MRC

lical Research Council

APPLICATION FOR AN MRC GRANT
Please type throughout and
return this form with nine photocopies

| 1. Applicant(s) | Applicant 1 | Applicant 2 | Applicant 3 |
|---|---|---|---|
| Surname | WILL | BRUCE | |
| Forename(s) | ROBERT | MOIRA | |
| Age | 43 | 45 | |
| Title | DOCTOR | DOCTOR | |
| Post held | CONSULTANT NEUROLOGIST | UG7 | |
| No. of hours pw on project | 2 | 5 | |

2. Institution/Authority (administering grant if approved)

University of Edinburgh

Addresses at which the work will be do
Neuropathogensis Unit
Ogston Building
West Mains Road
Edinburgh EH19 3JF

3. Title of investigation (*not* exceeding *116* characters including spaces)

STRAIN CHARACTERISATION OF THE CREUTZFELDT-JAKOB DISEASE AGENT BY TRANSMISSION TO MICE

4. Type of grant sou

PROJECT

5. Abstract of research (*not* exceeding 250 words)

In view of the concern that exposure to BSE or scrapie may pose a risk to humans, it is propos investigate the relationship between sporadic Creutzfeldt-Jakob disease (CJD), Bovine Spong Encephalopathy (BSE) and scrapie, by transmission studies in mice. Transmissions will be set up fr cases of sporadic CJD, all homozygous for methionine at codon 129 of the PrP gene (ie wild-type) sources will include two recent CJD cases in which there is an occupational link with BSE contemporary cases of CJD for which there is no suspicion of a link with BSE and two CJD cases oc before the onset of the BSE outbreak. The experiments will have the same design as a ser transmissions of BSE, scrapie and spongiform encephalopathies in other species, currently in progress AFRC/MRC Neuropathogenesis Unit, in which brain material is injected into a panel of five mouse stra transmission from the human material is successful, the disease characertistics of CJD in mice compared with the results of transmissions from other species. They will also be compared with a s eight attempted transmissions of CJD to mic (seven successful), performed in the 1970s by R.H. Kir using only two mouse strains, and over twenty previous transmissions of natural scrapie.

6. Proposed starting date: January 1994

Proposed duration (in months): 36

| 7. SUMMARY OF SUPPORT REQUESTED | Year 1 £ | Year 2 £ | Year 3 £ | Year 4 £ | Year 5 £ | TO |
|---|---|---|---|---|---|---|
| STAFF | 55,208 | 56,960 | 58,712 | | | 170 |
| TRAVEL & SUBSISTENCE | – | – | – | | | |
| CONSUMABLES | 22,335 | 6,475 | 6,475 | | | 35 |
| EXCEPTIONAL ITEMS | – | – | – | | | |
| EQUIPMENT | 67,886 | | | | | 67 |
| SUB-TOTAL | 145,429 | 63,435 | 65,187 | | | 27 |
| INDIRECT COSTS (40% of Staff costs) | 22,083 | 22,784 | 23,485 | | | 6 |
| GRAND TOTAL | 167,512 | 86,219 | 88,672 | | | 34 |

G1

93/10.12/1.1

8. Does the project require Local Ethical Committee approval? Yes (No)

9. DECLARATION

Applicants

I have read the standard conditions of grant set out in the Notes 'MRC Research Grant Schemes' and agree to abide by th any amendments which may subsequently be issued. I shall be actively engaged in, and in day-to-day control of, the proje

| To be signed by | Signature | Name in block capitals | Date |
|---|---|---|---|
| APPLICANT 1 | R Lall | DR RG WILL | |
| APPLICANT 2 | M. Bruce. | DR. MOIRA BRUCE | |
| APPLICANT 3 | | | |

10. This application should be submitted by/through (i) the Head of Department and (ii) the officer who will be responsibl administering any grant that may be awarded. Each should sign the following delcaration:

I confirm that I have read this application and that, if granted, the work will be accommodated and administered in th Department/Institution in accordance with the conditions in the Notes 'MRC Research Grant Schemes' (G300/21). Th gradings and salaries quoted are correct and in accordance with the normal practice of this Institution.

