Report of a WHO Consultation on Clinical and Neuropathological Characteristics of the New Variant of CJD and other Human and Animal Transmissible Spongiform Encephalopathies

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

Geneva, Switzerland
14 to 16 May 1996
Corrigendum

Page 6  Point 7.10  Tunisia

Replace the first sentence of the fourth paragraph with the following:

‘Of the five autopsies performed, consistent spongiosis was present in two; there was patchy vacuolation in two, and no significant spongiosis in one.’ . . .
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WORLD HEALTH ORGANIZATION
Division of Emerging and other Communicable Diseases Surveillance and Control
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1. INTRODUCTION

During a consultation on the newly reported variant of Creutzfeldt-Jakob disease (CJD) and other human and animal Transmissible Spongiform Encephalopathies (TSE), which was convened in Geneva from 14 to 16 May 1996, a group of international experts reviewed the clinical and neuropathological characteristics of these diseases. The consultation was opened by Dr. H. Nakajima, Director-General of WHO, who stressed the importance of the subject in view of the putative association of the emergence of the new variant of CJD with the satisfying of nutrition, an essential need of people.

This consultation was the second to be organized by WHO on TSE in 1996. The first was held on 2 and 3 April 1996 and issued conclusions and recommendations on certain cattle products and by-products in order to protect the health of the consumer.

As a follow-up to the April 1996 consultation, WHO decided to convene the present scientific meeting, the objectives of which were:

(a) to examine in detail the clinical, neurological and neuropathological findings associated with the new variant of CJD;

(b) to compare these findings to those in other TSE and further examine the putative relationship of human TSE to animal spongiform encephalopathies;

(c) to propose a protocol for diagnosis and surveillance of CJD and related diseases and promote international collaboration in surveillance activities;

(d) to review the tests developed for early TSE diagnosis and make recommendations on further research.

Dr. J. Gibbs was elected chairman and Drs. C. Weissmann and A.L. Taratuto were elected vice-chairpersons. Drs. K. Kenney, C. Keohane and J. Ironside were rapporteurs. The list of participants is attached as Annex 1.

2. NEUROPATHOLOGICAL ASPECTS OF THE NEW VARIANT OF CJD: EVIDENCE TO SUPPORT THAT IT IS A VARIANT

A new variant form of CJD, with a characteristic clinical and pathological phenotype, has been identified in the UK in a series of 10 young patients. The characteristic neuropathological features are:

- the presence of large numbers of kuru-type prion protein amyloid plaques surrounded by a halo of spongiform change in the cerebral cortex (particularly the occipital lobe); spongiform changes are most evident in the basal ganglia;

- thalamic gliosis;

- extensive deposition of prion protein (PrP) in all grey matter regions, particularly the cerebellum (including the molecular layer).

These cases share an early age at onset of symptoms, an unusual clinical course, with early psychiatric features and a prolonged duration of illness, all characteristics which had not been previously reported in the UK.

One similar case has recently been confirmed in France. Comparison of these cases with over 200 CJD cases in the UK Surveillance Project, with historical CJD cases in UK, and with CJD cases in other European surveillance projects, has failed to identify any similar cases in the past.

3. BOVINE SPONGIFORM ENCEPHALOPATHY (BSE) DISTRIBUTION AND UPDATE ON SOME TRANSMISSION STUDIES

The epidemic of BSE in the UK is progressively declining in response to the control measures being taken. Other countries with indigenous cases of BSE are Ireland (126 cases), Switzerland (210), France (18) and Portugal (35). Seven species of captive wild Bovidae and 18 animals in all have succumbed to SE probably via the same feed source as cattle. Domestic cats (71), puma (3), ocelot (2) and cheetah (4) have developed feline SE. The wild cats were probably infected after consuming
BSE-infected tissues from the central nervous system of cattle. BSE has been transmitted to cattle, sheep, goats, pigs, marmosets, mink, mice and squirrel monkeys by parenteral inoculation. Unsuccessful attempts have been made to transmit BSE to hamsters and chickens.

Experimental oral transmission has been attempted in all the above species except marmosets; it has been successful except in the case of pigs. In all these species incubation periods were longer than after parenteral challenge, despite the use of much larger doses. Pigs remain healthy for nearly 6 years post-challenge, and tissues from a 2 year interim kill which did not show clinical or pathological evidence of SE, did not transmit BSE to mice. The BSE agent is different from any known strains of historical or contemporary scrapie and retains its biological characteristics following natural or experimental passage through six species, despite differences in PrP gene sequences. The BSE agent sampled from nine different cattle sources are biologically identical. The only tissues from confirmed cases of BSE that have shown infectivity are the brain, retina, cervical and terminal spinal cord, and, in experiments involving orally challenged cattle, the distal ileum, which consistently carry infectivity during the incubation period of the disease from 6-18 months after the oral challenge. No infectivity has been found in muscle (meat), milk, mammary gland, placenta, bone marrow or peripheral nerve from clinical cases and over 40 other tissues obtained from clinical cases.

