DEPARTMENT OF HEALTH

From the Chief Medical Officer

Sir Kenneth Calman
KCB MD FRCS FRSE

Richmond House
79 Whitehall
London SW1A 2NS

PL CMO (96)5

New Variant of Creutzfeldt-Jakob Disease (CJD)

For Information
- All Doctors

1 July 1996

Dear Doctor

NEW VARIANT OF CREUTZFELDT-JAKOB DISEASE (CJD)

The purpose of this letter is to provide you with information about the new variant of CJD and with advice to help you respond to queries that patients may have following the announcements by the Secretary of State on 20 and 25 March. You should already have received brief communications from me on those dates, referring to ten cases of a newly recognised variant of CJD described by the CJD Surveillance Unit.

GRO-C

Sir Kenneth Calman
Chief Medical Officer

1. **CJD**

Creutzfeldt-Jakob Disease (CJD) is a rare neurological disease, first described in the 1920s and found worldwide. It usually presents in late middle-age (average age 63 years) with progressive dementia, and is usually fatal within 6 months. It is characterised by spongiform changes in the brain, but this can only readily be diagnosed at post-mortem. The agent of this and related transmissible spongiform encephalopathy (TSE) diseases in animals, such as Bovine Spongiform Encephalopathy (BSE) and scrapie, is believed to be a protein (the prion protein) which is highly resistant to physical and chemical inactivation. Associated nucleic acid has not yet been detected.

CJD occurs worldwide at an annual incidence rate of 0.5-1 per million population per annum. In view of concerns that BSE could possibly be transmissible to man, the CJD Surveillance Unit was set up in 1990 by the Department of Health and the Scottish Office Home & Health Department to monitor the incidence of disease in the UK. To date, the UK annual incidence remains within the worldwide range - in 1994 the incidence was 0.92 per million and the provisional figure for 1995 is 0.64 per million. Most cases in the UK and worldwide are sporadic; up to 15% may be familial, and in these rare cases a mutation in the prion protein gene can be identified.

The CJD Surveillance Unit analysis of cases includes detailed clinical and neuropathological investigation and full dietary, medicinal and occupational history. In addition, the Unit is carrying out a case control study, and has retrospectively analyzed cases presenting before 1990. The Unit's findings are published annually. Further details are provided in the Annex to this letter.

In March 1996, the CJD Surveillance Unit described a distinct variant of CJD in 10 cases, in people aged under 42, (average age 27 years) with dates of onset of illness in the last two years. The findings were published in the Lancet[1]. This variant has not been previously recognised and is characterised by behavioural change, ataxia, progressive cognitive impairment and a tendency to a prolonged duration of illness (up to 23 months). The EEG is not typical of classic sporadic CJD. Brain pathology shows marked spongiform change and extensive amyloid plaques throughout the brain. As with classic sporadic CJD, symptoms in the early stages may be fairly non-specific.

For further information
please contact
Dr Ailsa Wight
Room 510A, Skipton House
80 London Road
London SE1 6LW

Requests for further copies
should be addressed to:
Department of Health
Mailings
c/o Two-Ten Communications Ltd
Building 150
Thorp Arch Trading Estate
Wetherby, West Yorkshire
LS23 7EH
quoting code and serial number
appearing above.

For correction of any discrepancies in changes of address, practice or name,
please contact
The Medical Mailing Company
PO Box 60, Loughborough
Leicestershire LE11 0WP
Telephone Freephone 0800 626387

There is no predictive test for classical CJD or for the new variant (NVCJD). The definitive diagnosis can only be made by examination of brain material, typically on H and E staining, though newer techniques to detect the Prion protein (PrP) are increasingly being used. Other tests are currently under investigation and are likely to prove useful adjuncts to diagnosis.

The treatment for both classic CJD and NVCJD is palliative. There is no cure.

There is no reason for general practitioners to change their referral patterns to specialists in cases of dementia or ataxia because of NVCJD. However, all neurologists, including paediatric neurologists, have been advised of the new findings in detail by the CJD Surveillance Unit.

