 48 hours. However, this makes the tissue block brittle and more difficult to cut. Without this step, paraffin blocks may still be infectious.

4. All instruments, gloves etc. which came into contact with potentially infectious material must be decontaminated. Instruments that were contaminated by formaldehyde-fixed, non-formic acid-treated tissue are not decontaminated by autoclaving (insert reference) but should be immersed in 2N NaOH for one hour.

5. Tissue remnants, cutting debris and contaminated formaldehyde solution should be discarded within a plastic container as infectious hospital waste by burning.

6. Accidents involving parenteral exposure to material or contaminated wastes from TSEs should be recorded.

Decontamination

Which decontamination measures must be followed for surfaces, instruments, gloves and other devices that got in contact with tissue material and body fluids from patients with TSEs? Since conventional methods of sterilisation and disinfection do not decontaminate the CJD infectious agent, specific measures must be used. Several laboratories have developed and use differing but nonetheless effective procedures.

1. Steam autoclaving (glassware, instruments, safety gloves, etc.) 134°C recommended for 1 hour Comment: porous load is considered more effective than gravity displacement autoclaves. The required time periods have been debated. For porous load autoclaving, only 18 min. at 30 lbs. psi, or six separate cycles for 3 min. each at 30lbs psi have been recommended. However, some laboratories recommend two cycles of autoclaving for at least 1 hour during, or subsequent to, soaking in NaOH (see below).
2. Chemical decontamination of non-autoclavable materials and surfaces:

a) 2NaOH (80g per litre) for one hour is recommended; alternately, 1N NaOH may be used for two hours. Comment: some laboratories consider mere wiping off as sufficient for surfaces, but others require more extensive washes. Do not use NaOH for aluminium material.

b) Alternatively 5% NaOCl (at least 20 000ppm free chloride, fresh solution) for 2 hours. Comment: very irritating and corrosive for steel. Some laboratories use boiling of instruments or material in 3% SDS for at least 3 minutes as another option, either alone or in combination with autoclaving at 121°C for one hour.
Section 9: Recommended further reading

WHO documents


Recent scientific textbooks on TSEs


SELECTED REFERENCES

Sporadic CJD


Familial TSEs


**Iatrogenic CJD**


**Kuru**


**New variant CJD**


**Evidence for a BSE/nvCJD link**


**Pathology**


**BSE**


**Other animal TSEs**


**Electroencephalography**


**MRI scanning**


**CSF tests**


**Tonsillar biopsy**


**Nature of the infectious agent**


**Safety Issues**


Section 10: Surveillance reporting

The CJD case reporting forms are attached at the end of this document. They are designed to systematically obtain consistent quality data on CJD cases worldwide. Although from the scientific perspective, additional information on identified cases would be of interest, it is considered at this point in time that a more burdensome questionnaire would excessively compromise reporting completeness.

Given the relative rarity of the disease, it is recommended at present to that a national focal point for CJD surveillance should be nominated by each country or regional department of public health, and that CJD surveillance data filing, compilation, and analysis should be more or less be the responsibility at the central level, although this may need adaptation in large population countries, or in countries with highly decentralised health systems.

The focal point for CJD surveillance should assign, or specifically delegate to another person or unit to assign, unique identification numbers to each definite or probable case of CJD reported to the national CJD surveillance focal point.

See below for a suggested way of consistently assigning identification numbers to reported CJD cases worldwide

Once a year, preferably by the end of the month of February, WHO requests that all countries share with the emerging diseases (EMC) focal point in the respective WHO Regional Office, the updated CJD surveillance data for the entire preceding calendar year. After appropriate assessment at the WHO Regional Office level, a data set will be consolidated from separate regional reports, for a overview of the global distribution of CJD.

Attention should be paid to encouraging physicians to report suspect and known cases. Information on reporting should be disseminated through medical meetings, and through government circulars and memoranda. Review of the sources of case notification will be helpful in determining whether or not reporting is more or less complete. For example, if cases are only being reported from public health facilities, additional attention may be required with private medical doctors and health facilities.
Suggested protocol for assigning unique serial numbers to CJD cases worldwide

The following protocol for assigning a unique Serial Number is currently suggested by WHO:

1. The first 3 letters indicate the country of provenance of the reported case, written in capital letters, and using the WHO official three-letter code assigned to every country (see table of country codes, below).

2. The second set of 3 letters or digits should identify the political sub-division, hierarchically just after the national level, from where the case was reported; this 2 letter/2 digit code should be developed by each country, in coordination with the national CJD surveillance focal point.

3. The third set consists of 4 digits are to indicate the year of diagnosis (not year of report) of the CJD case.

4. The fourth set of 3 digits are to assign a case number in the series of CJD cases detected and reported in the country, or region of the country.

Fictitious Examples

FRA-069-1996-023  The Serial Number uniquely identifying the 23rd reported CJD case in French department of Rhône (69), year of diagnosis 1996

UNK-WAL-2000-019  19th reported CJD case in Wales, United Kingdom, year of diagnosis 2000

Codes of countries in SEARO and WPRO

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<th>SEARO</th>
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<td>MAV</td>
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<td>KRD</td>
<td>MMR</td>
</tr>
<tr>
<td>India</td>
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</table>

<table>
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</thead>
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<td>AMS</td>
<td>KIR</td>
</tr>
<tr>
<td>Australia</td>
<td>AUS</td>
<td>LAO</td>
</tr>
<tr>
<td>Brunei Daru.</td>
<td>BRU</td>
<td>MAC</td>
</tr>
<tr>
<td>Cambodia</td>
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<td>MAA</td>
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<td>China</td>
<td>CHN</td>
<td>MSI</td>
</tr>
<tr>
<td>Cook Islands</td>
<td>COK</td>
<td>MIC</td>
</tr>
<tr>
<td>Fiji</td>
<td>FIJ</td>
<td>NEC</td>
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<td>French Polynesia</td>
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<td>Japan</td>
<td>JPN</td>
<td>BLA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wallis/Futuna</td>
</tr>
</tbody>
</table>
Section 11: CJD surveillance reporting forms