(i) Signature of Head of Department

J. Douglas Miller

Title PROFESSOR OF SURGICAL NEUROLOGY
HEAD, DEPT OF CLINICAL NEUROSCIENCES

To be appended in typescript or block capitals

Name and initials (of (i) above) J. DOUGLAS MILLER

Institution UNIVERSITY OF EDINBURGH

Address WESTERN GENERAL HOSPITAL
EDINBURGH EH4 2XU

Date: 12 October 1993

(ii) Signature of Administrative Authority

Finance Officer/Bursar/Registrar/Secretary of Insti (delete as appropriate)

To be appended in typescript or block capitals

Name and initials (of (ii) above)

Institution

Address, telephone number and fax number if av (including STD code from London and extension)

Date:

11. Name, address, telephone number (including STD code from London and extension) and fax number in typescript (or block capitals) of the officer who should be contacted regarding the administration if awarded, if different from (ii) above

CLASSIFICATION: OFFICE USE ONLY

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |



93/10.12/1.2

12. HISTORY OF THE PROPOSED RESEARCH

TITLE OF INVESTIGATION:

(A) Is your research being supported by any outside body (other than the MRC)?

If so, please indicate (on additional sheets if necessary): (PLEASE SEE ATTACHED SHEETS)

(i) the topic

(ii) the supporting organisation

(iii) the value

(iv) the tenure

(B) Is this or a related application currently being submitted elsewhere? NO

If so,

(i) to which organisation

(ii) by what date is a decision expected

(C) Has this application been submitted elsewhere over the past year? NO

If so,

(i) to which organisation

(ii) what was the result

(D) Is the proposed research likely to lead to patentable or otherwise commercially exploitable results? NO

If so, please give brief details.

Other Grants

1. Department of Health and Scottish Home and Health Department
Surveillance of Creutzfeldt-Jakob Disease
1 January 1990 - 31 December 1993 (4 years)
£354,861
Administered through Department of Clinical Neurosciences, Edinburgh University.

2. Commission of the European Communities
Surveillance of Creutzfeldt-Jakob Disease in the European Community
1 January 1993 - 31 December 1995 (3 years)
£123,072
Administered through Department of Clinical Neurosciences, Edinburgh University.

3. Department of Health and Scottish Home and Health Department
Surveillance of Creutzfeldt-Jakob Disease - Neuropathology
1 January 1991 - 31 December 1995 (4 years)
£350,000 approx.
Administered through Department of Pathology, University of Edinburgh.

4. Medical Research Council
Prion Protein in Human Spongiform Encephalopathies.
1 January 1993 - 31 December 1996 (3 years)
£266,922
Administered through Department of Pathology, University of Edinburgh

5. Agricultural and Food Research Council
Neuropathological Targeting in Creutzfeldt-Jakob Disease - A Morphologi
Immunocytochemical and Quantitative Study.
1 September 1992 - 31 August 1995 (3 years)
£257,380
Administered through Department of Pathology, University of Edinburgh.

AGENT STRAIN VARIATION IN SPONGIFORM ENCEPHALOPATHIES

Other grants and sources of funding

1. Ministry of Agriculture, Fisheries and Food
Strain typing BSE pathogen in mice and comparison with strains from natural sheep scrapie
1 April 1990 - 31 March 1999 (9 years)
£500,000 approx.
Administered through Institute for Animal Health

2. Agricultural and Food Research Council
Targeting and cellular pathology of scrapie infection
1 August 1991 - 31 July 1994 (3 years)
£167,400
Administered through Institute for Animal Health

3. Agricultural and Food research Council and Medical Research Council
Strain variation in scrapie and related agents
Indefinite
£100,000 per annum approx.
Administered through Institute for Animal Health as part of core budget of Neuropathogenesis Unit