A total of nine different studies (6 experimental and 3 epidemiological) have examined the possibility of maternal transmission. The conclusions to date are that maternal transmission cannot be excluded but that, if it is occurring, it is at a level so low as to be undetectable.

An attack rate study in cattle has revealed that 1 gram of BSE-infected cow brain is sufficient to cause BSE in the cow by the oral route. A comparative bioassay in cattle and mice provisionally shows that the infectivity titre of cow brain tissue measured in mice is 100 to 1000 times lower than that measured in cattle. Spleen and lymph node pools have not transmitted BSE to mice, and cows inoculated with such pools remain alive for twice the incubation period of those inoculated with a 1/10 dilution of brain tissue.

4. IMMUNOCYTOCHEMICAL DETECTION OF PRION PROTEIN IN CJD

Sporadic CJD has been confirmed in 179 cases by immunocytochemical detection of prion protein (PrP) with both monoclonal and polyclonal antibodies on paraffin sections of various brain regions pretreated by hydrated autoclaving. PrP deposition patterns include fine granular labeling of synaptic type (in about 90% of cerebral and cerebellar cortical specimens), patchy/perivascular deposits (mostly in cerebrum ~38%) and plaque deposits (mostly in cerebellum ~25%). Types of deposition and amount of immunoreactive PrP vary between cases but remain relatively constant between different regions of the individual brain. The brain stem is only involved infrequently (21% with PrP deposits). It is concluded that PrP immunocytochemistry is a very reliable diagnostic tool and detects a limited range of characteristic types of PrP deposition that has a relatively uniform distribution in the individual brain. Presence of Alzheimer-type brain amyloid may modify PrP deposition.

5. PHYLOGENETIC ANALYSIS OF PRION GENES

A study of the prion protein from the perspective of evolutionary theory, has attempted to identify major trends in the evolution of the prion protein by means of a comparative analysis of healthy prion genes. Genetic differences among species, as well as genetic polymorphisms within species, may prove valuable in understanding the nature of the species barrier, and the more likely routes of transmission of the TSE.

6. CSF PROTEIN MARKER DETECTION TEST

A recently developed simple and rapid test using cerebrospinal fluid (CSF) should prove a useful aid in confirming the clinical diagnosis of spongiform encephalopathy in humans or animals. To date, the test has shown high sensitivity and specificity, and further validation
studies are in progress. Studies are underway to assess the test's reliability in BSE-affected cattle and in patients with the newly recognized variant form of CJD, and to clarify the association of proteins with these diseases.

7. NATIONAL REPORTS ON CJD AND RELATED DISORDERS

7.1 Argentina and other Latin American countries

Relatively few cases of CJD have been reported from Argentina since the first case was recognized in 1945, with a total of 9 cases by 1979. Since 1980, a national referral centre of the Institute of Neurological Research in Buenos Aires has confirmed CJD from brain biopsies and/or autopsies. The first ten cases were published in 1989 and by 1996 eight new CJD biopsies had been studied. Of the 18 patients with clinical probable or possible CJD seen during 1980-1996, 14 were examined by means of biopsy alone, 3 by autopsy alone and 1 by both biopsy and autopsy. There were 10 males and 8 females. Age at onset was 39 to 74 years, with a mean of 54 years. The total duration of disease was 3.5 to 24 months (mean 8.1 months). The neurological onset was gradual (weeks or months) in 16 cases and rapid or sudden (days), with a stroke-like episode, in two. At onset, behavioural abnormalities and/or mental deterioration were only observed in 8 cases, while neurological symptoms dominated in 10 cases. Clinical progression with a triad of dementia, myoclonus and periodic EEG was already present at the time of biopsy in 13 of the 18 patients. These 13 patients were all probable cases. Brain biopsies and/or autopsies showed spongiform changes, astroglial hyperplasia and variable neuronal depletion in the deep cortical layers, the cerebellar cortex or the subcortical grey matter.

During the last 16 years, 12 other neuropathologically confirmed cases with an age range similar to that of the previous series (one had a dura mater transplant) have been studied in other institutions in Argentina; this results in a total of 30 cases for the period 1980-1996. According to the 1991 census, the population of Argentina is about 32 million.

Cases of Gerstmann-Sträussler-Scheinker disease (GSS) or fatal familial insomnia (FFI) have not been reported. No atypical cases similar to the new variant of CJD reported in the UK and France, have been reported. Surveillance of BSE has been established and scrapie and BSE have not been reported. There is no official surveillance of CJD in Argentina where, despite awareness and recognition of CJD, accurate incidence/average annual mortality cannot be established without closer surveillance and neuropathological studies. A questionnaire was sent from Buenos Aires in May 1996 to neuropathologists in Brazil, Chile, Mexico, Uruguay and Venezuela. The answers were as follows:

Brazil: There is no surveillance of CJD. One or two cases have been reported in each region of the country in the last 5 years. One institute diagnosed 15 CJD cases by autopsy and 1 case through biopsy during the period 1974 to May 1996. There has been no increase in the number of classical CJD cases, and no case of the atypical variant form of Creutzfeldt-Jakob Disease has been reported. One familial case was reported in Sao Paulo.