INFORMATION ON THE PERSON REPORTING

PLEASE PRINT OR TYPE

Name & title of person reporting:

Date report prepared: __/__/____
    day month year

Name of institution:

Address:

Telephone number: ___________ - ________________
    Area/city code  Local number(s)

Fax number: ___________ - ________________
(if any)

Email address: ___________ @ __________________
(if any)
<table>
<thead>
<tr>
<th><strong>PATIENT DETAILS</strong></th>
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</thead>
</table>
| **Serial number:**  
| NOT KNOWN |
| **Date of birth:**  
| NOT KNOWN |
| **Sex:**  
| Male/Female/Unknown (Please underline) |
| **Country of birth:**  
| NOT KNOWN |
| **Town of residence:**  
| NOT KNOWN |
| **District of residence:**  
| NOT KNOWN |
| **Occupation:**  
| NOT KNOWN |
| **Date of onset:**  
| NOT KNOWN |
| **Age at onset:**  
| NOT KNOWN |
| **Current status:**  
| Alive/Dead/Unknown (Please underline) |
| **Date of death:**  
| NOT KNOWN |
# CLASSIFICATION OF CJD CASE

**CJD Subtype**

Sporadic/Iatrogenic*/Familial†/New variant/Unknown  (Please underline)

**Level of diagnostic confirmation**

Definite/Probable/Possible/Not known  (Please underline)

*Please fill in the box below ONLY if iatrogenic CJD

**Source of iatrogenic exposure:-**

Growth hormone/Gonadotropin/Dura mater/Other  (Please underline)

If Other, please specify below:-

............................................................................................................................... ..........................................
............................................................................................................................... ..........................................

† Please fill in the box below ONLY if familial CJD

**Has blood been taken for genetic analysis?**

Yes/No/Not known  (Please underline)

If yes, what was the result?

Mutation found (please specify) .................................................................

or Result awaited/Unknown/No mutation found  (Please underline)

**Is there a first degree relative with definite or probable CJD or GSS or FFI?**

Yes/No/Unknown  (Please underline)

If yes, does the relative have:-

CJD or GSS or FFI  (Please underline)
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<td>Rapidly progressive dementia</td>
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<tr>
<td>Cerebellar dysfunction</td>
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<tr>
<td>Myoclonus</td>
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<tr>
<td>Chorea</td>
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<tr>
<td>Visual dysfunction</td>
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<tr>
<td>Pyramidal signs</td>
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<tr>
<td>Extrapyramidal signs</td>
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<tr>
<td>Rigidity</td>
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<tr>
<td>Primitive reflexes</td>
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<td>Gait disturbance</td>
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<tr>
<td>Dysphagia</td>
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<tr>
<td>Akinetic mutism</td>
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<td></td>
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<tr>
<td>Seizures</td>
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<tr>
<td>Paraesthesia/dysaesthesia</td>
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<tr>
<td>Visual/auditory hallucinations</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Other *</td>
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* If other relevant or unusual signs or symptoms, please specify:

__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
__________________________________________________________________________
## DIAGNOSTIC INVESTIGATIONS

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<th>No</th>
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<td><strong>Lumbar Puncture:</strong></td>
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<td>Elevated CSF protein</td>
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<tr>
<td>Positive 14-3-3 protein assay</td>
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<tr>
<td><strong>Neuro-imaging:</strong></td>
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<tr>
<td>Atrophy on CT</td>
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<td><strong>Neuro-imaging:</strong></td>
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<tr>
<td>Basal ganglia abnormalities on MRI</td>
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<td><strong>PrP gene analysis:</strong></td>
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<td>Mutation found</td>
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<td><strong>PrP gene analysis:</strong></td>
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<td><strong>If yes, underline MM/MV/VV</strong></td>
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</table>

** If possible, please attach a copy of any relevant EEG segments.
NEUROPATHOLOGY

1. Was necropsy performed?
   Yes/No/Unknown  
   (Please underline)

   If yes, please indicate which of the following features were present.

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<th>Yes</th>
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<tr>
<td>Neuronal loss</td>
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<tr>
<td>Astrocytosis</td>
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<tr>
<td>Status spongiosus</td>
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<tr>
<td>Positive PrP immunocytochemistry</td>
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<tr>
<td>Scrapie associated fibrils (SAF)</td>
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</tbody>
</table>

2. Was a brain biopsy performed during life?
   Yes/No/Unknown  
   (Please underline)

   If yes, please indicate which of the following features were present.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Yes</th>
<th>No</th>
<th>Not done</th>
<th>Unknown</th>
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<td>Astrocytosis</td>
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<td>Status spongiosus</td>
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<td>Positive PrP immunocytochemistry</td>
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<td>Scrapie associated fibrils (SAF)</td>
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</table>
If there further relevant information please write below.
Section 12: Illustrations
Acknowledgements
We would like to thank the following for their help in producing this training document.

Dr J. Gibbs Jr
Mr R Bradley
Dr R. Knight
Prof. L. Bolis
Prof. H. Budka
Dr C. Masters
Dr R.G. Will
Dr G Stewart
Dr T. Esmonde
WHO Consultation on the Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies

Geneva, Switzerland
9-11 February 1998

Draft recommendations
Recommendations

1. The clinical diagnosis of CJD is currently based upon the combination of progressive dementia, myoclonus and multifocal neurological dysfunction, associated with a characteristic periodic EEG (see Annex 1). However, nvCJD, most growth hormone-related iatrogenic cases, and up to 40% of sporadic cases are not noted to have the characteristic EEG appearance. This hampers clinical diagnosis, and hence surveillance, and illustrates the need for additional diagnostic tests. Advances in CJD diagnostics have occurred in the past two years, in particular the 14-3-3 protein CSF assay, which appears to have a high sensitivity and specificity for sporadic CJD. We propose the following criteria for probable sporadic CJD.