official postal address of all applicants

ANT 1

DR R WILL

RTMENT CJD SURVEILLANCE UNIT

TUTION WESTERN GENERAL HOSPITAL

RESS EDINBURGH EH4 2XU

ST CODE EH4 2XU

ELEPHONE No (including STD code from London) 031 332 2117 EXTENSION DIRECT

AX No 031 343 1404

APPLICANT 2

NAME DR M BRUCE

DEPARTMENT INSTITUTE FOR ANIMAL HEALTH

INSTITUTION AFRC & MRC NEUROPATHOGENESIS UNIT

ADDRESS OGSTON BUILDING, WEST MAINS ROAD, EDINBURGH

ST CODE EH9 3JF

TELEPHONE No (including STD code from London) 031 667 5204 EXTENSION

FAX No 031 668 3872

APPLICANT 3

NAME

DEPARTMENT

INSTITUTION

ADDRESS

POST CODE

TELEPHONE No (including STD code from London) EXTENSION

FAX No



93/10.12/1.6

14. Full official postal address of all Collaborators**

COLLABORATOR 1

NAME

DEPARTMENT

INSTITUTION

ADDRESS

POST CODE

TELEPHONE No (including STD code from London) EXTENSION

COLLABORATOR 2

NAME

DEPARTMENT

INSTITUTION

ADDRESS

POST CODE

TELEPHONE No (including STD code from London) EXTENSION

COLLABORATOR 3

NAME

DEPARTMENT

INSTITUTION

ADDRESS

POST CODE

TELEPHONE No (including STD code from London) EXTENSION

** on whom the viability of the proposal is dependent. A copy of a statement of willingness to cooperate should be enc application.

PROPOSED INVESTIGATION

1. Title

Purpose

3. Background

4. Plan of investigation

5. Detailed justification for support requested

1. TITLE

Strain characterisation of CJD agent by transmission to mice

2. PURPOSE

The broad objective is to investigate possible links between sporadic CJD and BSE scrapie, by the characterisation of the causative agents in mice. The immediate objectiv to compare the transmission characteristics of two cases of CJD in which a possi epidemiological link with BSE has been identified with the transmission characteristic BSE from cattle. A further objective is to transmit from cases of sporadic CJD in wh there is no suspicion of a link with BSE, to provide a baseline and to supply characteri isolates for future studies in transgenic mice carrying variants of the human PrP gene.

3. BACKGROUND

Epidemiological studies of sporadic CJD in the United Kingdom and elsewhere have so given no indication of a causative link with scrapie or with any other environmental fact However, the emergence of BSE in cattle and novel spongiform encephalopathies in c and several zoo species clearly indicates that spongiform encephalopathies can sprea new host species[2]. This has caused considerable concern about possible risks to the hu population.

There are many strains of scrapie and related agents but they can only be distinguishe the incubation periods and pathology they produce in experimentally-infected animals particular in rodents. Extensive studies at the AFRC/MRC Neuropathogenesis Unit (N over the last 25 years have shown that strain variation occurs in natural scrapie in sh and goats and can be detected by transmission to mice[3]. Further mouse-to-mouse pas usually results in the selection of variants of the agent, depending mainly on genetic fac in the mouse[4].

At NPU it has been established that BSE is transmissible to mice, producing a character pattern of incubation periods in a standard panel of genetically-defined mouse strain primary passage; the distribution of vacuolar changes in the brains of these mice represented by the "lesion profile", is also highly characteristic for BSE[5]. The result these transmissions were remarkably uniform for a number of different BSE sour collected at intervals and from widely separated geographical locations, suggesting that is caused by a single major strain of agent. Trans mission results have so far indicated novel spongiform encephalopathies in other species (cat, kudu, nyala) have been cause the same strain of agent as BSE and that BSE can be experimentally passaged thr sheep, goats and pigs without changing the strain characteristics of the agent[6]. uniformity of the disease characteristics in mouse transmissions of BSE and the fact B unchanged when passaged through a number of other species indicate that it ma possible to identify positively a BSE-derived agent strain, should it be present in human material.

CONTINUE ON NO MORE THAN:
(i) 5 SEPARATE A4 SHEETS FOR PROJECT OR SPECIAL PROJECT (
(ii) 9 SEPARATE A4 SHEETS FOR PROGRAMME GRANT
Applications which exceed this length will be returned as unacceptable

Recently CJD has been reported in two dairy farmers who have had BSE on their farms. Epidemological evidence suggests that the occurrence of CJD in the two farmers is most likely to have been a chance occurrence rather than implying a causative link with BSE? However this evidence cannot be regarded as definitive and it is essential to obtain further information on the source of the transmissible agent in these two individuals because of the manifest public health implications if transmission of BSE to man has occurred.

To investigate the possibility that disease in these farmers was caused by the same agent that causes BSE in cattle we propose to set up a transmission to mice from these cases, in parallel with transmissions from four other cases of CJD. Transmissions will be carried out using the same panel of mouse strains used for typing scrapie and BSE. If the results of transmission from any CJD source are similar to BSE, this would be good evidence that infection was acquired either from BSE cattle or from the original source of BSE. If they are different, no conclusions about the source of infection could be made, as the properties of isolates may sometimes be changed by passage through a new species - in this case human. The results of the six CJD transmissions will also provide a baseline for future transmission to transgenic mice.