Chile: Chile has well-documented CJD cases. Between 1964 and 1986, 69 cases have been reported (the sex distribution was 38 females to 31 males). 78.3% of the cases were sporadic and 21.7% of familial origin; the mean age at death was 55.4 years, (23-75 years) and the mean duration of the clinical period was about 7 months (1.5 - 41 months). In the last 10 years, 22 neuropathologically-verified cases and 25 probable cases have been reported to one hospital.

Mexico: There is no surveillance of CJD. Most of the probable or possible cases are not submitted to neuropathological examination. Four biopsies and one autopsy of sporadic CJD have been reported by one institute. Apparently there is no increase in incidence. No documented cases of GSS or FFI were reported. There is surveillance for BSE and scrapie in place but no cases have been reported.

Uruguay: There is no surveillance of CJD. Four autopsies of sporadic CJD and 2 biopsies on siblings with GSS have been performed in one institute. There is no evident increase in
incidence. No atypical CJD cases have been reported.

Venezuela: There is no surveillance of CJD. One institute reported having practiced 5 autopsies and 2 biopsies. There are possible and probable cases which are not submitted to biopsy or autopsy confirmation. GSS has not been reported. No atypical CJD cases have been reported.

7.2 Australia and New Zealand

An active surveillance programme is now in place in Australia. The incidence of CJD is at the level of 1 case per million each year. The demographic profile of cases is similar to that of previously reported studies in Europe and North America. An atypical cluster of cases related to exposure to gonadotrophins of human pituitary origin has been identified. Other forms of iatrogenic CJD have also been recognized, as have most genetic forms (GSS, FFI, etc.).

To date, no cases fulfilling all criteria for the newly described variant form of CJD have been reported, although cases with some of the criteria of the case-definition of the new variant form of CJD such as lack of EEG changes and abundant PrP deposits have been observed.

The absence of BSE and scrapie in Australia and New Zealand makes the epidemiological surveillance of CJD an important source of information for assessing the zoonotic risk of these diseases.

7.3 Austria

Between 1969 and 1995 the diagnosis of CJD has been confirmed by autopsy or biopsy in 80 Austrian patients. The annual incidence has significantly increased in recent years (average per million: 0.18 in 1969-1985; 0.67 in 1986-1994; and 1.25 in 1995). In addition, the percentage of CJD patients over 70 years at death increased significantly until 1989 but has declined thereafter. There is no regional clustering, familial occurrence or recognized iatrogenic risk. The ages at death are symmetrically distributed around a median of 64 years. The median duration of disease is 4 months. Most patients (76%) died within 6 months of onset. Retrospectively, 86% of patients fulfilled clinical criteria of probable or possible CJD. Neuropathology demonstrated in most cases the classical triad of spongiform change, astrogliosis, and neuronal loss. Two cases did not show unequivocal tissue alterations but immunocytochemistry detected PrP deposits in these cases also. The recent rise in incidence of CJD in Austria most likely reflects increased awareness and diagnosis of CJD rather than a real increase in incidence. BSE has not been reported in Austria.

7.4 Germany

Systematic surveillance of CJD in Germany started in June 1993. Following the criteria of the EU Surveillance Group, 63 probable and definite cases were recorded in 1994 (incidence 0.77 per million), 64 cases in 1995 (incidence 0.78). The incidence rates are calculated on the basis of a population of 82 million. These rates are well within the limits observed in other European countries. Geographical clustering has not been observed.

Autopsy rates among possible and probable cases are close to 70%. The clinical and neuropathological features of the new variant form of CJD have not been observed in Germany.

The open reading frame of the PrP gene is investigated in almost all of the probable and definite CJD cases using the SSCP (single-stranded conformational polymorphism) technique. Seven hereditary cases with various mutations in the PrP gene, including two families with fatal familial insomnia (FFI), have been identified. Until then only three families had a known history of familial dementia.

A case control study involving more than 150 cases of CJD and 150 controls has not indicated occupational or other risk factors. Statistical analysis of a larger number of cases will be necessary to elucidate the role of risk factors.