**Progressive dementia; and**

- At least two out of the following four clinical features:
  - Myoclonus
  - Visual or cerebellar
  - Pyramidal/extrapyramidal
  - Akinetic mutism ; and

- A positive 14-3-3 CSF assay and a clinical duration to death < 2 years and/or

**A typical EEG and any length of clinical duration**

- Routine investigations should not suggest an alternative diagnosis.

Results from a recent study suggest that the detection of high signal from the basal ganglia on T2 and proton density-weighted MRI supports the diagnosis of sporadic CJD, particularly if a FLAIR sequence or diffusion weighted images are used. The Consultation recommends that further research be conducted into the use of MRI in human TSEs.

2. No widely agreed and validated definition of a diagnostic EEG tracing is available, leading to potential inconsistencies in case ascertainment between centres. To enhance CJD surveillance a workable definition of a diagnostic EEG is required. We propose that the following criteria devised by Steinhoff and Knight be adopted and undergo evaluation (see Annex 2 for important related information).

- Strictly periodic activity
- Variability of intercomplex intervals <500 ms
- Continuous for at least one 10 second period
  - Bi- or tri- phasic morphology of periodic complexes
  - Duration of majority of complexes 100-600 ms
  - Periodic complexes may be generalized or lateralized but not regional or asynchronous

3. New variant CJD cannot be diagnosed on clinical grounds at present. However, on the basis of the 23 neuropathologically confirmed cases the diagnosis of nvCJD should be considered as a possibility in a patient with a progressive neuropsychiatric disorder with at least 5 out of the following 6 clinical features:

- Early psychiatric symptoms
- Early persistent paraesthesia/dysaesthesia
- Ataxia
- Chorea/dystonia or myoclonus
- Dementia
- Akinetic mutism

The suspicion of nvCJD is strengthened by the following criteria,

- The absence of a history of potential iatrogenic exposure
- The absence of a PrP gene mutation
- The absence of a typical EEG
- Age at onset <50 years
- Clinical duration >6 months
- Routine investigations that do not suggest an alternative diagnosis
· An MRI showing abnormal symmetrical and bilateral high signal from the pulvinar on axial T2- and/or proton density-weighted images, with a signal intensity that exceeds that returned from the caudate or lentiform nucleus.

A patient meeting all of the above criteria should be considered as a suspect case of nvCJD for surveillance purposes.

4. The group discourages the use of cerebral biopsy except to make an alternative diagnosis of a treatable disease. The Group strongly recommends that brain biopsy is not used to confirm the clinical suspicion of CJD. The Consultation concurs with the previous WHO recommendation that instruments used for neurosurgery on patients with CJD should be discarded. If re-use is unavoidable, instruments must be immersed in 1N NaOH or fresh undiluted hypochlorite for one hour, cleaned, and then autoclaved at 134°C for one hour.

5. As part of WHO activities to promote the global surveillance of human TSEs the Consultation recommends that collaborating centres be established to aid in diagnosis and training (see Annex 3).

6. Screening cases of CJD for the mutations associated with the hereditary forms of disease raises ethical and logistical concerns. Written consent for genetic testing is considered mandatory in many countries but may be culturally unacceptable in others. The Consultation recommends that genetic counselling of patients and/or their families should be performed prior to any PrP gene analysis and that ideally written, but if not documented oral, consent should be obtained. The genetic counsellor should be provided with information on the genetics of the human TSEs to be used when seeking consent (for example see Annex 4). Because of the low PrP gene mutation detection rate in ‘sporadic’ CJD it is recommended that mainly those patients with a family history of a human TSE be considered for PrP gene analysis. This could be performed at one of the above collaborating centres.

All suspect cases of nvCJD should undergo PrP gene analysis (if consent is obtained) to exclude a mutation and, for research purposes, to identify codon 129 status.

7. When a diagnosis of CJD is made the initially geographical attribution should be the country of residence at the onset of clinical disease. Final attribution should be decided on a case by case basis.

8. The communication of any important new information to the public benefits from planning. This is particularly the case when the information is complex and has the potential to cause great concern. The Consultation recommends that each national authority plans a strategy for disseminating information that may result from CJD surveillance. Maxims for effective communication on health and risk issues are reproduced in Annex 5. A copy of this Report and the Global TSE Surveillance Training Document should be sent to all the WHO regional offices.

9. A definite diagnosis of CJD, including nvCJD, is established only by neuropathological examination. The group recommends that autopsy be strongly encouraged in any suspect case of CJD. Where autopsy is not possible or permitted, post-mortem biopsy should be sought.

10. Experience to date of the use of palatine tonsillar biopsy in CJD diagnosis is limited. Because the abnormal isoform of PrP has been detected in tonsillar tissue from patients with nvCJD but not patients with sporadic CJD, analysis of tonsillar tissue may provide potentially diagnostic information in nvCJD, but requires further post-mortem evaluation.
11. The Group concluded that at present there is no available therapy that is known to alter the underlying disease process for any human TSE. Animal and in vitro studies have demonstrated that a number of therapeutic compounds with the potential for interfering with the underlying disease process. Although some compounds are known to delay the onset of disease (in some cases beyond the animal’s natural lifespan), no compound is known that can ‘cure’ a clinically affected animal.