It will be important to compare the results of the above transmissions with a series of several "pre-BSE" CJD transmissions, performed by R.H. Kimberlin in the 1970s. These produced no clinical disease in mice, but did produce unequivocal vacuolar degeneration indistinguishable from that in scrapie-infected mice; frozen tissues, suitable for further passage were collected from these mice. Depending on the results of the present set of transmissions, further mouse-to-mouse passages from selected CJD sources in the present and previous series may be performed at a later date to provide a more detailed comparison between CJD sources and for comparison with mouse-passaged strains derived from other species. Another possibility, if the CJD transmissions are successful, is that decontamination standards can be tested directly on CJD-derived material, rather than relying on extrapolation from mouse-passaged strains of scrapie.

## 4. PLAN OF INVESTIGATION

### Source brains

Six CJD transmission experiments will be set up: two from the CJD-affected farmers, two from recent cases of sporadic CJD with no suspicion of a BSE link (material supplied by RGW) and two from cases occurring before the widespread outbreak of BSE (material stored at NPU). The criteria for selecting these sources will be that they have none of the mutations in the PrP gene which are associated with familial CJD and that they are homozygous for methionine at the 129 codon (ie wild-type).

### Transmission experiments

As far as possible, inocula for transmission will be prepared from areas of brain showing CJD pathology. 10% brain homogenates will be injected both intracerebrally and intraperitoneally, as experience with BSE has shown that this combination of routes maximises the chances of a successful transmission. A panel of four inbred mouse strains and one $F_1$ cross will be used (RIII, C57BL, VM, IM and the $F_1$ cross between C57BL and VM), with group sizes of 24 mice of each strain per transmission. Before preparing each CJD inoculum, all the glassware and equipment to be used will be rinsed with sterile saline and this saline will be injected into groups of 6 mice of each strain, to control for laboratory contamination. Uninjected groups of 6 mice of each strain will also be included and housed with the experimental groups, to control for spread of infection between injected mice. Previous experience over many years at NPU indicates that neither laboratory contamination nor spread of infection between intact animals is a problem in transmission experiments, but

it is considered necessary to include these formal controls to avoid any ambiguity in interpretation of successful transmissions.

Injected mice will be maintained in a Category 3 containment suite at NPU, within thin isolators. Saline-injected and uninjected control mice will be housed alongside CJD-inje mice. All mice will be monitored throughout their lifespan for signs of neurological dise according to well-established protocols which have been used at NPU for many year scrapie and BSE in mice. Mice showing neurological signs will be killed at a defined cli end-point. Others will be maintained until they have to be killed due to intercurrent dis or old age. Brains will be collected from all mice; approximately 1/3 of each brain w frozen for possible future passage and the remainder will be formol fixed histopathological examination. In addition spinal cord samples will be collected from mi the later stages of the experiment for histopathological examination.

Pathological assessment

Samples for histology will be treated with formic acid after fixation to greatly re infectivity. Processing and paraffin embedding of tissues and preparation of sta sections will be carried out within the Category 3 containment suite at NPU, u equipment dedicated to handling CJD samples. Coded brain sections will be assesse the presence of the pathological changes associated with spongiform encephalopa (vacuolation, amyloid plaques, pathological accumulation of PrP). For any brains sho such pathology, the severity of vacuolation will be scored in 12 areas of brain, accordi established methods, to construct a "lesion profile".

## 5. DETAILED JUSTIFICATION FOR SUPPORT REQUESTED

Staff

The SO is required to assist at injections, to supervise the running of the experiments the containment suite, to coordinate supplies, waste disposal, autoclaving etc. to asse clinical status of the mice and to collate and analyse experimental data. The A required to breed and supply the mice for experiments, to assist the SO in the mainte and monitoring of experimental animals and to collect tissues for histopathology and transmissions. The SO and ASO will be responsible for the day-to-day care of the 365 days a year. The additional cost of work at weekends and holidays, calculated basis of double time, is included in the costing.

The EWs are required for general maintenance of the containment facility and as tec support for the project. Their duties will include cleaning, laundry, packing sup cleaning instruments etc. and packing for autoclaving.