All four BSE cases reported from Germany concerned cattle which had been imported from the United Kingdom. BSE in native cattle has not been reported.
7.5 India

No cases of the new variant form of CJD have been detected or reported in India. Cases reported from India in 1990 totalled 30 (20 definite and 10 probable). The definite cases have been confirmed through autopsy (13) or cortical brain biopsy (7). From the Bombay region about 15 cases were detected over a period of 20-25 years. Of these, 6 were proven at autopsy, including 2 vegetarians and 4 "non-vegetarians". These 6 cases have been studied neuropathologically by light and electron-microscopy. The main morphological features in 5 of these cases with classical CJD, with an average duration of neurological symptoms of 2-8 months, were spongiform changes, loss of neurons, astrocyte proliferation and absence of inflammatory reaction. Fine structural examination showed in all cases an increase of membrane profiles, forming "cysts" and "daughter-cysts". These membranes appeared proteinous, with many RER cisterns in close proximity. No virion could be seen. One case with a neurological history of 36 months and cerebellar signs showed, in addition, plaques with glyco-proteinous material in their centre. This case therefore resembled GSS. There is no definite evidence that scrapie occurs in sheep in Western India.

7.6 Ireland

From death certificate information there have been 17 deaths from CJD since 1980. Two of these occurred before the age of 48. None has been familial. Neuropathological data are available in seven cases. It is not yet clear whether these are all included in the 17 cases death-certified CJD. There have been no genetic or transmission studies on these cases. Ireland has a population of just under 4 million.

Since the first report in 1989, 126 cases of BSE have been confirmed in Ireland. Approximately one third were in animals imported from the UK. Bone meal feed may account for the remainder. The annual incidence has been steady and averages 17 cases per year.

7.7 Japan

The incidence of CJD in Japan has been analysed on the basis of death certificates since 1979. From 1987 through 1990 the incidence was 216 cases among subjects aged 15 or over from a population of 97.3 million people. No case of the new variant of CJD has so far been reported from Japan. A research group for national surveillance on CJD and related diseases in 1996, sponsored by the Ministry of Health and Welfare has been established. Some of the details are as follows:

- approximately 3,400 hospitals with psychiatric and/or neurological facilities will participate in the surveillance;
- the participating hospitals will submit the reports on the cases diagnosed as CJD, GSS, and other atypical dementia, or suspect cases, between January 1985 and May 1996;
- pathological and genetic investigation will be performed, if specimens are available;
- the results will be reported by March 1997;
- the research proposal will be fixed in May 1996.

Although BSE has not been reported in Japan, a surveillance system for BSE and scrapie has been established since 17 March 1996.

7.8 Senegal and sub-Saharan Africa

CJD and related disorders are exceptional in sub-Saharan Africa. Only one case of CJD has been reported and confirmed histologically from Dakar, Senegal, since 1976. In Senegal many factors exist for the potential establishment of a transmissible spongiform encephalopathy:

- neurosurgical interventions including dural-matter grafts;
- the fact that disposable material is not used for biopsies and lumbar taps;
- the use of over 20 drugs containing material of bovine origin used for antianemic and antiasthenic purposes, which have only been withdrawn since 1992;
- the existence of about two million sheep and goats and about one million head of cattle;

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the introduction of meat originating from countries where transmissible spongiform encephalopathies of sheep and bovines may exist.

The very low recorded incidence of CJD and similar diseases in Senegal can mainly be explained by:

- the absence of a policy for the surveillance of these diseases;
- the low level of attendance for qualified medical treatment in the population, many of whom consult traditional practitioners;
- the small number of specialists, with less than two neurologists per million inhabitants and only one neurological department in the capital city;
- the relative under-representation of the age groups at risk in the general population, where the over-60s represent only 3% of the total and where life expectancy at birth lies between 46 and 48 years.

In addition, no case of scrapie or of bovine encephalopahathy has been recorded in sub-Saharan Africa. Only a surveillance and control policy directed towards CJD and related disorders will help elucidate the real incidence in sub-Saharan Africa.

7.9 Thailand

Up to now, there have been no official statistics of CJD in Thailand. However, it has been estimated from data accumulated in three university hospitals that no more than 25 cases occurred during the last 20 years. All of these cases were similar to classical sporadic cases reported elsewhere in terms of age at onset, clinical presentation, EEG changes and duration of illness. Unfortunately, definite diagnosis (autopsy with classical neuropathological features) could be reached only in approximately a quarter of these cases. There was no report of familial or iatrogenic CJD cases. Interestingly, the first case diagnosed in Thailand was a man who regularly ate pig brain. However, our limited surveillance study afterwards showed no causal link between the consumption of pig brain and the development of CJD.

Since the outbreak has only recently emerged, a systematic and well organized study on classical CJD as well as newly described CJD variant is warranted.

7.10 Tunisia

CJD seems to be rare and sporadic in Tunisia, if we exclude the high incidence reported in Israel among Jewish immigrants of Tunisian origin. The population of Tunisia is 9 million inhabitants.

The first suspected case observed in 1980 was in a young man, 32 years of age, with rapid onset of dementia, extrapyramidal and pyramidal signs, myoclonus, epilepsy and severe agitation but no case confirmation could be made. Since that time ten other patients were recognized clinically as having CJD.