12. The Consultation noted that the possibility of a significant epidemic of nvCJD occurring within the next 10-15 years cannot be dismissed and therefore emphasized that the early identification of an effective therapy is of paramount importance. Such a treatment would also offer hope to those individuals who are at risk of developing familial or iatrogenic disease.

13. The Consultation stressed the pressing need for further research into the molecular properties of the TSE agent that could lead to potential disease modifying compounds. In parallel, efforts should be made to identify presymptomatic diagnostic tests, to enable any future therapy to be used as early as possible in the disease course.
ANNEX 1. CURRENT STANDARD CASE DEFINITION OF CJD SUBTYPES.

Sporadic CJD.

Definite:
Neuropathologically confirmed; and/or
Immunocytochemically confirmed prion protein (PrP) (or on Western blot); and/or
Presence of scrapie-associated fibrils.

Probable:
Progressive dementia; and
Typical EEG (1-2 Hz generalised repetitive triphasic periodic complexes); and
At least two out of the following four clinical features:
Myoclonus; visual or cerebellar, pyramidal/extrapyramidal, akinetic mutism.

Possible:
Progressive dementia; and
No EEG or atypical EEG; and
Duration <2 years; and
At least two out of the following four clinical features:
Myoclonus; visual or cerebellar, pyramidal/extrapyramidal, akinetic mutism.

Iatrogenic CJD

Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone; or
Sporadic CJD with a recognised exposure risk.

Familial CJD.

NB. For the purpose of surveillance this includes Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI).
Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or
Neuropsychiatric disorder plus disease-specific PrP mutation.
ANNEX 2. EEG INTERPRETATION

Preliminary notes

- The finding of a characteristic periodic EEG pattern is very helpful in the diagnosis of sporadic CJD.
- Some cases of sporadic CJD never show this pattern. A ‘negative’ result cannot exclude the diagnosis.
- A periodic EEG like that seen in CJD may be found in a number of other conditions and these must be considered in the clinical context. A list of these conditions is given below.
- The EEG changes in CJD undergo evolution. A periodic pattern may not be seen in the early phases of disease. Serial EEG recordings should be undertaken whenever possible. In sporadic CJD, it is recommended that they should be repeated at intervals of one to two weeks.
- If a typical periodic EEG is obtained, then it is not absolutely necessary to repeat it, although this should be considered if there is any clinical doubt about other possible causes of the EEG pattern (such as metabolic factors).
- A repeatedly normal EEG is not consistent with a diagnosis of sporadic CJD.

Technical notes

- Bipolar montages including the vertex should be used
- Referential montages including vertex and CZ reference electrodes should be used
- The ECG should be coregistered
- External alerting stimuli should be used
- The whole record should be viewed whenever possible and a five minute continuous sequence as a minimum

Footnote

The EEG criteria are based on considerable experience with the EEG in CJD but have not been formally evaluated prospectively in large numbers of suspect CJD cases. Such evaluation is being undertaken and the results of this may necessitate some revision of them.

Conditions which may cause a CJD-like EEG

Alzheimer's disease
Lewy body disease
MELAS syndrome
Hyperparathyroidism
Post-anoxic encephalopathy
Binswanger's disease
Baclofen, mianserin, metrizamide & lithium toxicity
Hyperammonemia
Hypo and hypernatraemia
Hypoglycaemia
Hepatic encephalopathy
AIDS dementia
Multiple cerebral abscesses
Annex 3. Proposed WHO Collaborating centres

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(Argentina)

(Australia)
Annex 4. Genetic Information

Information to be given to relatives of CJD patients when consent is being obtained for blood to be taken for genetic studies

The cause of CJD in the great majority of patients is unknown.

A small proportion of cases are hereditary in nature due to a faulty gene.

In nearly all the hereditary cases, the family are already aware of other affected family members. In these families about half the family members can be affected by CJD and the disease may occur from generation to generation.

The chances of finding a faulty gene in a case of CJD without any other affected family members is very small, probably less than 1 in 50.

We wish to take blood from cases of CJD in order to look for abnormalities in the gene and we also store blood for future research.

In this way we hope to advance knowledge in CJD which may, in the future, lead to a better understanding of the disease.

If you do not want to know the result of this test, we will not inform you, your family doctor or the hospital doctor of the result.

If you do want to know the result of the test, this will be done through the local genetic counselling clinic even if the test is negative which is the most likely outcome.

The chances of finding an abnormality in the genetic test are very low and in the great majority of cases there is not increased risk of developing the disease in family members. It is particularly important to know that CJD is not infectious and that there is no risk from contact with patients during their illness.

Summary
There is no risk of developing CJD by contact.
Only a small proportion of cases are hereditary.
The blood sample will help research.
The result of the genetic test will only be made available IF YOU WANT IT TO BE.

Annex 5. Maxims for effective communication on health and risk issues

I. Develop a theme/goal with common interest(s) (e.g., "we are interested in the health and safety of our community").
Identify clear and explicit objectives (short-term and long-term).
Establish a common agenda while recognizing political/economic interests and hidden agendas.
Base information on needs assessment and ethical community values.

II. Identify all parties that have an interest in the issue (non-governmental organizations, trade associations, media, government, public, etc.).
Build coalitions/partnerships with those integral for successful delivery of information.
Work with other credible sources.
Recruit competent spokes people with your participants.
Establish roles for the media, advocacy groups, organizations, the public, etc.

III. Identify the intended audiences, their concerns, and the potential mechanisms to reach them.
Listen and understand your audience, including cultural variables. 
Measure public opinion-survey, polls, baseline, etc. 
Conduct formative research-focus groups, observational studies, survey/baseline. 
Identify communication patterns of the audience (e.g. how do they get information)

IV. Develop a strategic approach to communicate with public(s). 
Open communication channels immediately in crisis.
Choose a competent spokesperson, recognize emotions, speak clearly and understandably.
Choose a message, pre-test and adapt it, and establish tracking mechanism(s).
The actual audience may care more about fairness, competence, and empathy than data and statistics.
Build trust with honest and open disclosure-never lie.
Use objective criteria, standards, and benchmarks for your planning and implementation.

