Annex

# MEDICAL RESEARCH COUNCIL

IN CONFIDENCE

Circulation
Participants

CJD 78/5

MEETING ON THE FEASIBILITY OF CARRYING OUT EPIDEMIOLOGICAL STUDIES ON CREUTZFELDT-JAKOB DISEASE

Minutes of meeting held on Thursday 9 March 1978 at 20 Park Crescent London WIN 4AL

---

Present: Professor J N Walton (Chairman), Dr A M Adelstein, Professor J R Batchelor, Mr K N Burns (ARC), Professor J A N Corsellis, Dr T J Crow, Dr R Levy, Professor W B Matthews, Dr J T Stamp, Professor B E Tomlinson, Professor M P Vessey, Professor P Wildy, Dr A Smithies (Health Department Observer).

Headquarters staff: Dr Katherine Levy, Dr Victoria Harrison, Miss Roberta Withnall.

Apologies for absence: Professor A N Davison, Dr R H Kimberlin, Dr W A Lishman, Professor C A Mims.

1. Introduction and background

The Chairman opened the meeting by explaining that its purpose was to advise the Neurosciences Board on the value and feasibility of carrying out epidemiological studies on Creutzfeldt-Jakob (C-J) disease; suggestions for work on other aspects of the disease were not, however, precluded. The meeting had been called following the Agricultural Research Council's (ARC) report of their Advisory Committee on Scrapie, a document which should be regarded as confidential. One of the main issues which merited discussion was whether those whose occupation suggested they might be in contact with scrapie had a higher risk of developing C-J disease. While fully appreciating that the problem of infectivity was one of great concern the present meeting was not constituted to discuss this problem per se. The recently set up ARC Advisory Group on Scrapie would be taking up this question; it was also of concern to the Health Departments who wished to be kept informed of developments. Mr Burns reported that the ARC had already had preliminary discussions on the safety aspects which would be necessary in the event of C-J work being carried out in their Institute at Compton. Dr Levy agreed to act as liaison officer between the two Councils and the Health Departments.

2. [illegible] mortality data

The meeting considered the mortality data provided by OPCS (CJD 78/2) and that provided by Professor Matthews (paper tabled). The interpretation of these data was complicated by possibilities of both under-and over-reporting. Under-reporting was likely in that C-J disease might: (a) be undiagnosed, particularly in large mental hospitals; and (b) not appear on death certificates either because the actual cause of death was eg. bronchial pneumonia, or because reference to dementia (in any form) was excluded to spare the feelings of the family. Over-reporting might occur because, although the rapidly progressive form of the disease was readily diagnosed in life, the less dramatic forms were more difficult to recognise clinically and could be diagnosed in error (see below). It was noted that the OPCS data showed an apparently higher incidence of the disease in social class I: a possible explanation was that this group was investigated more carefully. An added difficulty, common to all occupational data obtained from death certificates alone, was that it was based solely on information provided by the person registering the death. Professor Vessey drew attention to the temporal differences between the OPCS data and those provided by Professor Matthews.

The meeting then considered the implication of: a) incompleteness; and b) inaccuracy of the data. Incompleteness would matter if it was associated with the factor under study, eg. if only those cases occurring in certain occupational groups were missing: if accurate incidence, prevalence or mortality rates were required; and in examining space/time clustering (see below). Inaccuracy would matter less since the dilution of the mortality data with diseases other than C-J would merely tend to weaken any association present.

3. Accuracy of clinical diagnosis: neuropathology

The neuropathologists present explained that it was now generally considered that there were 3 categories of the disease: (i) a rapidly progressive form of subacute spongiform encephalopathy (the Nevin-Jones Syndrome) usually leading to death within 6-9 months; this is the only form which has been transmitted to animals; (ii) a variant in which the cerebellum appears to bear the brunt of the pathology; and (iii) "classical" C-J disease which follows a more protracted course. Diagnosis is based on the typical EEG picture - which in the slower forms of the disease may not arise until late in the course of the illness - and on the characteristic spongiform features seen on neuropathological examination. The less rapidly progressive forms could be confused with other forms of dementia or arteriosclerotic disease, Alzheimer's disease with myoclonus, myoclonic epilepsy, corticostrionigral degeneration, Pick's disease or motor neurone disease.

While there could be doubt about a diagnosis made on a biopsy specimen it would be very rare for a neuropathologist to make a mistake at autopsy. However, in less specialised hands there was a very significant chance that cases could be missed.

Dr Stamp pointed out that in scrapie no spongiform encephalopathy was detected and that in many cases confirmed by transmission experiments no neuropathological abnormality could be found.

4. Specialist care of C-J patients

The question of whether C-J patients were in the main looked after by neurologists or by psychiatrists was discussed. The view of the meeting was that most patients were seen by neurologists, but that there might be an unknown, even considerable number of cases (presumably of the more chronic form) in major mental hospitals.

5. Frequency of biopsies and post mortems

Until a few years ago a biopsy was carried out in the majority of suspected case. referred to major centres: the situation had now changed and biopsies were performed less often, partly because diagnosis could be based on the clinical ar EEG picture.

Dr Adelstein pointed out that 50% of C-J deaths recorded in the OPCS figures had come to post mortem, during the six year period up to 1976. The figures may be dropping for both biopsies and post mortems not only because they are thought unnecessary in view of the improvement in other methods of diagnosis but also because of both the shortage of neuropathologists and their awareness of the possible infectivity of the agent.*

*There is no evidence to suggest that there is only one agent; there may well be several. But for the purposes of this record the term 'agent' is used throughout

6. Gajdusek's evidence

The Chairman invited Professor Wildy to speak to his paper (CJD 78/3) on the hazards of the C-J agent and other possible agents to hospital staff and pathologists. Professor Wildy emphasised that in general Gajdusek's evidence should be treated with great caution since his hypothesis was based on the presumed analogy with the scrapie agent (or agents). Hard data were not available about the C-J agent itself. It was resistant to many physical and chemical treatments: there was a need to establish a reliable means of sterilisation, as Gajdusek's published data on autoclaving was open to criticism. It is likely that, as with scrapie, some C-J strains would prove to be much more resistant than others.