The first clinical manifestations were ataxia (50%), confusion, visual hallucinations and dementia. The mean age of onset was 57 years (range 32-75). The clinical presentation showed some variation in the severity of evolution and degree of neurological signs. Dementia (or confusion), myoclonus, extrapyramidal and pyramidal signs, were present in 10 cases, tonic seizures in four. The EEG showed a periodic pattern in 5 cases. The CSF was normal in all cases and the CT scan showed no major abnormalities.

Consistent spongiosis was present in 2 of the 5 autopsies performed, and a patchy vacuolation in the 2 others; there was no significant spongiosis. Loss of neurones and astrogliosis occurred in all cases. Thalamus, striatum, occipital lobes were the most affected regions. No inflammation or senile plaques were seen. Molecular biology and immunostaining were not carried out.

Considering the difficulty of diagnosis for general practitioners, even for neurologists or psychiatrists, the incidence of CJD is underestimated. In addition an autopsy is not always possible. Surveillance of CJD and a CJD register should be established. Collaboration
should be established with the veterinary authorities to study the epidemiology of scrapie and the putative relationship between CJD and animal spongiform encephalopathies in Tunisia.

8. CONCLUSIONS AND RECOMMENDATIONS

8.1 Clinical and neuropathological criteria for the diagnosis of clinical CJD and other human TSE

CJD classically occurs as a rare disorder worldwide (estimated worldwide incidence one case per million population per year) in adults (approximate average age 64 years) with rapidly progressive dementia, myoclonus, ataxia, and a characteristic EEG with a triphasic wave pattern. A broad spectrum of clinical features is recognized in this disorder, and patterns of onset may vary from case to case. The duration of illness is around 5 months on average, but cases with a prolonged clinical history have been encountered in many countries. The neuropathological features of CJD include spongiform change, neuronal loss and astrocytosis, with amyloid plaques in a minority of cases; neuropathology at present provides the only means of establishing a diagnosis of CJD. Most cases of CJD occur sporadically, but familial and iatrogenic cases are also recognized.

(a) Clinical diagnostic criteria

The following diagnostic criteria should be utilised:

Definite CJD is diagnosed by standard neuropathological techniques and/or, in reference laboratories, by additional methods [PrP immunocytochemistry, Western blot and/or preparation of scrapie-associated fibrils (SAF)].

Probable or possible CJD is diagnosed according to the following scheme:

Sporadic CJD

A probable CJD case shows:

- progressive dementia;
- typical EEG - Approximately 70% of cases of CJD exhibit the typical EEG pattern which consists of generalized triphasic periodic complexes occurring at a frequency of approximately one per second. There is, however, variation in the duration of the periodic complexes and the proportion of any record with such suggestive appearances.

At least two out of the following clinical features must be met:

- myoclonus;
- visual or cerebellar disturbance (ataxia);
- pyramidal/extrapyramidal dysfunction;
- akinetic mutism.

A possible CJD case shows:

- Same clinical criteria as probable CJD but no EEG available or without a typical EEG (as described above) and a duration of illness of less than two years.

Accidentally transmitted CJD

- progressive cerebellar syndrome in a pituitary hormone recipient;
- sporadic CJD with a recognized exposure risk (e.g. dura mater transplant).

Familial CJD

- definite or probable CJD plus definite or probable CJD in a first degree relative;
- neuropsychiatric disorder plus disease-specific PrP gene (PRNP) mutation.

(b) Neuropathological diagnostic criteria

The definite diagnosis of (CJD) and other human transmissible spongiform encephalopathies requires neuropathological confirmation on brain at autopsy or, in carefully selected cases, cerebral biopsy. This is of paramount importance in view of the steadily growing spectrum of clinical and pathological phenotypes. The many historically described CJD variants with different names have been
shown to be parts of this spectrum. The considerable morphological variation may be influenced by length of the disease, by the PrP genotype, and by as yet unidentified factors including strains of the infectious agent.

Extensive sampling from various brain areas (at least the frontal, temporal, and occipital lobes, from the basal ganglia, and from the cerebellum) is mandatory in every autopsy of suspected spongiform encephalopathy. The comparison of cerebral and cerebellar involvement is especially important.

When handling tissues and other materials from suspected CJD, specific safety precautions are mandatory to avoid accidental transmission and to eliminate any infectivity.12

Neuropathological diagnostic criteria for CJD and other human transmissible spongiform encephalopathies are summarised as follows:

**CJD - sporadic, iatrogenic (recognized risk) or familial (same disease in first degree relative):**

- Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter; and/or
- Encephalopathy with PrP immunoreactivity (plaque and/or diffuse synaptic and/or patchy/perivascular types).

**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.

**Familial fatal insomnia (FFI)** (in member of a family with PrP178 mutation):

- Thalamic degeneration, variable spongiform change in cerebrum.

**Kuru** (in the Fore population of Papua New Guinea):

- While most neurological features correspond to those of CJD with plaques, it should be diagnosed only in members of the Fore population in Papua New Guinea.