V. Communicate a consistent and credible message.
Create inter- and intra-organizational mechanisms for delivery of messages.
Consult with appropriate parties before making major decisions or announcements.
Use risk comparisons to help put risks in perspective; avoid comparisons that trivialize.
Focus on credibility with a high-level, consistent messenger.

VI. Establish mechanisms for direct public/audience communication. 
Utilize existing media with openness and accessibility.
Establish trust and interactivity-new media, radio call-in, free calls, bulletin boards, etc.
Tell people what your limitations are; you cannot do everything.
Discuss actions underway or to be taken.
If in doubt, share more rather than less information.

VII. Maximize your communication effectiveness.
Acknowledge and respond to emotions.
Avoid instant, abstract, or harsh language about deaths, injuries, and illnesses.
Speak with compassion, using simple, non-technical language.
Use visual, vivid, and vocal images that connect at a personal level.
Use examples and anecdotes that are culturally sensitive and make data come alive.
Create a relationship with the public(s) by offering realistic, compliance-prone actions.

VIII. Evaluate your interventions/efforts on intended audiences.
Tracking-Did your audience make the desired decision?
Assess and evaluate with outcome and impact measures.
Did you build relationships with key participants?
Are you more prepared for the next intervention...the next steps?
## Annex 6. Pathological characteristics of nvCJD

The neuropathology of new variant CJD shares the key characteristics of all human transmissible spongiform encephalopathies - spongiform change, neuronal loss, reactive astrocytosis and the accumulation of the disease-associated isoform of prion protein (PrP) in the brain. However, the nature and distribution of the neuropathology in new variant CJD is relatively constant from case to case, and differs in key respects from other forms of human spongiform encephalopathy. These key features can be summarised as follows:

1. Multiple fibrillary PrP plaques in the cerebral and cerebellar cortex, often surrounded by a halo of spongiform change (the "florid" plaque).
2. Multiple small PrP plaques which are only detectable by immunocytochemistry, occurring in clusters within the cerebral and cerebellar cortex, not related to spongiform change.
3. Amorphous PrP deposits around neurones and blood vessels in the cerebral and cerebellar cortex, best visualised on immunocytochemistry.

The other commoner features of sporadic CJD - perivacuolar accumulation of PrP, widespread confluent spongiform change and status spongiosus have not been identified in the 22 cases of new variant CJD in whom brain biopsy or autopsy has been performed. Immunocytochemistry for PrP is an invaluable aid to diagnosis, although the large fibrillary plaques are easily visualised on haematoxylin and eosin sections; both the large fibrillary plaques and the small cluster plaques can also be visualised on period acid/Schiff preparations. Gallyas silver impregnation will stain the large and small plaques, and also demonstrates some of the amorphous PrP deposits although these are best visualised on immunocytochemistry. New variant CJD can be diagnosed on brain biopsy, but limitations exist with respect to sampling error; Western blotting studies may help establish a diagnosis under such circumstances.

The full spectrum of the characteristic neuropathology of new variant CJD also includes:

1. Spongiform change most marked in the basal ganglia, with dense perineuronal and periaxonal PrP deposition.
2. Severe thalamic gliosis and neuronal loss, particularly involving the dorsomedial and posterior nuclei (including the pulvinar).
3. Massive accumulation of PrP, often in the focal distribution, in the cerebellar cortex including the molecular layer and granular layer with occasional plaques in the white matter.
4. Punctate neuronal staining for PrP in the pontine nuclei.
ANNEX 7. NEUROPATHOLOGICAL DIAGNOSTIC CRITERIA FOR CJD AND OTHER HUMAN TSES

1. Creutzfeldt-Jakob disease
1.1. Sporadic, iatrogenic (recognised risk) or familial (same disease in 1st degree relative or disease-associated PrP gene mutation): Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter; and/or Encephalopathy with prion protein (PrP) immunoreactivity (plaque and/or diffuse synaptic and/or patchy/perivacuolar types).

1.2. New variant CJD Spongiform encephalopathy with abundant PrP deposition, in particular multiple fibrillary PrP plaques surrounded by a halo of spongiform vacuoles («florid» plaques, «daisy-like» plaques) and other PrP plaques, and amorphous pericellular and perivascular PrP deposits especially prominent in the cerebellar molecular layer.

2. Gerstmann-Sträussler-Scheinker disease (GSS) (in family with dominantly inherited progressive ataxia and/or dementia and one of a variety of PrP gene mutations): Encephalo(myelo)pathy with multicentric PrP plaques.

3. Familial fatal insomnia (FFI) (in member of a family with PRNP178 mutation): Thalamic degeneration, variably spongiform change in cerebrum.

Report of the WHO Workshop on the Surveillance of Creutzfeldt-Jakob disease (CJD) and other Transmissible Spongiform Encephalopathies (TSEs)

With the participation of the Office International des Epizooties (OIE)

Bangkok, Thailand
6-8th October 1997
1. INTRODUCTION

In March 1996 the occurrence in the United Kingdom of ten cases of an apparently new clinicopathological variant of Creutzfeldt-Jakob disease (nvCJD) was announced. The temporal and geographical association between these cases and the bovine spongiform encephalopathy (BSE) epidemic of cattle raised the possibility of a causal link, leading to great public concern. The size of the human population exposed and susceptible to the BSE agent in the United Kingdom is not known and in addition to uncertainties relating to the potential length and distribution of the incubation period, make a useful prediction of the future number of nvCJD cases difficult. Other populations may have also been exposed to the agent through importation from BSE-affected countries of live cattle or cattle by-products, food containing contaminated bovine offals, or from medicinal products containing bovine tissues. Thus the importance of analysing risks, conducting surveillance and monitoring for the occurrence of BSE is widely recognised as being essential to aid authorities to judge any risks there may be to the human population. Monitoring CJD incidence itself is also clearly important and it is noteworthy that this is not currently undertaken in many parts of the world.

