(10)

DEPARTMENT OF HEALTH SC4/5/91

APPLICATION FOR A RESEARCH GRANT

1. Applicants' Surname(s) Forename(s) Professor/Dr/Mr Mrs/Miss/Ms

WILL ROBERT GEORGE

Official Address

CJD Surveillance Unit
Western General Hospital
Edinburgh EH4 2XU

Telephone Number

031 332 2117

Fax No. 031 343 1404

(Please complete a copy of Appendix 3 for all applicants)

2. Post(s) held if not permanent, please indicate tenure

Consultant Neurologist
Part-Time Senior Lecturer in Neurology

3. Title of Project

SURVEILLANCE OF CREUTZFELDT-JAKOB DISEASE

4. Abstract of Research (Details in Appendix 1)
No more than 200 words covering the following topics:
Aims of project
Sample (size, type, location)
Methods to be used

The identification of Bovine Spongiform Encephalopathy (BSE) as one of the transmissible spongiform encephalopathies has led to speculation that transmission to humans may occur. The Southwood Committee, although judging this possibility remote, recommended that monitoring of Creutzfeldt-Jakob disease (CJD) should be carried out in order to identify any change in the pattern of the disease.

A grant was awarded in 1990 by the Department of Health and Scottish Home and Health Department to reinstitute the national surveillance of CJD and the current application is for a renewal of this grant for a further 4-year period.

The original aims of the project have been fulfilled in that monitoring of CJD throughout the United Kingdom has been successfully carried out from May 1990 to the present time. Two reports have been submitted to the Departments which indicate no major change in the epidemiological or clinical parameters of CJD. There has however been a rise in the annual incidence during the first three years of the study and two individuals with possible occupational contact with BSE have been identified. The potentially prolonged incubation period in the spongiform encephalopathies indicates that continued surveillance is necessary to exclude any change in CJD over the next 4 years at least.

5. Proposed starting date: JAN '94 Proposed duration: 48 months

6. Total estimated cost: £473,620

7. Have you received assurances that the co-operation you will require in the conduct of the proposed research will be forthcoming from the relevant bodies (eg NHS, Local Authority or University)?

8. ..... Signature of Applicant

15.11.93 Date

9. I have examined this tender and agree that, if a contract is awarded, the research will be carried out under my general supervision.

..... Head of Department

9 November 1993

..... Date

10. I agree that the gradings and salaries quoted in appendix 2A are in accordance with the practice and scales applying in this University/Institution; and that any grant awarded will be administered by this University/Institution in accordance with the Department of Health's Standard Conditions of Contract.

..... Secretary/Finance Officer or other person qualified to make this statement on behalf of the Institution

Assistant Director of Finance

11 November 1993 ..... Date

IMPORTANT

The completed application form should be returned to:

RESEARCH MANAGEMENT DIVISION
DEPARTMENT OF HEALTH
ALEXANDER FLEMING HOUSE
ELEPHANT & CASTLE
LONDON SE1 6BY

Attachments

Appendix 1 - Details of proposed research
Appendix 2 - Analysis of costs
Appendix 3 - Curriculum Vitae of applicant

(9)

Appendix 1

DETAILS OF PROPOSED RESEARCH

Detailed outline of proposed research (see notes attached for further details).

Please leave blank

INTRODUCTION

The identification of Bovine Spongiform Encephalopathy (BSE) as one of the transmissible spongiform encephalopathies has led to speculation that transmission to humans may occur. The Southwood Committee recommended the reinstitution of the epidemiological surveillance of CJD and a grant from the Department of Health and the Scottish Home and Health Department was awarded in 1990 for this to be carried out.

Detailed information on the epidemiological and clinical characteristics of CJD in England and Wales was available from the study by Professor WB Matthews for the years 1970-1984 and all the data from this study has been transferred to the CJD Unit in Edinburgh. The first task identified in the original grant proposal was to establish the epidemiological characteristics of CJD retrospectively for the years 1985 to April 1990 in England and Wales and in Scotland and Northern Ireland for the years 1980 to April 1990. This task was completed in 1992 and the results have been documented in the first annual report (Addendum 1) and in a publication relating specifically to Scotland and Northern Ireland.