The UG7 principal investigator will provide overall supervision and will prepare inocula the mice and be responsible for the histopathological assessment of the tissues.

Equipment

The containment suite at NPU has recently been completed, but will need extra equ to enable this experiment to be undertaken. The proposed study would be the firs carried out with CJD material in the suite and the listed items are essential before an work can be started.

One microbiological safety cabinet is required for preparing CJD inocula and injectir The other is needed for the dissection of mice and the collection of potentially i tissues.

The isolators are needed for the protection of staff from potentially CJD-infected materi. intact animals are thought not to present a significant hazard, but deaths of mice with cages and cannabalism by their cagemates could contaminate bedding, food and wat bottles. Housing of animals within isolators also simplifies cage-cleaning and protects st. from animal allergens.

The halothane apparatus is needed to anaesthetise mice for injection.

The PC is needed for the storage and analysis of experimental data and is essential f sending information to and from the containment suite, via the internal network which h been installed at NPU.

The balance will be used to weigh CJD-contaminated tissue samples for the preparation inocula.

The tissue processor, embedding centre and microtome are necessary for t histopathological preparation of slides for microscopy.

REFERENCES

1. Will RG. BSE and the Spongiform Encephalopathies. In: Recent Advances in Clini Neurology. Ed: Christopher Kennard, Published Churchill Livingstone 1992, Chapter 5, 115-127.

2. Bradley R. Bovine spongiform encephalopathy (BSE): the current situation and researc Eur J Epidemiology 1991; 7: 532-544.

3. Kimberlin RH. Transmissible Encephalopathies in Animals. Can J Vet Res 1990; 54: 30-37.

4. Bruce ME, McConnell I, Fraser H, Dickinson AG. The disease characteristics of differ strains of scrapie in Sinc congenic mouse lines: implications for the nature of the agent a host control of pathogenesis. J Gen Virology 1991; 72: 595-603.

5. Fraser H, Bruce ME, Chree A, McConnell I, Wells GAH. Transmission of bovine spongifc encephalopathy and scrapie to mice. J Gen Virology 1992; 73: 1891-1897.

6. Bruce ME, Chree A, McConnell I, Foster J, Fraser H. Transmission of BSE and scrapie mice: strain variation and the species barrier. Abstract: Discussion meeting on Molec Biology of Prion Diseases, The Royal Society, London, 22-23 September 1993.

7. Sawcer SJ, Yuill GM, Esmonde TFG, Estibeiro P, Ironside JW, Bell JE, Will RG. Creutzfe Jakob disease in an individual occupationally exposed to BSE. Lancet 1993; 341: 642.

DETAILS OF SUPPORT REQUESTED (summarised in Section 7 of the application form) ANNEX

| DETAILS OF POSTS (see NOTES) NAME | Grade | Start Point on Scale | Incremental Date | Starting Salary £ | London Weighting £ | Other Allowances £ | Combined Superann and National Insurance £ | C Y |
|---|---|---|---|---|---|---|---|---|
| (A1) RESEARCH STAFF | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| (B1) TECHNICAL STAFF | | | | | | | | |
| 1 K. Lamza | SO | | Performance | 13,651 | – | 1,950* | 3,413 | 1 |
| 2 | ASO | | " | 11,138 | – | 1,591* | 2,785 | 1 |
| 3 | EW | | " | 8,272 | – | – | 2,068 | 1 |
| 4 | EW | | " | 8,272 | – | – | 2,068 | 1 |
| (C1) OTHER STAFF | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| ANNUAL COSTS OF ABOVE POSTS | Effort on Project | | YEAR 1 | YEAR 2 | YEAR 3 | YEAR 4 | YEAR 5 | |
| (A2) RESEARCH STAFF | % | months | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| TOTAL A2 | | | | | | | | |
| (B2) TECHNICAL STAFF | | | | | | | | |
| 1 K. Lamza (SO) | 100 | 36 | 19,014 | 19,892 | 20,766 | | | |
| 2 ASO | 100 | 36 | 15,514 | 16,388 | 17,266 | | | |
| 3 EW | 100 | 36 | 10,340 | 10,340 | 10,340 | | | |
| 4 EW | 100 | 36 | 10,340 | 10,340 | 10,340 | | | |
| TOTAL B2 | | | 55,208 | 56,960 | 58,712 | | | |
| (C2) OTHER STAFF | | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| TOTAL C2 | | | | | | | | |
| GRAND TOTAL (A2) + (B2) + (C2) | | | 55,208 | 56,960 | 58,712 | | | |

