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PHLS COMMUNICABLE DISEASE SURVEILLANCE CENTRE

From The Director
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2 August 1996

CLRB/rg

Dr R G Will
Consultant Neurologist
National Creutzfeldt-Jakob Disease Surveillance Unit
Western General Hospital
Crewe Road
Edinburgh EH4 2XU

cc Dr Ridley
Dr Farrer
Dr Farrer
Dr Jones 2/9

File

GRO-C

GRO-C

Dear Dr Will

I am delighted that Roland has already had a chance to attend two home visits with Martin and that the joint bid for funds to establish a panel of CSF specimens has gone off to the MRC. I thought that it would be helpful to prepare a memorandum of understanding of our collaboration. May I suggest the following:

ROUTINE SURVEILLANCE OF NEW VARIANT CJD

Analysis of new variant CJD incidents.

Purpose.

The purpose of this collaboration is to provide routine monitoring of the trend in incidence of new variant CJD (NVCJD).

Proposed analyses.

The NVCJD incidence curve would be analysed on a regular basis. Analyses will be undertaken both by date of confirmation of NVCJD and, if possible, by date of onset of clinical symptoms. The latter will seek to incorporate adjustments for the delays between the date of onset, the date of referral to the CJD Unit, and the date of confirmation of NVCJDs. These adjustments will be based on the estimated ascertainment delay distribution and on the proportion of suspected cases eventually confirmed as NVCJD. As data accumulate, further analyses stratified by relevant covariates may also be undertaken. Similar analyses may also be undertaken for CJD other than NVCJD, if required.

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Proposed procedures.

Dr Paddy Farrington will spend up to a week, in the second half of September, at the CJD Unit to familiarise himself with the detail of case ascertainment, case definition, data collection and handling. This will enable a suitable standard data set to be determined, which would then be regularly updated. The analyses will be undertaken by staff at the PHLS Statistics Unit in CDSC, at regular intervals (for instance, quarterly) to be agreed with the Director of the CJD Unit. Data for the analyses will be provided in confidence. The report and analyses will be made to the Director of the CJD Unit, and to the Director of CDSC. The use and publication of these analyses will be determined by the Director of the CJD Unit.

PUBLICATION OF SURVEILLANCE INFORMATION IN THE CDR.

Purpose.

The purpose is to assist in the dissemination of routine surveillance information.

Proposed Procedure.

The PHLS has been given permission by the Department of Health to publish information on CJD after publication in the CMO Update. It is proposed that the CJD Unit provides CDSC with copies of the data and text once it has been agreed with the DH. The CDSC editorial staff will edit to CDR format and submit the draft copy to the Director of the CJD Unit for approval and DH. New tabular and graphical ways of presenting data will be reviewed from time to time.

ASSISTANCE IN FIELD INVESTIGATION

Purpose.

The purpose is to provide experienced field epidemiologists input into descriptive and analytical epidemiology questionnaire design.

Proposed procedure.

An experienced field epidemiologist from CDSC, initially Dr Roland Salmon, will accompany the CJD Unit Research Registrar on home visits to suspected cases. The home visits will not be confined to cases of NVCJD. Initially the epidemiologist will attend solely as an observer, but later with the consent of the Director CJD Unit will add supplementary questions after the Research Registrar completes his history taking. The CDSC epidemiologist will be expected to identify ways of refining the questionnaire, particularly those parts that relate to exposures. It is proposed that the Directors of the CJD Unit and CDSC meet together with the field staff from time to time to review progress in this area.

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Assistance in analytical epidemiological studies.

Purpose.

To advise and assist in all aspects of control selection, recruitment and interviewing.

Proposed procedure.

This work will be undertaken in collaboration with the CJD Unit and London School of Hygiene and Tropical Medicine. Experienced field epidemiological input will help to identify any current sources of bias and the means of reducing them, in hospital controls. In addition, the CDSC epidemiologist will be willing to advise and assist in the selection of community controls, particularly in relation to an analytical study of the cluster of NVCJD cases.

I hope the above sets out our proposed collaboration accurately. Roland Salmon mentioned that a new Research Registrar will start work in the National CJD Unit in the Autumn and I would like to offer the services of CDSC to provide him/her with a short period of practical training in field epidemiology through attachment to CDSC Wales or CDSC, Colindale. May I suggest that Roland Salmon visits the CJD Unit in late September or early October at the same time as Paddy Farrington. Perhaps on one day towards the end of that week I could visit to review discuss with you and appropriate members of both teams the progress to date, particularly to consider Roland Salmon's first impressions of the descriptive epidemiological methods used in the field.

Finally, may I thank you for agreeing to speak at the Conference of Epidemiology and Control of Infectious Diseases and Environmental Hazards. I look forward to our future collaboration.