In the absence of PrP immunocytochemistry the crucial feature is the spongiform change accompanied by neuronal loss and gliosis. This spongiform change is characterised by diffuse or focally clustered small round or oval vacuoles in the neuropil of the deep cortical layers, cerebellar cortex or subcortical grey matter, which may become confluent. Spongiform change (status spongiosus) should not be confused with non-specific spongiosis. Status spongiosus comprises irregular cavities in gliotic neuropil following extensive neuronal loss (including also lesions of "burnt-out" CJD), "spongy" changes in brain oedema and metabolic encephalopathies, and artefacts such as superficial cortical, perineuronal, or perivascular vacuolation disease. Focal changes indistinguishable from spongiform change may occur in some cases of Alzheimer's and diffuse Lewy body disease.

Recently, immunocytochemistry for PrP has been added to classical histological techniques and has rapidly evolved into a most useful diagnostic tool (see section 4). However, it is at present a rather delicate procedure that should be used for diagnostic purposes only by an experienced laboratory. In CJD, immunoreactivity for PrP is seen mainly in three patterns which frequently overlap: plaque, diffuse synaptic and patchy/perivascular types.

Very rare cases might not be diagnosed by the criteria outlined above. Confirmation must then be sought by additional techniques such as immunoblotting, preparations for electron microscopic examination of scrapie associated fibrils (SAF), molecular biologic studies, or experimental transmission.

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2 Committee on Health Care Issues, American Neurological Association, Precautions in handling tissues, fluids and other contaminated materials from patients with documented or suspected CJD, Annals of Neurology, Vol.19 No.1.
8.2 Clinical and neuropathological criteria for the diagnosis of the newly recognized variant of CJD

Eleven patients have recently been identified in the UK and one in France with a newly recognized variant form of CJD; 9 of these 12 patients have since died. All patients were aged 41 years or less at death.

The following clinical features are characteristic:

- a psychiatric presentation with anxiety, depression, withdrawal and other behavioural changes with progression to neurological abnormalities;
- onset of a progressive cerebellar syndrome within weeks or months of presentation;
- forgetfulness and other memory impairment, with dementia in the late stages;
- myoclonus or chorea in the late stages;
- the EEG does not show the changes normally observed in classical CJD.

Less common features include early onset of dysaesthesia in limbs and face at presentation, and extrapyramidal and pyramidal signs later in the illness.

The diagnosis of the newly recognized variant form of CJD can only be made on neuropathological examination, which is mandatory for confirmation of suspected clinical cases. The neuropathological diagnostic criteria are:

- abundant kuru-type amyloid plaques surrounded by vacuoles (clearly visible in H&E and PAS stains);
- spongiform change most prominent in the basal ganglia;
- marked thalamic astrocytosis;
- abundant PrP deposits on immuno-

cytochemistry, including prominent "pericellular" deposition in cerebral and cerebellar cortex (especially in the molecular layer).

Genetic analysis is required in every suspected case to exclude familial CJD; patients should have no history of exposure to human pituitary-derived products or any other source of iatrogenic CJD.

The present meeting considered that this recently described disorder is part of the CJD spectrum; it is a new variant form of CJD on grounds of its unique clinical and pathological features. BSE has been transmitted naturally and experimentally to a range of other animal species by the oral route, and it has been suggested that the emergent cluster of the new variant form of CJD may be a consequence of exposure of the human population to the BSE agent. It should be emphasised that such a link has not been proven.

After a thorough review of the characteristics of natural and experimental TSE, the consultation concluded that the type of lesions and the clinical presentation of the new variant form of CJD do not provide information on the possible origins of this disorder.

8.3 Surveillance of CJD and related disorders

The initiation of disease surveillance systems should help in establishing the geographic distribution of the newly described variant of CJD, and establishing the true incidence of CJD — all types and subtypes. It should also help to investigate the possible relationship of CJ to spongiform encephalopathies in animals and to establish epidemiological parameters and risk factors for CJD. It should finally provide the public with accurate information; this is especially important because of great public concern.

It is accepted that with any surveillance programme reported cases will increase. There are different ways of approaching surveillance, and methods depend on available resources. Mechanisms of surveillance can be active or passive and various methods are already in use in some countries (see section 7).
(a) Mechanisms for data collection

All methods of disease surveillance have advantages and disadvantages, and it was agreed that for maximum comparability of data, a single method of surveillance should be promoted by WHO. After obtaining permission from the EU and making any necessary modifications, the questionnaire-based method elaborated by the EU for CJD Surveillance should be used by WHO to develop a standard protocol for global surveillance of CJD and its variants. In a given country, this protocol should be made available to health institutions for further adaptation to prevalent conditions. The adapted protocol should then be used by targets groups for the identification of suspect (possible and probable) cases.