Prospective surveillance of CJD in the United Kingdom was instituted in May 1990 and has been carried out successfully up to the present time. The results of this research have been documented in two reports prepared for the Department of Health and Scottish Home and Health Department (Addendum 1 and Addendum 2) and in a number of publications (listed in Addendum 3). The methodology of the original proposal has been adhered to in order that data comparable to the previous epidemiological investigation of CJD can be obtained.

No major change in the epidemiological or clinical characteristics of CJD have been identified. However there has been an increase in the incidence of CJD in each year of the study and two individuals with possible occupational exposure to BSE have been identified. Although the increase in incidence is most likely to be due to improved ascertainment of cases, and the occurrence of CJD in potentially occupationally exposed individuals is most likely to have been a chance phenomenon, these findings provide a powerful incentive to continue the surveillance programme. It is important to ensure that there is not an incremental rise in the incidence of CJD and that any potential occupational links with BSE continue to be monitored.

The identification of a change in CJD that might be attributable to BSE relies primarily on the descriptive epidemiological evidence but consideration has been given to other means by which such an occurrence might be identified. There are four other areas of specific interest.

1. Case-Control Study.
2. Analysis of Clinical Features.
3. Molecular Biological Evidence.
4. Transmission Studies.

(8)

Please leave blank

1. Case-Control Study

Since the start of the study, an attempt has been made in every case to obtain parallel information on risk factors from a hospital-based age- and sex-matched control patient. The relatives of patients and controls are interviewed using a standard questionnaire (Addendum 4). Up to the present time 103 patients with appropriate controls have been identified and preliminary analysis of this study has been included in the two annual reports.

No biologically significant difference between cases and controls has been identified in relation to exposure to animals or a range of dietary factors, nor in relation to occupational history.

2. Clinical Features

Since the original application, a body of evidence has accumulated indicating that in iatrogenic CJD related to human pituitary derived hormones, the clinical features are distinct from sporadic CJD. The likeliest explanation for this unexpected finding is that the route of inoculation influences the clinical presentation. In the context of BSE in which dietary exposure or peripheral inoculation in relation to occupation are primary concerns, analysis of clinical features might provide evidence of a change potentially attributable to BSE. Analysis of clinical features up to the current time shows no change in the clinical characteristics of CJD in relation to previous experience.

3. Molecular Biology

Blood has been taken for molecular studies in all possible incident cases of CJD. Ethical approval for this research was obtained on two occasions from the local Ethical Committee but developments in this field since the start of the study have resulted in major ethical dilemmas. This issue was addressed at a meeting at the MRC in April 1993 and new guidelines have now been agreed.

Important scientific information has been obtained on the frequency of prion protein gene mutations and the relative proportion of individuals with sporadic CJD with specific genotypes at codon 129 of the prion protein gene. Preliminary data is included in the second annual report and a publication on this topic is in preparation.

The relative frequencies of gentoypes at codon 129 are distinct in iatrogenic CJD in relation to sporadic CJD. Continuing analysis of genotypes at this locus may therefore be important in the identification of any change in CJD that might be attributable to a peripheral source of infection.

4. Transmission Studies

Transmission studies using four geographically separate isolates of BSE and from BSE in a number of other species have unexpectedly shown remarkably similar incubation periods and lesion profiles in five inbred strains of mice.

(7)

Please leave blank

This important finding has the potential to provide evidence for the source of infectivity in cases of CJD. A grant proposal to initiate transmission studies in cases of sporadic CJD pre- and post-BSE and in the two potentially occupationally exposed individuals has been submitted to the MRC.

METHODOLOGY

The methodology of the current proposal is identical to that in the previous proposal.

IDENTIFICATION OF CASES

Cases of CJD may be identified from death certificates, but this alone is unlikely to provide adequate monitoring. Errors are made in certification and diagnosis; in the Oxford study death certificates were obtained on a series of known confirmed cases and CJD was mentioned in only 66% of certificates. In another series of 175 certified cases, 42 patients were judged not to have suffered from CJD after examination of case notes. Death certificates are nevertheless an important method of case ascertainment and subsequent examination of case notes provides relevant information not directly available from the certificates.

Direct notification of cases by neurologists and neuropathologists provides a further mechanism of ascertainment. In a case-control study of CJD in England and Wales 107/144 cases were identified from this source. In combination with information from death certificates that this method of case ascertainment results in reasonably complete and accurate monitoring of CJD. It is however important to stress that from 1980-1984 and from 1990-1993 only about 50% of all notified cases have been found to have definite or probable CJD and that direct verification of the diagnosis is an essential component in obtaining accurate data.