Total, sporadic and NVCJD figures will be published regularly in CMO's Update. Since the ten NVCJD cases were announced, a further case has been confirmed, bringing the total of NVCJD cases to eleven in the UK. Total CJD figures for the first quarter of 1996 do not show an increase compared with the same period in 1995.

The ten cases have been carefully assessed by independent experts in neurology, neuropathology and epidemiology, and do not appear to be explained by improved national ascertainment. Advice has also been sought from the Spongiform Encephalopathy Advisory Committee (SEAC) which is chaired by Professor J R Pattison and has a range of expertise (public health, medical, veterinary and scientific) and advises the Government on all matters relating to TSE diseases. Although there was and is no direct evidence of a link, SEAC's opinion was: "that in the absence of any credible alternative, the most likely explanation at present is that these cases are linked to exposure to BSE before the Specified Bovine Offal (SBO) ban was introduced in 1989". The SBO ban prohibits the use of those tissues (brain, spinal cord, thymus, tonsils, spleen and intestines) most likely to contain the infective agent of BSE in products for human consumption.

The statement announcing the cases, even though not conclusive about a link between CJD and BSE, has generated requests for advice on the safety of various products containing bovine material such as foodstuffs, medicines, pharmaceutical devices and cosmetics.

2. **Transmissibility of CJD**.

CJD has been transmitted experimentally, and iatrogenically in certain circumstances for example via contaminated human pituitary derived growth hormone or dura mater preparations.

It appears that the important factors in transmission of iatrogenic CJD are the source of the extraneous tissue (brain-derived tissues appear to present the highest risks) and the route of administration.

There is no epidemiological evidence that blood, blood products or whole organ transplants pose a risk of transmission. However, as a precautionary measure exclusion criteria for blood and organ donors are in place, and these are kept under regular review.

CJD is not transmitted from mother to child in pregnancy, or through breast milk. Data from the Kuru epidemic in Papua New Guinea demonstrate the absence of transmission by these routes.

Evidence from iatrogenic disease and from Kuru suggests that the incubation period may be very variable, the average being between 5 and 15 years. CJD does not behave like a conventional infectious disease and there is no risk of spread within families.

3. **Occupational exposure to BSE**

UK surveillance includes detailed occupational histories of cases referred to the CJD Surveillance Unit. Although four cases of classic sporadic CJD have been confirmed in farmers with cases of BSE on their farms, a similar excess of cases in farmers has been observed in countries where there is no BSE. Equally, an excess of CJD has been recorded in groups who have no apparent increased exposure to BSE, such as clergymen. No association has otherwise been demonstrated with any occupational group.

Since 1990, guidance has been issued to a range of occupational groups, including abattoir workers, farmers, veterinarians, zookeepers and laboratory workers by the Ministry of Agriculture Fisheries and Food (MAFF) and the Health and Safety Executive (HSE) in consultation with the professional sectors.

Guidance[2] was issued in 1994, primarily aimed at laboratory workers, on minimising risks when working with the agents of transmissible spongiform encephalopathies. All existing guidance is currently being reviewed and will be revised where necessary. The principles of the control measures previously recommended remain valid, for example the need for high standards of personal and occupational hygiene.

4. **Environmental risks from BSE.**

Since 1988, all definite and suspected cases of BSE in cattle have been slaughtered and incinerated. Specified bovine material (SBM)(see section 6) from all cattle is also sent for incineration. Meat and bone meal derived from rendering non-SBM from cattle less than 30 months old and for human consumption can be safely disposed of by landfill, as can incinerated bovine waste. Particulate matter from abattoir outflows should be trapped and treated as SBM. Liquid waste poses a negligible risk when disposed of by land spread. This reflects SEAC's opinion on these issues in the light of the NVCJD findings.

5. **Research**

The DH Director of Research and Development has been remitted by the Secretary of State for Health to lead a directed programme of R&D involving other funders, in relation to BSE/CJD. The R&D funders in this field are DH, Medical Research Council (MRC), MAFF, Biotechnology and Biological Sciences Research Council (BBSRC) and The Wellcome Trust.