The following mechanisms for data collection should be used:

- reports with individual examination of each case from the specific groups involved in surveillance, e.g., neurologists, neuropathologists and health care workers especially those involved in the surveillance of flaccid paralysis within the framework of the poliomyelitis eradication programme;
- specialized referral centres for screening and reviewing individual cases referred to by target groups;
- central registration via death certification and postal register surveillance.

The questionnaire developed by the EU surveillance project comprises four sections (A, B, F and R); A and R are further divided into subsections (A1 to 10, R1 to R9). A list of titles of the sections and subsections is attached as Annex 2. Section A of the EU questionnaire (including for 'cases only' data on clinical presentation, further investigations including EEG, neuropathological and genetic tests) could be used after adaptation to the techniques usually available in the targeted regions and countries. In section R, subsections R7 to R9 dealing with identification of risk factors by interviewing cases and controls on their occupation, diet and animal contacts, should be simplified and used only within the context of special research projects. The person completing the questionnaire will differ in each country, but it was considered that the final WHO questionnaire should be applicable to any country. When reporting to WHO, each country should specify the mechanisms of data collection used.

Central registration via death certification and postal register surveillance or country-wide investigation via neurologists and neuropathologists could be used where appropriate and feasible. All centres may not be able to complete all aspects of the surveillance. If they do not have resources at the outset, they could concentrate on identifying cases of the newly-described variant of CJD, which are likely to occur in younger subjects.

(b) International collaboration

There is a need to plan international collaborative studies, including appropriate controls to identify possible risk factors in the newly described variant of CJD. Collaboration has already started and should continue between various institutions and the UK. Suspected cases should initially be checked with the CJD Surveillance Unit in Edinburgh.

WHO should further expand and coordinate international collaboration, including surveillance, through its Division of Emerging and other Communicable Diseases Surveillance and Control (EMC). WHO should identify specific reference centres, with due regard to geographic balance, where various specific aspects of collaboration and standardization could be undertaken: EEG interpretation, immunostaining, genetic analysis, CSF tests, epidemiology, transmission experiments, etc. EMC, in collaboration with the Neurosciences unit of the Division of Mental Health and Substance Abuse (MSA) should assist in this by facilitating the transfer of material and personnel to reference centres, and in training as appropriate.

TSE should be further investigated in other species, and WHO should facilitate international collaboration in these studies with OIE, FAO, EU, and other international bodies dealing with veterinary medicine and veterinary public health.
(c) Handling of information

Because of the great media interest in these diseases, and the sensitive nature of the cases, it is essential that the incoming data be handled carefully.

Initially, at least 3-monthly reports of diagnosed cases should be released, with publication of any additional cases of the newly described variant form of CJD, as reported by a country, in the Weekly Epidemiological Record.

WHO should be informed as early as possible if any such cases occur. Because of media interest and economic consequences, participating key figures in each country should be alerted so that they are able to deal accurately with media interest and further disseminate the information within their own country.

8.4 Evaluation of ongoing research and definition of future research needs

The group reviewed current TSE research and recommended this be continued and extended as indicated below for the following six categories: basic science, transmission studies, diagnostic methods, biosafety studies, genetic studies and treatment methods.

(a) Basic science

Because the precise nature of the causative agent and the mechanism of development of disease are not yet known, further basic science research is essential. The studies should include the following:

- clarification of the nature of the agent;
- determination of the function of PrP;
- determination of the mechanism of pathogenic PrP production;
- pathogenesis.

(b) Transmission studies

There is a need to seek evidence for the natural transmission of spongiform encephalopathies of animals to man in order to determine the distribution of BSE infectivity in tissues and derived products from infected cattle that enter the human food or animal feed chain during the incubation period. It is also necessary to expand current studies on the CJD infectivity of human non-CNS tissues such as those used for transplantation and, in particular, blood and blood products (although there is no proven risk of CJD transmission from these sources).

To this end, the following studies are recommended:

- neuropathological and epidemiological surveillance of human and animal TSE worldwide;
- transmission of the agent of the newly described variant form of CJD in the UK and France (V-CJD), as well as agents of all other distinct human TSE (Kuru, GSS and FFI) and previously described CJD variants into:
  - conventional inbred strains of mice for strain-typing by lesion profile/incubation time bioassay (work on this is already in progress);
  - PrP-null transgenic mice carrying multicoopies of the human PrP gene to determine if this assay can distinguish agent strains and, if so, if the system is quicker for strain typing than using conventional inbred strain of mice; and
  - cattle.
- Inoculation, although this is of lower priority, of brain tissue from the various human variants of spongiform encephalopathies into non-human primates for comparative purposes.
- Although there is no evidence of infectivity (using the mouse bioassay) in tissues from cattle infected with the BSE agent, other than the CNS and distal ileum, transmission studies are recommended using tissues and derived products from BSE-infected cattle into:
  - PrP-null transgenic mice carrying multiple copies of the bovine PrP gene;
• cattle (testing infectivity of products and
tissues such as milk, muscle, gelatin);

(The purpose of these two types of
transmission studies is to improve
sensitivity by eliminating the species
barrier.)