With best wishes.

Yours sincerely

GRO-C

CLR Bartlett
Director

cc Dr Diana Walford
Dr Noel Gill
Professor Stephen Palmer
Dr Roland Salmon
Dr Tony Swan

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ASSISTANCE WITH FIELD INVESTIGATION OF CREUTZFELDT-JAKOB DISEASE

A Progress Report

Background:

Further to discussions between the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC) and the Creutzfeldt-Jakob Disease Surveillance Unit (CJD Unit), as set out in Dr Bartlett's letter to Dr Will of 2nd August 1996, it was agreed that a CDSC field epidemiologist would accompany the CJD Unit Research Registrar on visits to suspected cases of Creutzfeldt-Jakob Disease (CJD), including the newly described variant (NVCJD). This will help, hopefully, to identify ways of refining the questionnaire and will feed into advice and assistance to be given by CDSC in the design and conduct of future analytical studies.

Activity:

Since July, Dr Roland Salmon has accompanied Dr Martin Zeidler, Research Registrar, CJD Unit, on a total of six visits encompassing England (South and West, West Midlands, Mersey/North Western), Wales and, with the permission of Dr Dan Reid, Director, Scottish Centre for Infection and Environmental Health (SCIEH), Scotland. This has involved observing 6 interviews of suspected cases' relatives, 3 interviews of controls and seeing 5 cases suspected cases (of which 3 had been referred as candidates for NVCJD).

Findings:

<u>The conduct of the study</u>

Dr Zeidler is an excellent interviewer and combines an adherence to the questionnaire with the intelligent flexibility and sensitivity necessary to sustain a rapport with the interviewees during a contact lasting 3 to 4 hours, under what is unusually stressful circumstsances for the interviewees, that is, usually, in the hospital ward where the case, their next of kin, is dying. The biggest problem is the amount the research registrar is expected to achieve in the course of the day which goes rather beyond the gathering of epidemiological information.

He:-

i) Educates the interviewees about CJD and, de facto, performs what is in effect a counselling role.

ii) Obtains consent to take diagnostic specimens.

iii) Obtains a clinical history of the illness.

iv) Examines the case.

v) Obtains blood for genotyping from the case and, with NVCJD, for transmission studies of the infectivity of blood. He frequently has to liase with pathology to arrange for blood to be spun down and for dry ice for transportation to Edinburgh etc.

vi) Organises for cerebro-spinal fluid (CSF) to be obtained for onward transmission to the US National Institutes of Health to assist in the validation of their CSF test for CJD.

vii) Conducts the structured questionnaire based interview with the case's relatives.

viii) Conducts the same interview on a hospital based control nominated by the team caring for the case.

It will be appreciated, therefore, that the epidemiological investigation of risk factors for CJD constitutes only a part of the Research Registrar's responsibilities, the majority of which are clinical/diagnostic.

Regarding the actual epidemiology two aspects are worth commenting upon:

First the questionnaire addresses last of all the three most important topics in the investigation of possible environmental risk factors for CJD, i.e. occupation, diet and animal exposure. Thus respondent arrive at these topics fatigued. Much of their co-operation and goodwill has been used up in a structured enquiry into prodromal symptoms, which merely frequently re-iterates the clinical history taken, and in cataloguing all the addresses they have ever lived at, where possible down to post-code, detail which, given what is now known about the length and variability of the incubation period of CJD, is likely to be unhelpful and non-contributory.

The occupational history section is broadly adequate especially as it is supplemented by a list of questions on specific occupations which may be relevant (tanneries, abbattoirs, farms etc). The section on diet and the ranked ordinal scale that has been devised to quantify it, is an excellent format which may, inter alia, contribute to containing any effects of recall bias. Respondents find the questions easy to answer precisely. The main criticism is the list of foods could usefully be much longer with some items such as "beef", "meat pies" and "sausages", particularly, subdivided to give information on the many different preparations which may have been consumed which could be of interest. This might be informed by information on the destination of the various parts of the cattle which is generated by the Leatherhead Food RA's project, funded by the Ministry of Agriculture Fisheries and Foods (MAFF), on "Ruminant Products Audit". Further textual information on the retail sources and preparation of these products could be appended. Food preparation undertaken by the case could be enquired about more extensively also. Finally the section on animals is inadequate. John Wilesmith has suggested modifications. Similarly questions from the CDSC(Welsh Unit) study of occupational exposure to animals could be modified and introduced. Thought needs to be given to this area and further veterinary help such as Mr Bill Reilly, SCIEH, or Professor Kenton Morgan, Professor of Veterinary Epidemiology, Liverpool University, enlisted.