* Weekend work/Overtim



93/10.12/1.12

| 3. TRAVEL AND SUBSISTENCE DESTINATION and PURPOSE (see NOTES) | Number of | | MODE of TRANSPORT | FARE/ MILEAGE | SUBSISTENCE | FEES |
|---|---|---|---|---|---|---|
| | Journeys | Days | | | | |
| (i) Within the UK | | | | | | |
| (ii) Overseas | | | | | | |
| TOTAL ANNUAL COSTS £(i) + (ii) | Year 1 | | Year 2 | Year 3 | Year 4 | Year 5 |

| 4. CONSUMABLES ETC Please specify | Year 1 £ | Year 2 £ | Year 3 £ | Year 4 £ | Year 5 £ |
|---|---|---|---|---|---|
| Laboratory equipment: incubator, waterbath, glassware, staining set, drying cabinet, instruments, other small items | 4500 | | | | |
| Airflow helmets x2 | 650 | | | | |
| Fridge and freezer | 700 | | | | |
| Trolleys x2 | 440 | | | | |
| Flammables & anaesthetics cupboards | 350 | | | | |
| Laboratory furniture | 1300 | | | | |
| Protective clothing, towels | 2300 | | | | |
| Printer | 300 | | | | |
| Laboratory consumables | 5000 | 5000 | 5000 | | |
| SUBTOTAL ANNUAL COSTS £ | 15540 | 5000 | 5000 | | |

| 4. CONSUMABLES ETC CONTINUED<br>Please specify | Year 1<br>£ | Year 2<br>£ | Year 3<br>£ | Year 4<br>£ | Year 5<br>£ | T( |
|---|---|---|---|---|---|---|
| ANIMALS—Purchase<br>(i) intended source of supply<br>(ii) species and microbiological quality required<br>(iii) number required<br>(iv) purchase price per animal<br><br>1080 mice - produced within NPU<br>Cost covered by salaries listed | | | | | | |
| ANIMALS—Maintenance<br><br>Cages, lids, bottles | 5320 | | | | | |
| Recurrent costs: food, bedding.<br>Mice maintained up to lifespan | 1475 | 1475 | 1475 | | | |
| TOTAL ANNUAL COSTS £ | 6795 | 1475 | 1475 | | | |

| 5. EXCEPTIONAL ITEMS Detail items applied for (see NOTES) | T |
|---|---|
| | |

| TOTAL ANNUAL COST £ | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| | | | | | |

93/10.12/1.14

| 6. EQUIPMENT<br>Description of items and Country of Manufacture | EXPIRY DATE OF QUOTATION | LIKELY DELIVERY DATE | BASIC PRICE £ | IMPORT DUTY £ | VAT £ | TO |
|---|---|---|---|---|---|---|
| (1) Class II microbiological safety cabinets x2, Envair, UK | 1/12/93 | 1/ 1/94 | 13640 | – | – | 136 |
| (2) Thin – film isolators (60 cage) x3, Moredun Isolators, UK | 1/12/93 | 1/ 1/94 | 20236 | – | – | 202 |
| (3) Tissue processor, Shandon, UK | List | 1/ 1/94 | 20800 | – | – | 208 |
| (4) Embedding centre, Miles, UK | List | 1/ 1/94 | 5090 | – | – | 50 |
| (5) Microtome, Jung, Germany | List | 1/ 1/94 | 4305 | – | – | 43 |
| (6) Halothone apparatus, UK | List | 1/ 1/94 | 1200 | – | – | 12 |
| (7) Computer, Viglen, UK | List | 1/ 1/94 | 1320 | – | – | 13 |
| (8) Balance, Sartorius, Germany | List | 1/ 1/94 | 1295 | – | – | 13 |

| ANNUAL COST OF ABOVE ITEMS | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | |
|---|---|---|---|---|---|---|
| (1) | | | | | | |
| (2) | | | | | | |
| (3) | | | | | | |
| (4) | | | | | | |
| (5) | | | | | | |
| (6) | | | | | | |
| (7) | | | | | | |
| (8) | | | | | | |
| TOTAL ANNUAL COST £ | | | | | | |