PROPOSALS FOR THE SURVEILLANCE OF CJD

1. All newly certified cases of CJD will be notified by OPCS or the equivalent in Scotland and Northern Ireland. Case notes of these patients will be obtained and relevant information extracted.

2. All neurologists, neuropathologists and neurophysiologists will continue to be circulated and asked to report all cases of suspected CJD; and cases of subacute dementing illness or progressive cerebellar dysfunction in specific occupational groups (veterinarians, herdsmen, slaughtermen, farmers, butchers, laboratory workers). Clinical and epidemiological information will be obtained by standard questionnaire which contains sections on the following specific topics:

    1. Clinical and investigative features.
    2. Past medical history and drug history.
    3. Family history.
    4. Residential history.
    5. Occupational history.
    6. Dietary history.
    7. Exposure to animals.

(6)

Please leave blank

Adequate information for the purpose of monitoring is unlikely to be obtained unless affected patients are visited, the diagnosis is verified and detailed information is obtained directly.

From the nature of the disease it is rarely possible to obtain a history from patients with CJD and this information may have to be obtained from relatives. Experience suggests that relatives of affected patients are likely to be very cooperative in responding to a questionnaire and often find the opportunity to discuss the illness to be of benefit.

4. The clinical diagnosis of CJD is highly accurate in those patients with a characteristic electroencephalogram, but in 20% of cases the EEG is either not obtained or non-specific. Pathological confirmation of the diagnosis is an essential component of the monitoring in CJD.

Pathologists in many centres are reluctant to examine CNS tissue from cases of suspected CJD and a dedicated 'high risk' laboratory is required to prepare sections. In 1990 a laboratory dedicated to the pathological examination of cases of CJD was established, funded by the Department of Health and Scottish Home and Health Department. Approximately 70% of all suspect cases of CJD identified in the surveillance project have undergone post mortem examination and the majority of these cases have been examined in detail in Edinburgh.

5. The proposed monitoring of CJD has provided information on variables including sex, age, incidence and geographical distribution of cases. Statistical analysis of temporal changes in these variables will continue to be carried out by Professor PG Smith, Department of Epidemiology, The London School of Hygiene and Tropical Medicine, who retains data from previous studies of CJD.

6. The incubation period of CJD ranges from 18 months to 23 years in iatrogenic cases and may extend to decades in kuru. The Southwood Committee stated that 'it may be a decade or more before complete reassurance can be given' (that BSE is not transmissible to humans). In experimental transmission the route of inoculation affects the incubation period with peripheral or oral inoculation resulting in more prolonged incubation. The laboratory and epidemiological evidence suggests that monitoring of CJD will be necessary for 15 to 20 years in order to exclude a change in the pattern of the condition due to transmission of BSE to humans.

POTENTIAL FUTURE DEVELOPMENTS

The systematic identification of cases of CJD throughout the United Kingdom provides an important resource for research. Collaboration with many other centres in the United Kingdom and elsewhere have been established. In particular, collaboration with the Prion Protein Group at St. Mary's Hospital has been fruitful and we have a firm commitment to continue to supply information on all familial cases of CJD to this research group.

One drawback to the methodology of the surveillance project is the necessity to rely on historical data for comparative purposes. In order to obtain contemporary

5

Please leave blank

comparative data a proposal was made to the BIOMED1 programme funded by the European Community for the coordination of the surveillance programmes of CJD in the EC. This was awarded in 1992 and close collaboration has been established with a number of centres in the EC responsible for national surveillance programmes of CJD in individual countries. The countries involved in this project include France, The Netherlands, Germany, Italy and Slovakia. The aim of the coordination proposal is to harmonise the methodologies of the studies in the various countries and all projects now use common diagnostic criteria and epidemiological protocols. Collaboration has also been established with a recently initiated CJD surveillance programme in Australia.

COSTS

If monitoring CJD is to be effective it is essential to achieve a high degree of case ascertainment and to obtain sufficient clinical information to allow validation of the diagnosis. The current mechanism of identifying cases is relatively cheap and allows the accumulation of a range of clinical and epidemiological information. A priority in analysing this data is the efficient storage and retrieval of information and this requires computing facilities. Funding for computer equipment was awarded in the original grant and this is now situated in a dedicated office adjacent to the neuropathology laboratory.