Secondly control selection is problematic and on some of the visits it has not proved possible to interview a control that day. The clinical teams simply nominate one individual in their care who is prepared to take part and fulfils the matching criteria. They are supposed to have a relative of the same degree as the case's to act as their respondent but this is frequently not possible. One suspects that participation bias occurs as "helpful" or "co-operative" patients get nominated, which could be very important, for example, in examining occupation. Ideally, if hospital controls are to be used, they should be selected at random from a register of in-patients, possibly with a limited number of permitted common diagnoses to ensure they are representative of those unexposed to the relevant exposure in the population from which the cases are drawn. This is likely to be

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laborious and controls selected from General Practitioner's lists would, in practice, be as easy to obtain and more likely to be appropriate overall. There is merit, overall, however, in retaining a hospital control as GP controls could conceivably be over-matched by locality of residence. More time will need to be invested in this process and, were it not for the fact that this is the only controlled data, it would be surprising that such extensive analysis of the case-control study data has been carried out without these issues, as yet, being addressed.

The interviews to date

The suspected cases consisted of 5 females and 1 male. Their ages were 35, 43, 51, 75, 76, 77. With the older patients the ante-mortem diagnosis appears able to be based with some confidence on a number of consistent features: rapidly progressive history, myoclonus and a characteristic EEG appearance. The younger patients, who are of course candidates for NVCJD, have a much more heterogenous presentation which, I understand, has been the case with the series of NVCJD. The younger patients have also had routes of referral. One was referred by a former CJD Unit Research Registrar; a second by a neuropathologist who had the patient, who was under the care of psychogeriatricians, drawn to his attention ante mortem because of the patient's previously expressed desire to leave his body for research; a third by their next of kin via a CJD self help group.

Regarding exposure histories I have not been disabused of my view that direct zoonotic spread may be important. If the 6 interviews attended are typical, which, of course, they may not be, it is difficult not to be struck by the rural nature of the lives of the cases and the extent of animal contact, which would be unusual to find in other epidemiological fieldwork settings.

The cases also consume a variety of products that might have contained beef offal but, superficially at least, this is less of remark. It is clear that the CJD Unit believe beef offal products to be the explanation for NVCJD and, clearly, as they are on the spot and have interviewed all the cases, that view should be the starting point for any subsequent development of the epidemiological study. It should be observed that the experimental introduction of NVCJD into a cynomogulus macaque monkey by intra-cerebral inoculation of BSE infected cow's brain is, in the advance of the results of strain phenotyping experiments on NVCJD human brain at the Animal Neuropathogenesis Unit, in Edinburgh, a strong piece of corroborative evidence for the CJD Unit's view that NVCJD does come from BSE, although the route of transmission would still be open to debate.

Some general proposals for future developments

The CJD Unit do not feel that NVCJD has resulted from increased ascertainment. Nevertheless it would be as well to examine this question systematically, particularly in the younger age group. There is also the question as to what extent atypically presenting older CJD cases (ie with longer histories and without EEG changes) may currently be being missed. This could also usefully be systematically examined via a post mortem survey of brains from a random selection of older patients dying with dementia.

Regarding the current CJD Surveillance there would be much to be said for separating the acquisition of epidemiological data on risk factors and exposures from the activities aimed at corroborating the diagnosis and obtaining diagnostic specimens. The epidemiological components might reasonably be deferred until post mortem had put the case diagnosis beyond doubt. The additional administrative effort which is needed to be confident of obtaining representative controls

would then be made in the knowledge that the case would indeed be entering the study. The interviewing for this part could just as readily be carried out by someone experienced in foodborne or zoonotic illness who might be a scientist, environmental health officer or veterinarian, rather than a clinician. PHLS has a number of such people. It is at least possible that the circumstances for the interview would be easier after death for the next of kin than, as at present, whilst coping with the terminal illness. Given that the information is mostly lifelong and obtained from proxy respondents the delay is unlikely to affect its quality.
I understand DH may be in discussion with the CJD Unit as to how further epidemiological support might be provided. Indeed if there is an acceleration in the rate of referrals of suspect cases the CJD Unit may well find it difficult to cope. PHLS could readily assist here as, one assumes, could SCIEH. Details of how control selection and questionnaire design might be modified are given above.

Afterword

It is a privilege to sit in on these interviews and listen to families give their accounts of relatives with CJD. One appreciation I have acquired, or certainly had reinforced, is the extent to which all forms of CJD represent a considerable human tragedy. It is easy to loose sight of the basic consideration, among considerations of economic loss and market confidence, that this disease is worth trying to prevent.

Dr R.L. Salmon
PHLS Communicable Disease Surveillance Centre (Welsh Unit)
20th August 1996