• non-human primates (CNS tissues only
by the oral and intra cerebral routes).

• Transmission of scrapie (from sheep and
goats in the UK and other countries with
and without BSE) to:

• non-human primates (by the oral and
intra cerebral routes) as a control for
the study above involving the BSE
agent.

• Studies of distribution of infectivity within
various tissues of TSE-affected animals at
different times of the illness (preclinical,
early and late clinical stages) by:

• expanding the pathogenesis studies in
BSE-infected cattle already in progress
or near completion, should any
infectivity be found in cattle tissues
other than the CNS and distal ileum;

• considering re-evaluating the
distribution of tissue infectivity of the
scrapie agent in sheep with newer
methods (e.g. the use of transgenic
mice).

• Studies to further investigate horizontal
and vertical (maternal) transmission of
BSE in cattle.

• Studies to determine the tissue distribution
of infectivity for CJD and other human
TSE using PrP-null transgenic mice
carrying multiple copies of the human PrP
gene (from whole blood, buffy coat and
plasma).

• Consideration should be given to
convening a future WHO meeting
regarding the infectivity of human non-
CNS tissues of CJD patients such as the
tissues used for transplantation, in
particular blood and blood products. The
pathogenesis of CJD may differ with the
route of exposure and strain of agent.

(c) Diagnostic methods

A recent investigation on CSF marker proteins
(see section 6) appears to provide potential for
a sensitive in vivo test for CJD and related
disorders. However, further studies on cases of
CJD, other neurological disorders and control
cases are required to establish the diagnostic
value of this test in human and animal TSE.

The group recommended:

• The development of rapid, reliable tests
with high sensitivity and specificity,
particularly in the early or pre-clinical
stages of illness, from easily obtained
sources (e.g. body fluids). These are
desperately needed to diagnose both human
and animal TSE.

• The start of further validation studies for
existing diagnostic tests, as well as for those
currently under development.

(d) Biosafety studies

Further studies should be performed on current
physicochemical protocols, alone and in various
combinations, and new protocols toward the
complete inactivation of infectivity from:

• contaminated surgical instruments,
equipment and accommodation;

• animal products and animal waste, using
the most sensitive methods now available
(e.g. the use of transgenic mice).

Research should be considered to examine any
risks that may arise during conventional
slaughter of TSE-infected but clinically healthy
animals in abattoirs.

Investigations of the complete pathway of all
tissues from food animals should be carried out
to determine their fate, whether they are used in
food, feed, medicinal products and devices, or
in other products.
(e) Genetic studies

The studies outlined below should be carried out:

- extension of the molecular genetic studies of the PrP gene (and other genes possibly associated with TSE) in humans and animals, especially cattle and sheep;
- the extent of polymorphisms in the PrP gene of humans and animals, in order to identify genetic associations between distantly related species (in progress).

(f) Treatment methods

There is an urgent need to develop a strategy for the prevention and treatment of human TSE based on genetic, biological and chemical approaches. It is noted that some preventive strategies for some animal TSE are already in place.

(g) Use of in-vitro tests and animals for research

It is strongly recommended that every effort be made to develop in-vitro tests for diagnosis and research, and that studies requiring the use of laboratory and other animals should involve the smallest number of animals possible.

8.5 Proposed WHO monograph on TSE

There is already a wealth of scientific literature and books available on the current state of knowledge on TSE. However, the publication by WHO of a short monograph on human and animal TSE for both practising medical and veterinary officers would be extremely useful within the framework of the surveillance system.

9. CONCLUDING REMARKS

Dr H. Nakajima closed the meeting by thanking all participants for their outstanding scientific contribution to the consultation and for the very productive and exemplary collaboration between the different domains of expertise involved, for example, clinical neurology, neuropathology and veterinary pathology and epidemiology. He expressed the willingness of WHO to continue to provide a forum for discussions on this and other subjects requiring the sharing of experience and knowledge from both the human and animal health sectors.

10. ACKNOWLEDGEMENTS

In its discussions and preparation of this report, the group took into consideration: (a) Consensus Report on Neuropathological Diagnostic Criteria for CJD and other Human Spongiform Encephalopathies by H. Budka et al, Brain Pathology, 5: 459-466 (1995), (b) Surveillance of prion diseases in humans by R. Will in method in molecular medicine: Prion diseases, edited by H. Baker & R.M. Ridley, Humana Press, Inc. Totawa, New Jersey, pp. 119-137 (1996) and (c) Questionnaire for the surveillance and clinical criteria for the diagnosis of CJD and related disorders prepared by the participants in the EU supported Biomed 1 concerted action for "CJD surveillance in the EU".
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### EUROPEAN UNION QUESTIONNAIRE FOR CJD SURVEILLANCE IN EUROPE

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