Clerical support is essential for the day to day running of the project, involving frequent liaison with other centres, and clerical support is also essential for data analysis. A medically trained research worker (registrar grade) is necessary in order to visit all notified cases, validate the diagnosis and interview relatives of affected patients.

The recurrent annual costs are relatively low and it is difficult to envisage a more economical method of accurately monitoring CJD.

(4)

ANALYSIS OF COSTS

Appendix 2

Part A Salaries and Related Costs

Name	Grade or Post held	Salary Scale* and actual Salary	1st Year		2nd Year		3rd Year		4th and Subsequent Years		Total for Project	
			Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £
Dr R de Silva	AM2	23,785	24,071	6,499	25,215	6,808	26,355	7,116	27,964	7,550	103,605	27,973
Miss J Mackenzie	AS1	12,828	13,021	3,516	13,800	3,726	14,593	3,940	15,339	4,142	56,753	15,324
Totals			37,092	10,015	39,015	10,534	40,948	11,056	43,303	11,692	160,358	43,297

Part A Salaries and Related Costs (cont)

Name	Grade or Post held	Salary Scale* and actual Salary	1st Year		2nd Year		3rd Year		4th and Subsequent Years		Total for Project	
			Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £	Gross Salary inc. London Wting £	Employs NI and Superannuation £
Totals brought forward												
Totals c/f to Part G			37,092	10,015	39,015	10,534	40,948	11,056	43,303	11,692	160,358	43,297

(3)

Part B Capital Equipment/Apparatus. Single items costing £500 plus (each must be itemised separately).

Item	1st Year Cost £	2nd Year Cost £	3rd Year Cost £	4th and Subsequent Years Cost £	Total Over Period £	Comments
Medical Equipment	Nil					
Computer Equipment	Nil					
Office Equipment (including furniture)	Nil					
Other Equipment	Nil					
Total carried forward to Part G						

Part C Other Equipment/Apparatus. Single items costing less than £500.

Item	1st Year Cost £	2nd Year Cost £	3rd Year Cost £	4th and Subsequent Years Cost £	Total Over Period £	Comments
Medical Equipment	Nil					
Computer Equipment	Nil					
Office Equipment (including furniture)	Nil					
Other Equipment	Nil					
Total carried forward to Part G						

(2)

Part D Expenses and Other Costs

Item	1st Year Cost £	2nd Year Cost £	3rd Year Cost £	4th and Subsequent Years Cost £	Total Over Period £	Comments
Accommodation	2,000	2,200	2,420	2,662	9,282	
Telephone	2,771	3,048	3,353	3,688	12,860	
Printing Stationery Photocopying	4,442	4,886	5,375	5,912	20,615	
Travel and Subsistence (UK only)	17,035	18,739	20,612	22,674	79,060	
Data Processing/Computing Costs	7,967	8,764	9,640	10,604	36,975	
Books and Journals	1,000	1,100	1,210	1,331	4,641	
Postage	2,771	3,048	3,353	3,688	12,860	
Other Items (Please Specify) CD-ROM	1,792	1,792	1,792	1,792	7,168	
Death Certificates	100	100	100	100	400	
Mortuary/Transport costs for PM	1,000	1,100	1,210	1,331	4,641	
Total carried forward to Part G	40,878	44,777	49,065	53,782	188,502	

Part E Only where VAT is to be charged on the overall bill

VAT on Services (c/f to Part G)						

F Administrative charges/overheads to be agreed with Department of Health

ısis of calculation, ie whether ı a % of salaries or other ınominator	1st Year Cost £	2nd Year Cost £	3rd Year Cost £	4th and Subsequent Years Cost £	Total Over Period £	Comments
40% of labour costs incl. NI & SS	18,843	19,820	20,802	21,998	81,464	

G Summary of costs

	1st Year Cost £	2nd Year Cost £	3rd Year Cost £	4th and Subsequent Years Cost £	Total Over Period £	Comments
ılaries and London Weighting	37,092	39,015	40,948	43,303	160,358	
ıployer's NI and Superannuation	10,015	10,534	11,056	11,692	43,297	
ıpital Equipment	-	-	-	-	-	
her Equipment			-	-	-	
penses and Other Costs	40,878	44,777	49,065	53,782	188,502	
T on services	-	-	-	-	-	
erheads	18,843	19,820	20,802	21,998	81,464	
:al Estimated Cost	106,828	114,146	121,871	130,775	473,620	