The potential future global public health implications of nvCJD were addressed by a WHO expert consultation in May 1996 which recommended the establishment of worldwide surveillance of the new variant and other forms of CJD. Throughout 1997 and 1998 WHO will be running a series of regional workshops, particularly in developing countries, with the intention of helping individual countries establish national surveillance of CJD and its variants. The meeting in Bangkok was the second workshop, the first having been held in June 1997 in Dakar, Senegal, for western African countries. Further workshops have been planned to take place early next year in Cairo for eastern Mediterranean countries, China for countries in the Western Pacific region and in Buenos Aires for South American countries.

It is anticipated that WHO’s global CJD surveillance activities will lead to a greater understanding of CJD and its variants, including the potential causes of iatrogenic CJD and the distribution of the various hereditary forms, and will provide information important for enhancing the protection and planning of public health worldwide.

The second WHO workshop on Global CJD surveillance was held at the Prasat Neurological Institute in Bangkok between 6-8 October 1997. Representatives from each of the following countries participated in the meeting: Bangladesh, Indonesia, Myanmar, Sri Lanka and Thailand. Two countries, Indonesia and Sri Lanka, also sent veterinary representatives. A further six participants from Thailand in addition to approximately 20 students were also in attendance. The meeting was opened by Dr. Suchart Phudhichareonrat, Head of Prasat Neurological Hospital and Institute’s Department of Neuropathology. Professor Thiravat Hemachudha then welcomed the participants and speakers and introduced the first lecture.
2. PRESENTATIONS

The first lecture, ‘An overview of the human TSEs’, was given by Dr. Martin Zeidler, former research fellow at the United Kingdom National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh, Scotland, and now a medical officer with WHO in Geneva. He gave the history of CJD and kuru, presented the characteristic clinical features and discussed the diagnosis and aetiology of these conditions.

The second lecture, ‘The epidemiology of CJD, incidence, risk factors and survival in the European Union Collaborative Study’, was given by Dr. Dorothée Wientjens, former research fellow at the Department of Epidemiology and Biostatistics of the Erasmus University in Rotterdam, the Netherlands. She presented an overview of CJD epidemiology, emphasising the relatively consistent incidence of CJD in those populations studied (approximately 1 case per million persons annually), the familial occurrence of disease in almost 10% of cases and the lack of evidence to suggest important environmental risk factors for the development of sporadic CJD.

The third lecture, ‘The new variant of Creutzfeldt-Jakob disease’ was given in the afternoon of the first day. Dr. Zeidler presented up-to-date information on the new variant form of CJD, including important research that had been published the previous week in the journal Nature, which concluded that the agent causing BSE and nvCJD was the same, thus supporting a causal link between the diseases. An overview of the clinical, investigative and epidemiological features of nvCJD was also given in addition to a discussion on the evidence of an association between nvCJD and BSE.

National reports were then given by representatives from each of the five attending countries in the afternoon of the first day.

Thailand

Thailand has an estimated population of 60 million people. Although there had been no official statistics on CJD in Thailand, it was estimated from data accumulated from five different university hospitals that no more than 30 cases had been diagnosed in the previous 20 years. Approximately one in four cases would have undergone autopsy. There had been no reported case of iatrogenic CJD. Three new cases had been diagnosed in the previous year, one was a case of sporadic CJD and the other two were considered clinically to be fatal familial insomnia.

Myanmar

It was reported that four neurologists, two neuropathologists and 240 epidemiologists were available for a population of 46 million people. Six centres were known with EEG facilities, two in Upper and four in Lower Myanmar. There had never been a reported case of CJD.

Sri Lanka

Eight neurologists served a population of 18 million people. Three centres were known to have EEG facilities but there were no neurophysiologists. There was a very low social acceptance of autopsy. Cadaveric-derived growth
hormone had been used, but very rarely. Cadaveric-derived *dura mater* homografts had not been used. CJD was not a notifiable disease and no confirmed case had been documented.

**Bangladesh**

Fifteen neurologists were currently working in Bangladesh, a country with a population of 120 million. EEG facilities were available in urban areas but autopsies were reported to be uncommon for religious reasons. It was noted that there was a department of neuropathology in Dhaka. Cadaveric-derived dural homografts and pituitary growth hormone had been used very little. No case of CJD had ever been documented.

**Indonesia**

The population of Indonesia was reported to be 200 million people and the country has approximately 80 EEG departments. No case of CJD had been reported.

The first two lectures on the second day, ‘The pathology of human TSEs’ and ‘Safety Issues’, were given by Prof. Herbert Budka, Professor of Neuropathology at the University of Vienna, Austria, and Head of the European Union Concerted Action ‘The human prion diseases from neuropathology to pathology and molecular genetics’. The first lecture gave an overview of the neuropathology of human TSEs, including advances in immunocytochemistry and other molecular biological techniques. The unusual pathological features of the familial TSEs, including fatal familial insomnia, were demonstrated and a further clarification of the unproven prion hypothesis of disease aetiology given. Prof. Budka noted that the previous evening it had been announced that Professor Stanley Prusiner’s pioneering work on the prion hypothesis was to be rewarded by the 1997 Nobel Prize for Medicine. The second lecture concentrated on safety aspects relating to the TSEs. The inability to inactivate the infectious agent by conventional sterilisation techniques was noted and guidelines for appropriate decontamination procedures given. The morning session ended with a 30 minute video presentation on the clinical features of kuru.