A TSEs Funders Coordination Group, under the Chairmanship of Professor John Swales, has met three times and aims to ensure that the programmes of R&D in this field continue to address issues of national priority and constitute a coherent strategy when considered across all the funding bodies.
The DH and MRC have jointly set up a Research Advisory Group, to advise on research priorities and commissioning. They have recently issued a call for further R&D proposals that will contribute through basic or applied research to the key issues relevant to human health in this field. The Secretary of State for Health has announced that £4.5 million is being made available for applied R&D.

6. **Foodstuffs**

The measures in place since 1989, including recent strengthening of the controls on carcase handling (specifically, prohibition on the use of head meat, with the exception of the tongue, so that the head and SBOs now comprise SBM, and on the use of spinal column for mechanically recovered meat), should, properly enforced, ensure that any risk associated currently with eating beef or beef products (such as oxtail, soups, pies, stock cubes) is extremely small. The Government has as an extreme precautionary measure prohibited the sale of beef for human consumption from cattle over the age of 30 months.

No BSE infectivity has ever been found in milk from clinically affected cows. SEAC is satisfied that milk and dairy products can be safely consumed. This conclusion has been endorsed by the World Health Organisation.

This advice also applies to infants, children of school age and vulnerable groups such as the immunosuppressed, patients in hospital and pregnant women. If exposure to the BSE agent occurs, none of these groups is likely to have an increased susceptibility to infection.

Advice was sought on gelatin because it is used in a wide range of products. Gelatin is produced by acid hydrolysis from bovine bone, excluding the SBM, and there is no reason to suggest that its use in food, pharmaceuticals or medical devices poses a risk. Similarly, rendered fats (tallow, glycerol) in food, medicines or cosmetics do not present a risk.

7. **Pharmaceuticals**

On pharmaceutical products, you will be aware of the letter from the Deputy Chief Medical Officer which was sent to doctors on 19 April 1996. This made clear that: injectable products (including vaccines and biologicals) manufactured in the UK do not contain bovine material of UK origin; gelatin used in pharmaceuticals manufactured in the UK is sourced from non-UK bovine material and is safe; and for those medicines which contain tallow derivatives the rigorous processes of extraction and purification eliminate the causative agent of BSE and with it the risk.

This is consistent with European opinion published on 16 April 1996. The position has not changed since the DCMO's letter, and all pharmaceutical products containing materials of bovine origin are therefore considered to carry no risk.

8. **Medical Devices**

No bovine tissue or product used either in the manufacture or in the processing of medical devices (heart-valves, pericardial patches, gelatin and collagen coatings for vascular stents, surgical sutures) are sourced in the UK.

9. **Cosmetics**

Cosmetic companies observe the guidelines adopted in 1989 for the production of pharmaceuticals and medical devices, with respect to source materials. This means that products currently on the market can be used safely.

References

1. Lancet 1996; 347: 921-925.
2. "Precautions for Work with Human and Animal TSEs" HMSO 1994.

Year	Referrals	Deaths of Definite & Probable Cases					
		Sporadic	Iatrogenic	Familial	GSS	NVCJD	TOTAL
1985	-	26	1	1	0	-	28
1986	-	26	0	0	0	-	26
1987	-	23	0	0	1	-	24
1988	-	21	1	1	0	-	23
1989	-	28	2	1	0	-	31
1990	52*	26	5	0	0	-	31
1991	75	32	1	3	0	-	36
1992	96	44	2	4	1	-	51
1993	78	37	4	2	2	-	45
1994	115	53	1	2	3	-	59
1995	79	33	4	1	2	3	43
1996 end May	46	12	0	0	1	6	19

Plus 2 definite cases of NVCJD still alive
Total number confirmed cases NVCJD = 11

* The CJD Surveillance Unit was set up by the Department of Health and the Scottish Home and Health Department in May 1990

NOTES TO TABLE

Referrals: This is a simple count of all the cases which have been referred to the Unit for further investigation in the year in question. CJD may be no more than suspected; about half the cases referred in the past have turned out not to be CJD. Cases are notified to the Unit from a variety of sources including neurologists, neuropathologists, neurophysiologists, general physicians, psychiatrists, electroencephalogram (EEG) departments etc. As a safety net, death certificates coded under the specific rubrics 046.1 and 331.9 in the 9th ICD Revision are obtained from the Office for National Statistics in England and Wales, the General Register Office for Scotland and the General Register Office for Northern Ireland.