(-)

art H Quarterly breakdown of costs for the first year

	Quarter 1 Cost £	Quarter 2 Cost £	Quarter 3 Cost £	Quarter 4 Cost £	Total For Year £	Comments
Salaries and London Weighting	9,273	9,273	9,273	9,273	37,092	
Employer's NI and Superannuation	2,503	2,503	2,503	2,506	10,015	
Capital Equipment	-	-	-	-	-	
Other Equipment	-	-	-	-	-	
Expenses and Other Costs	10,219	10,219	10,220	10,220	40,878	
VAT on services	-	-	-	-	-	
Overheads	4,710	4,710	4,710	4,713	18,843	
Total Estimated Cost	26,705	26,705	26,706	26,712	106,828	

uarter 1 = 1 January - 31 March
uarter 2 = 1 April - 30 June
uarter 3 = 1 July - 30 September
uarter 4 = 1 October - 31 December

Appendix 3

CURRICULUM VITAE OF APPLICANT

1. Surname	Forename(s)	Age
WILL	Robert George	43 30.7.50

2. Degree, etc (subject, class, university and date)

BA 2nd Class Honours in Pharmacology & Comparative Pathology, University of Cambridge 1971
MB Chir, University of Cambridge 1974
MRCP, 1978
MD, University of Cambridge 1985
FRCP (Edin) 1989
FRCP 1993

3. Posts held (with dates)

Jul 1974-Dec 1974	Pre-registration HP, North Middlesex Hospital.
Jan 1975-Jul 1975	Pre-registration HS, The London Hospital.
Aug 1975-Jul 1976	SHO General Medicine, North Middlesex Hospital.
Sep 1976-Aug 1978	Registrar General Medicine, North Middlesex Hospital.
Sep 1978-Apr 1979	Registrar Neurosurgery, National Hospital, Queen Square.
May 1979-Oct 1979	SHO Neurology, National Hospital, Queen Square.
Nov 1979-Jan 1982	Hon. Registrar Neurology, University of Oxford.
Feb 1982-Oct 1983	Registrar Neurology/Psychiatry, St Thomas' Hospital.
Nov 1983-Jul 1985	Registrar Neurology, National Hospital, Queen Square.
Aug 1985-Aug 1987	Senior Registrar Neurology, National Hospital, Queen Square/Guy's Hospital.
Oct 1987-Present	Consultant Neurologist, Western General Hospital, Edinburgh. Tenure with Lothian Health Board

4. Recent publications (title and refence); also papers accepted for publication (references should indicate first and last pages).

1. Will RG. Epidemiological surveillance of Creutzfeldt-Jakob disease in the United Kingdom. European J Epidemiology 1991; 7: 460-465.
2. Will RG. Slow virus infection of the central nervous system. Current Medical Literature (Neurology) 1991; 7(3) 67-69.
3. Esmonde TFG, Will RG. Magnetic resonance imaging in Creutzfeldt-Jakob disease. Ann Neurol 1992; 31(2): 230-231.
4. Esmonde TFG, Will RG. Creutzfeldt-Jakob disease in Scotland and Northern Ireland 1980-1989. Scot. Med. J. 1992; 37: 181-184.
5. Brown P, Preece MA, Will RG. 'Friendly fire' in medicine: hormones, homografts and Creutzfeldt-Jakob disease. Lancet 1992; 340: 24-27.
6. Will RG, Ironside JW, Bell JE. Bovine spongiform encephalopathy and risk to health. BMJ 1992; 305: 53.
7. Will.RG. Prions in animals. Virus & Life 1992; 4: 6-8.
8. Esmonde TFG, Will RG, Slattery JM, et al. Creutzfeldt-Jakob disease and blood transfusion. Lancet 1993; 341: 205-207.
9. Sawcer SJ, Yuill GM, Esmonde TFG, Estibeiro P, Ironside JW, Bell JE, Will RG. Creutzfeldt-Jakob disease in an individual occupationally exposed to BSE. Lancet 1993; 341: 642.
10. Esmonde TFG, Will RG. Transmissible spongiform encephalopathies and human neurodegenerative disease. BJHM 1993; 49: 400-404.