The final lecture, ‘The Animal TSEs’, was given by Mr. Ray Bradley, a BSE consultant representing the OIE, from the Central Veterinary Laboratory, Weybridge, England. An overview of the animal TSEs was presented, particularly describing the occurrence and the epidemiology of BSE and the control methods used in the United Kingdom and the European Union. Also presented were recommendations from the OIE *International Animal Health Code* relating to BSE risk analysis, the need to develop a risk management strategy and institute continuous surveillance and monitoring for BSE.

The final morning was given over to an in-depth discussion of the practicalities of initiating surveillance of CJD and BSE in the nations represented.

3. DISCUSSION

**Logistics of national Surveillance**

The participants stated that they considered surveillance of nvCJD of more importance than other forms of CJD. They also emphasised that although CJD surveillance was important, it had to be appreciated that there were many other areas of human medicine with more pressing needs for the resources of their countries. Dr. Zeidler stressed that although WHO concurred with the view that the ascertainment of nvCJD would be the main objective of surveillance, it would be detrimental to separate this from surveillance of other forms of human TSEs for two main
reasons. First, nvCJD and some cases of sporadic CJD may be clinically indistinguishable and, second, the necessary diagnostic skills required to detect a case of nvCJD are likely to be greatly strengthened through the experience gained in surveillance of the more common forms of CJD. With regard to funding, WHO should be able to largely cover the cost of establishing national surveillance by supporting the organisation of national training workshops, training key personnel, providing educational material and assisting with laboratory diagnosis of disease.

Clarification of the definition of a ‘case’ for surveillance purposes was requested and Dr. Zeidler explained that standard diagnostic criteria were printed at the back of the training booklet. He emphasised that in the correct clinical context the occurrence of the characteristic periodic EEG predicts a pathological diagnosis of CJD with almost 100% accuracy. A clinically probable case with a typical EEG, but who dies without pathology being performed, is therefore included as a case of CJD for surveillance purposes. As the possibility of a characteristic tracing increases with time, it was recommended that following a non-diagnostic recording further tracings should be repeated at regular intervals (days or weeks) depending on the tempo of the patient’s illness. The lack of provision of EEG facilities in some countries was noted, and it was suggested that if an EEG could not be performed CSF should be taken if possible, and stored frozen for the 14-3-3 assay. This could then be tested at a later date at one of WHO’s collaborating centres.

The logistics of surveillance were discussed at length, in particular which group of medical professionals should be targeted and the method of collecting information. Prof. Hemachudha noted that he had recently had a very poor response to a mail-out to neurologists in Thailand asking them to provide information on cases of multiple sclerosis. Methods of encouraging referrals of cases were discussed and Dr. Zeidler said that he hoped that the general level of concern regarding CJD, in addition to educating the relevant professional groups and requesting zero reporting, should hopefully help to attain a high degree of case notification. The possibility of using death certificates for additional ascertainment of cases was raised by Dr. Zeidler. The national representatives explained that this was unlikely to provide any significant and useful information because often only the immediate cause of death, such as bronchopneumonia, was recorded, records may be inaccessible or they may be coded inadequately.

A discussion followed on whether making CJD notifiable would aid case ascertainment. It was pointed out, however, that this had paradoxically led to decreased detection of cases in Slovakia. Furthermore, experience with other notifiable diseases questioned whether this would benefit surveillance.

Mr. Bradley suggested that it would be useful to define clear objectives for CJD surveillance and the meeting identified the following major aims:

1. To provide information important for enhancing the protection and planning of public health worldwide
2. To provide information that would be helpful in establishing more accurate diagnosis of all forms of CJD
3. To prevent iatrogenic spread of disease (e.g. through the use of contaminated neurosurgical instruments or via human-derived tissue/material)
4. To increase global scientific knowledge of the human and animal TSEs
5. To help to identify underlying occult risk factors
6. To established a baseline that would allow any relevant change to be detected (e.g. in clinical features, pathology and incidence)
Diagnosis

It was noted that in view of difficulties in obtaining an autopsy, clinical diagnostic tests were likely to be of the utmost importance in identifying cases of CJD. As the diagnosis of a probable case of sporadic CJD currently relied on the presence of a typical EEG, one participant requested the definition of such an appearance. Dr. Zeidler stated that unfortunately no widely accepted and validated criteria existed for a ‘typical’ EEG, but that examples were given in the back of the training document. It was suggested that the criteria recommended by Steinhoff could be used in a case whose EEG was considered borderline (1996, Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche, Zerr I, Kretzschmar H, and Weber T, Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Archives of Neurology, 53:162-166)

Questions were also raised about potential new diagnostic tests, in particular CSF assays and tonsillar biopsy. It was explained that the 14-3-3 CSF test has recently become available at some specialist centres in Europe and North America, and that initial results suggest a very high sensitivity and specificity in sporadic CJD. However, it was noted that false positives had been documented, in particular in patients with recent strokes, but also in other conditions such as Alzheimer’s disease. The experience of the test in nvCJD was limited, but provisional results suggest that it may be less useful than in sporadic CJD. Other CSF markers were currently being investigated, including S100, tau and neuron-specific enolase. It was advised that CSF, particularly for some of the latter tests, should be stored deep frozen immediately after being taken. The results of a palatine tonsillar biopsy have been published for a single case of nvCJD. The biopsy was performed post-mortem and demonstrated the presence of abnormal prion protein with the type 4 glycosylation pattern characteristic of nvCJD. Although there have been press reports of a young British patient with a positive tonsil biopsy taken during life, this is currently unconfirmed. A Japanese study failed to identify abnormal prion protein in the lymphoreticular of 11 patients with conventional CJD or GSS.