Deaths: These columns show the number of deaths which have occurred in definite and probable cases of CJD in the year shown. The figure includes both cases referred to the Unit for investigation while the patient was still alive and those where CJD was only discovered post mortem (including a few cases picked up by the Unit from death certificates). There is therefore no read across from these columns to the referrals column. The figures will be subject to retrospective adjustment as diagnoses are confirmed.

Definite and Probable: This refers to the diagnostic status of cases. In **definite** cases the diagnosis will have been pathologically confirmed, in most cases by post mortem examination of brain tissue (rarely it may be possible to establish a definite diagnosis by brain biopsy while the patient is still alive). **Probable** cases are those with a history of rapidly progressive dementia, typical EEG and at least two of the following clinical features; myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs or akinetic mutism. Some cases are never confirmed pathologically because a post mortem examination does not take place (for instance where the relatives of the patient refuse consent) and these cases remain permanently in the probable category.

Sporadic: Classic CJD cases with typical EEG and brain pathology. Sporadic cases appear to occur spontaneously with no identifiable cause and account for 85% of all cases.

Iatrogenic: Where infection with CJD appears to have occurred accidentally as the result of a medical procedure. Most of the cases shown resulted from treatment with human growth hormone but others have occurred through contaminated neurosurgical instruments, dural grafts etc.

Familial: Cases occurring in families associated with mutations in the PrP gene (10 - 15% of cases) .

GSS: Gerstmann-Sträussler-Scheinker syndrome - an exceedingly rare inherited autosomal dominant disease, typified by chronic progressive ataxia and terminal dementia. The clinical duration is from 2 to 10 years, much longer than for CJD.

NVCJD: the hitherto unrecognised variant of CJD discovered by the National CJD Surveillance Unit and reported in the Lancet on 6 April 1996. This is characterised clinically by a progressive neuropsychiatric disorder leading to ataxia, dementia and myoclonus (or chorea) without the typical EEG appearance of CJD. Neuropathology shows marked spongiform change and extensive florid plaques throughout the brain.

Definite NVCJD cases still alive: these will be cases where the diagnosis has been pathologically confirmed (by brain biopsy).

The CJD Surveillance Unit

Cases of suspect CJD are mainly ascertained by the CJD Surveillance Unit directly from targeted professional groups including neurologists, neuropathologists and neurophysiologists, although cases are also identified from a number of other sources. As a safety net, details are sought from all death certificates coded under the specific rubrics for CJD. Each case referred in life is visited by a research registrar in order to obtain clinical information and details on possible risk factors by the use of a standard questionnaire. Information from an age- and sex-matched hospital control patient is also gathered in order to obtain information on comparative risk.

Confirmation of the diagnosis of CJD depends on neuropathological examination of brain tissue and there is a dedicated neuropathology laboratory in the Unit. Approximately 70% of all cases of suspect CJD have undergone post mortem since the start of the study and the remaining cases are classified according to validated diagnostic criteria. Overall about 50% of all suspect cases are judged to have definite or probable CJD reflecting a high level of co-operation with the study particularly by the neuroscience community in the referral of any case in which the diagnosis of CJD is considered.

Information from the study is provided in an annual report which includes details on incidence, age and sex distribution, occupation, regional distribution and analysis of putative risk factors as well as clinical, neuropathological and molecular biological analysis of CJD cases. Important developments are reported in peer-reviewed journals.

Since 1993 the CJD Surveillance Unit has been liaising with similar projects in other countries in Europe (France, Germany, Italy, the Netherlands, Slovakia and Spain) in order to obtain comparative data from countries with a low or zero incidence of BSE. Up until now the overall incidence of CJD in collaborating countries has been remarkably similar and the findings from an extensive case-control study are to be published shortly.