1. Surname BRUCE Forename(s) Moira Age 45 d.o.b. 18..

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

BSc (Hons), III, Biochemistry, Birmingham, 1969
PhD, Brain Research, Open University, 1980

3. Posts held (with dates); please identify tenure and source of funding of present post.

| | | |
|---|---|---|
| 1970-1981 | SO/HSO | Animal Breeding Research Organisation, Edinburgh |
| 1981-present | SSO/UG7 | Institute for Animal Health, Neuropathogenesis Unit, Edinburgh<br>Permanent position<br>AFRC funded |

4. Recent publications; also papers in press

Bruce, M.E., McConnell, I., Fraser, H. & Dickinson, A.G. (1991) The di characteristics of different strains of scrapie in Sinc congenic mouse implications for the nature of the agent and host control of pathogenesis. Jour General Virology 72, 595-603.

Eikelenboom, P., Rozemuller, J.M., Kraal, G., Stam, F.C., McBride, P.A., Bruce & Fraser, H. (1991) Cerebral amyloid plaques in Alzheimer's disease but n scrapie-affected mice are closely associated with local inflammatory process. Vi Archiv B Cell Pathol 60, 329-336.

Fraser, H., Bruce, M.E., Chree, A., McConnell, I. & Wells, G.A.H. (1992) Transm of bovine spongiform encephalopathy and scrapie to mice. Journal of General Vi 73, 1891-1897.

Jeffrey, M., Goodsir, C.M., Bruce, M.E., McBride, P.A., Scott, J.R. & Halliday (1992) Infection specific prion protein (PrP) accumulates on neuronal plasmale scrapie-infected mice. Neuroscience Letters 147, 106-109.

McBride, P.A., Eikelenboom, P., Kraal, G., Fraser, H. & Bruce, M.E. (1992) PrP p is associated with follicular dendritic cells of spleens and lymph nodes in unin or scrapie-infected mice. Journal of Pathology 168, 413-418.

Bruce, M.E., McBride, P.A., Jeffrey, M. & Scott, J.R. (1993, in press) PrP in pat and pathogenesis in scrapie-infected mice. Molecular Neurobiology.

Bruce, M.E., Chree, A., McConnell, I., Foster, J., Pearson, G. & Fraser, H. (1 press) Transmission of bovine spongiform encephalopathy and scrapie to mice: variation and the species barrier. Philosophical Transactions of the Royal Soc

CURRICULUM VITAE OF APPLICANT

1. Surname WILL Forename(s) Robert George Age 43 d.o.b. 30.

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); please identify tenure and source of funding of present post.

| | |
|---|---|
| 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; also papers in press


1. Will RG, Matthews WB. Creutzfeldt-Jakob disease in England and Wales II: Epidemiology. JNNP 1986; 49: 749-755.
2. Harries-Jones R, Knight R, Will RG, Cousens S, Smith PG, Matthews WB. Creutzfeldt-Jakob disease in England an 1980-1984: a case-control study of potential risk factors. JNNP 1988; 51: 1113-1119.
3. Cousens S, Harries-Jones R, Knight R, Will R, Smith PG, Matthews WB. Creutzfeldt-Jakob disease in England and Geographical distribution of cases 1970-1984. JNNP 1990; 53: 459-465.
4. Scott PR, Aldridge BM, Clarke M, Will R. Bovine spongiform encephalopathy in a cow in the United Kingdom. 1989, Vol 195, No 12, December 15.
5. Will RG. Prion disease. Lancet 1990; 336: 369.
6. Will RG. Editorial: Spongiform Encephalopathies. JNNP 1991; 54: 761-763.
7. Will RG. An overview of Creutzfeldt-Jakob disease associated with the use of human pituitary growth hormone. Biol. Standard 1991; 75: 85-86.
8. Will RG. Subacute spongiform encephalopathies. In: Current Medicine-3. Ed: D.H. Lawson, 1991; Chapter 9 143.
9. Will RG. Epidemiological surveillance of Creutzfeldt-Jakob disease in the United Kingdom. European J Epidemiol 7: 460-465.
10. Will RG. Slow virus infection of the central nervous system. Current Medical Literature (Neurology) 1991; 7(3) 67
11. Esmonde TFG, Will RG. Magnetic resonance imaging in Creutzfeldt-Jakob disease. Ann Neurol 1992; 31(2): 230-2
12. Esmonde TFG, Will RG. Creutzfeldt-Jakob disease in Scotland and Northern Ireland 1980-1989. Scot. Med. J. 1 181-184.
13. Brown P, Preece MA, Will RG. 'Friendly fire' in medicine: hormones, homografts and Creutzfeldt-Jakob diseas 1992; 340: 24-27.
14. Will RG, Ironside JW, Bell JE. Bovine spongiform encephalopathy and risk to health. BMJ 1992; 305: 53.
15. Will RG. Prions in animals. Virus & Life 1992; 4: 6-8.
16. Esmonde TFG, Will RG, Slattery JM, et al. Creutzfeldt-Jakob disease and blood transfusion. Lancet 1993; 341: 2
17. Sawcer SJ, Yuill GM, Esmonde TFG, Estibeiro P, Ironside JW, Bell JE, Will RG. Creutzfeldt-Jakob disease in an occupationally exposed to BSE. Lancet 1993; 341: 642.
18. Esmonde TFG, Will RG. Transmissible spongiform encephalopathies and human neurodegenerative disease. BJ 49: 400-404.
19. Esmonde TFG, Leuck CJ, Symon L, Duchen LW, Will RG. Creutzfeldt-Jakob disease and lyophilised dura ma report of two cases. JNNP 1993; 56: 999-1000.