The participants reiterated that their main concern was diagnosing nvCJD, and the difficulties with this were discussed, particularly the current lack of ante-mortem diagnostic test and clinical diagnostic criteria. It was noted that bilateral MRI abnormalities of the thalamus may be a useful sign and that this was currently undergoing further investigation. The importance of neuropathological examination in any suspect case of nvCJD was emphasised A question was raised about the possibility of performing brain biopsy during life. Dr. Zeidler cautioned against this procedure, noting that brain biopsy was unlikely to significantly benefit the patient unless a potentially treatable condition was also considered a possibility and therefore, although diagnostic in most cases, brain biopsy could not be recommended to confirm the clinical suspicion of CJD. Furthermore he noted that brain biopsy was potentially hazardous, not only to the patient (who may develop a surgical complication such as infection or haemorrhage) but also to hospital staff. He added that it would be mandatory to store and destroy the neurosurgical instruments if the diagnosis of CJD was confirmed, as adequate inactivation could not be guaranteed.

It was noted that approximately 10-15% of cases of CJD were familial, associated with a mutation of the prion protein gene. Screening cases for these defects was possible but raised ethical questions, many of which were common to other hereditary disorders, such as Huntington’s disease. It was suggested that if genetic testing was to be performed it would probably be best to test those cases with a family history before deciding whether it would
be possible to screen all cases (sometimes cases are found to have a mutation without a clear family history of CJD). It was recommended that informed consent be sought and genetic counselling performed, before genetic testing. WHO collaborating centres should be able to perform the DNA analysis if sent a small sample of blood. Consent forms as used in other countries for genetic testing in CJD would be available from Dr. Zeidler at WHO in Geneva.

Concern was expressed by several delegates regarding the logistics of performing an autopsy on a suspect case of CJD and the incineration of potentially contaminated materials. Prof. Budka reassured the participants that an autopsy could be performed safely and that he would consider the risks to medical personnel from occupational exposure to be very small in comparison to other disorders such as HIV or hepatitis B. It was noted that no case of a health professional or laboratory research worker contracting a TSE through occupational exposure had ever been documented. It was apparent that religious and cultural objections may lead to difficulties in obtaining an autopsy in many populations and Prof. Hemachudha suggested that a *post-mortem* retro-orbital biopsy may be more acceptable. This technique had been used in rabies diagnosis and would involve the insertion of a needle and trocar through the supra-orbital fissure into the brain. No external sign of trauma should therefore be apparent, but the body would need to be handled with care after such a procedure because of possible contamination of the skin, particularly of the head and face. Biopsy material could be either fixed for conventional histology and/or frozen for western blotting. A request was made for histological slides of CJD using both conventional and immunocytochemical stains and Prof. Budka kindly offered to help in this regard. Mr. Bradley pointed out that electron microscopy could be used to detect scrapie-associated fibrils (SAFs) in countries where immunological techniques using anti-PrP sera were not available, and that the presence of SAFs was considered diagnostic.

N.B. WHO is hoping to hold a consultation in early 1998 to discuss the state-of-the-art regarding diagnostic tests in CJD and the possibility of establishing provisional clinical diagnostic criteria for nvCJD and the methods by which these could be validated.

**Animal TSE Surveillance**

Delegates reported that there was considerable concern in their countries regarding BSE and the possible transmission of the BSE agent to humans. The possible modes through which a population may have been exposed to the BSE agent were discussed, including the importation of infected animals, contaminated meat and bone meal, human food and medicinal products. It was considered that if the BSE agent was the cause of nvCJD, and assuming an origin from cattle CNS tissues, a logical preventative step would be to ensure effective surveillance for BSE as recommended by the OIE. If any cases of BSE were found it would give advance warning of a potential human health risk because disease in cattle would probably ante-date any associated occurrence of nvCJD as the incubation period of BSE in cattle is likely to be significantly shorter than nvCJD in man. Mr. Bradley placed an emphasis on the importance of conducting a BSE risk assessment and developing a risk management strategy to deal with any risks identified and to initiate a programme of continuous surveillance and monitoring for the disease in line with the recommendations of the OIE *Code*.
Particular assistance was requested by some of the delegates to aid countries to set up diagnostic procedures for BSE according to the protocols set out in the OIE Manual of Standards or otherwise to provide facilities in the Region or elsewhere.
RECOMMENDATIONS

The meeting recommended that:

- Participants should disseminate information relevant to national CJD surveillance to the appropriate professional groups in their countries, particularly neurologists, neurophysiologists and epidemiologists, using established networks, such as neurological societies, and printed material.

- In each country, the health care professionals most likely to be in a position to diagnose cases of CJD should be contacted on at least an annual basis reminding them to report cases of definite or probable CJD.

- Each of the countries represented would identify a national focal point, most probably one of their delegates attending the workshop, who would be responsible for organising a national CJD surveillance meeting in their own county.

- The national focal point would collect data on the number of probable and definite cases of CJD in their country and forward this (even if zero) on an annual basis to WHO.

- WHO will financially support the national workshops and help provide training material.

- WHO, through its CJD collaborating centres, will provide short periods of training in diagnostic techniques, including neuropathology, molecular genetics and the emerging CSF assays, for key personnel.

- The usefulness of the retro-orbital post-mortem cerebral biopsy will be ascertained by assessing its use in a number of suspect CJD autopsies performed in WHO collaborating centres and the Prasat Neurological Hospital and Institute in Thailand. The results of this study will be published.

- WHO, through its collaborating centres, will make slides available to interested pathologists of various forms of CJD, using both conventional and immunocytochemical stains.

- Workshops should be set up to enable the OIE Code recommendations on BSE to be implemented. Training at the bench should be included.
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