7. Risk of infection

The two reports of iatrogenic man-to-man transmission of C-J disease have involved corneal grafting and neurosurgery respectively. While the implications for sterilisation of instruments etc. had been widely discussed in the literature the additional point was made that corneae for grafts were often obtained from old peoples' homes: caution should therefore be exercised in using tissue from this source.

Overall there was no indication either from OPCS data or from anecdotal evidence that pathologists, mortuary attendants or research workers had ever developed C-J disease. On available evidence it was,however, clear that contact between C-J infected material and lacerated skin must be avoided. Nor wasthere evidence that anyone working with scrapie diseased animals (veterinary surgeons, slaughter house workers, butchers, shepherds and shepherdesses or research workers) have developed the disease. It was nonetheless worth undertaking retrospective epidemiological studies if only to provide reassurance that there was no excess mortality from C-J disease in these and other professional groups - including neurosurgeons, neurologists, undertakers and embalmers. It should however be borne in mind that some of the latter categories may be under-represented, occupation euphemisms having been used on the death certificates.

8. Prevalence and mode of infectivity of C-J agent

While the prevalence and mode of infectivity of the C-J agent are unknown it would be difficult to account for the world wide distribution of the disease unless the agent were common. If prevalence were low it would be difficult to postulate how the agent would replicate. This suggested that one might be dealing with a transferred ubiquitous and relatively banal agent - the analogy being measles and SSPE. It was agreed that while this was pure speculation, the possibility could not be ruled out. Dr Crow pointed out that the age incidence of C-J disease would not suggest that it was due to an infective agent. In this connection Dr Stamp reported that both lateral and vertical transmission occur in scrapie: genetic factors determine the incubation period and so-called "resistant" sheep may die before there was time for them to show clinical signs of the disease. It was not known how scrapie was transmitted, though it can exist outside its host for an indefinite period. However the usefulness of the scrapie analogy is uncertain. Dr Stamp emphasised that in scrapie the innoculated and natural disease are two very different conditions.

9. Clusters, familial incidence and conjugal C-J disease

Geographical and temporal clustering have been reported; these however had been small and difficult to evaluate statistically. In Professor Tomlinson's experience all cases of C-J were referrals from the better known neurological or psychiatric centres, implying that clustering could be an artefact. Professor Vessey offered with colleagues to examine the data provided by OPCS and Professor Matthews to see if these revealed any evidence of clustering. Different incubation periods could be built in and contact between cases could be looked for - the complex statistics had been worked out for Hodgkin's disease. The technique involved was nevertheless a crude one. Familial cases had been reported but the numbers involved were too low to be significant. Occurrence of the disease in cousins (2 in the UK, and 2 in the USA) and two cases of conjugal C-J disease were briefly mentioned.

10. Genetic screening, including HLA status

Professor Batchelor confirmed that the HLA status of C-J patients had not been investigated. Dr Stamp reported that there was no association with mouse histo-compatibility antigens in scrapie; this had not been investigated in sheep. Professor Batchelor said that typing would not be difficult: 30-60 patients would be required depending on the rarity of the antigen. General genetic screening might also be worthwhile; he suggested that the Galton laboratories might be approached with a view to studying various isoenzymes in such cases. Samples of serum should be stored for future study of antibody profiles.

11. General conclusions

(i) The meeting could only confirm that the epidemiology of C-J disease is poorly understood.

(ii) The existing mortality data were likely to be inaccurate; so far as they went no occupational association with the disease could be demonstrated. The prevalence and mode of infectivity of the agent were unknown and clusters reported had been small and difficult to evaluate statistically.

(iii) Gajdusek's evidence was open to criticism: however, while his assertions are unsupported by hard data, his claims might nonetheless have substance.

(iv) While the analogy with scrapie was interesting and the scrapie and C-J agents displayed similarities in behaviour and character, there was no proof that the scrapie agent was in any way associated with C-J disease.

12. Possible action

The following suggestions were made about action which might be taken:

(i) OPCS might be asked to provide data on the occupations listed for all deaths due to dementia and the other diseases with which C-J might be confused recorded within, say, the last 3 years.

(ii) OPCS might be asked to collect prospectively notifications of all deaths from C-J disease, the dementias and other diseases with which it might be confused.

(iii) The data provided by OPCS might be correlated with that obtained by Professor Matthews (confirming diagnoses from case notes etc. in at least a sample of these cases) to see how many of the same C-J patients were involved. These data should be analysed for evidence of clustering.

(iv) Data provided by the Doll/Hill study of 34,000 doctors on the medical register in 1953 might (with the authors' agreement) be utilised to see if any excess death rates from C-J disease, the dementias or other diseases with which it may be confused, could be identified among certain specialist groups.

(v) HLA status of C-J patients should be determined.

(vi) General genetic screening might be undertaken of patients with C-J disease.

(vii) Samples of serum from C-J patients should be stored for future study of antibody profiles.

(viii) Although technically outside their remit the meeting recommended that good work should be encouraged on the isolation, characterisation, distribution in the body, routes of infection and methods of destruction of the C-J agent.

The Chairman closed the meeting by thanking the participants for attending and for their help in reaching these conclusions.