CURRICULUM VITAE OF PROPOSED RESEARCH STAFF/VISITING SENIOR SCIENTIST

1. Surname | Forename(s) | Age d.o.b.

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

3. Posts held (with dates); please identify tenure and source of funding of present post.

4. Recent publications; also papers in press

1. Surname | Forename(s) | Age d.o.b.

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

3. Posts held (with dates); please identify tenure and source of funding of present post.

4. Recent publications (title and reference)

Please return form on completion to:
Medical Research Council, Grants and Training Awards Section, 20 Park Cresent, London W1N 4AL



93/10.12/1.18

For each and every MRC Grant which you or any one of your co-applicants have held as principal applicant and which has beg terminated over the past five academic years, please give the information requested below, copying this sheet as necessary us one sheet for each grant.

1. Project title:

2. Started:

3. Finished:

4. Grant holder(s):

5. Brief summary of your current perception of the significance of the work done (eg as increment to knowledge, conceptual c methodological advance, contributiuon to medical practice, training, industrial exploitability/applicability/spin-off), and of the project's significance for your own, your assistants', and your colleagues' scientific development.

6. Scientific papers directly resulting from this grant (full papers published or "in press" in refereed journals with title, full pagination and co-authorship: please asterisk the key paper(s) and underline the names of any assistant(s) on the grant among authors). For "Shared Equipment Grants" with three or more sub-projects, you could cite up to two papers per sub-project to illustrate the use to which the equipment was put.

You may wish to retain a copy of this report for updating in the context of future applications to MRC.

Agricultural and Food Research Council
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21st October 199

Statement by the Director

Although this application is being submitted by Dr. R. Will, all of the work will b carried out within the purpose-built, category 3 containment suite recently completed at NPU While the work involves the biological characterisation of 6 sources of CJD agent, th essential question being addressed is whether it is possible to confirm that two recent cas of CJD, occupationally linked to BSE, may have their origins associated with BSE. T nature of the work does require the purchase of dedicated equipment for the facility (anim holding equipment and the capacity to process the highly infectious brain material f histopathological examination) and the appointment of staff as indicated in the proposal. addition to the staff positions identified and costed, existing members of staff paid for c of the core budget will contribute to the project.

Since the project addresses questions of public concern about CJD and its relation BSE I think it is appropriate that Dr. Will is the "senior" applicant who would be responsib for interfacing with the Department of Health and the public in communicating results. would also expect the neuropathologists at the Western General Hospital to be involved the histopathological assessment of experimental material. Since Dr. Bruce and her staff NPU have the experience of strain typing BSE and scrapie it is right that this work is do at NPU. It has my full support and all existing resources of the Institute will be ma available to the project. However, I would not wish this work to interfere with the co scientific programme recently reviewed and approved by both AFRC and MRC and it is b this reason that the additional funds are required.

Professor F. J. Bourne
Director, Institute for Animal Health

**93/10.12/1.20**