News of three important projects investigating prion disease

Research at the Prion Unit

Dr Simon Mead, Clinical Research Fellow, MRC Prion Unit, St Mary’s Hospital, London

Two of the most important research goals for the MRC Prion Unit at the Imperial College School of Medicine are to develop a diagnostic blood test for variant CJD and to find drugs that slow the progression of or stop the disease. We have many studies underway which aim to understand the fundamental molecular basis of prion diseases. It is from this scientific understanding that we hope to make medically useful discoveries. The ongoing research projects are numerous and diverse - an explanation of all of these is beyond the scope of this article - but there are three which may be of particular interest.

Therapeutic drug development

All prion diseases are caused by a normal brain protein (known as the prion protein) changing its shape. These rogue prion proteins act by converting more normal protein into the rogue form and this process kills brain cells. We believe that drugs which bind to the normal prion protein and protect it from this change in shape may help treat all forms of prion disease. The MRC Prion Unit has developed a method using robotic technology that can screen many thousands of drugs in the hope of finding one or more that do this. This research is going well and we hope to have completed a screen of over 100,000 potential drugs before the end of this year. However, much more work will then be required before we will know whether such drugs slow down prion disease in animals, and if they are safe for human use. This exciting development is the first step along the way to a potential treatment.

Developments in diagnosis

As you know, we have been doing a great deal of research to try to develop better means of diagnosing variant CJD. Some time ago we introduced a tonsil biopsy for this purpose. So far, the tonsil test has been completely accurate in diagnosis of the disease, but it would be far preferable to have a blood test. A blood test would not only help in the diagnosis of individuals that might have variant CJD but could also be used in large scale anonymous screening studies to try to get some idea of how many people in the population might be going to get the disease. Earlier diagnosis will also be vital once treatments become available so that the disease can be blocked before major damage has been done to the brain. The difficulty with developing a blood test is that the rogue prion protein is likely to be present in the blood in only tiny amounts. We have made some dramatic improvements in our ability to detect very small concentrations of the rogue prion protein through chemical purification techniques and by using specially made antibodies against the prion protein. We still do not know how long it will take to develop a blood test, but expect to make further significant improvements in our ability to detect the rogue protein over the next year.

Screening project

Many tonsils are removed every day in routine operations on people with throat problems. We are undertaking a large anonymous screening project on these tonsils, which would otherwise be discarded, to see if there are people in the normal population who have the rogue prion protein seen in variant CJD in their tonsils. Unfortunately, if we find no positive tonsils this will not mean that an epidemic will not happen. This is because even the 2,000 tonsils we will initially screen is still a relatively small sample of the population. Also, there is no way at present of knowing how early following infection with BSE the tonsil test would be positive, so we...
Predictions

Research published in Nature indicated that it was unlikely there would be an epidemic of vCJD. At current incidence rates, in 20 years’ time there will be no more than 630 cases of vCJD in the UK.

Commenting in The Times (10.8.00), Clive Evers said: ‘We might take some encouragement from these figures. However, we have to be cautious. There have already been 15 cases of vCJD this year, which is a significant increase on last year. It could still be the case that we are talking about thousands of people being affected in the future. We need another five years’ figures before sound statistical predictions can be made.’

Maternal transmission

Fears have been expressed that CJD can be passed from mother to baby. A young mother who has since died with vCJD gave birth to a baby 11 months ago while she had the disease. The baby was born with extensive brain damage. Extensive tests have been carried out on the baby but no reason for the brain damage has been found other than the mother’s illness.

Variant CJD statistics

The Spongiform Encephalopathy Advisory Committee (SEAC) has agreed criteria for diagnosing vCJD in living people. This is considered reliable enough for the Department of Health to publish monthly the number of patients known to have ‘probable’ variant CJD in addition to numbers of confirmed vCJD deaths.
appearances in a central part of the brain called the pulvinar in two early cases, prompting the study. The scientists analysed MRI scans from 36 patients with vCJD and 57 control patients without CJD. Twenty-eight of the vCJD cases but none of the controls had prominent pulvinar abnormalities. According to the investigators, ‘In an appropriate clinical context the MRI identification of bilaterally increased pulvinar signal is a useful non-invasive test for the diagnosis of vCJD.’ The study involved only patients unwell with suspected vCJD and did not investigate whether MRI scanning could identify people incubating the disease.

**A way to block CJD**

Scientists in New York believe they may have found a way to block the development of vCJD. Claudio Soto and an international team of scientists said their findings might be of use in blocking the development of all the spongiform encephalopathies. Their work centred on preventing the changes in the prion protein that lead to spongiform encephalopathies developing. They found that the treatment reversed the changes in the prion protein (The Guardian, 14.1.00).

**Department of Health**

The Department of Health has set up a CJD incidents panel as a subcommittee of the Spongiform Encephalophathy Committee and the Advisory Committee on Dangerous Pathogens. The panel will advise on incidents involving potential transmission of CJD and vCJD between patients through clinical interventions.

A report has already been prepared which, according to The Times (30.8.00), will recommend the destruction of surgical instruments in certain circumstances. The panel will draw up guidelines on safety and on ethical issues in relation to patients and confidentiality.

The panel consists of experts on CJD, blood transfusion, disease infectivity and sterilisation, surgical procedures and hospital management and ethics. Two members of the panel represent patient interests: Harry Cayton, chief executive of the Alzheimer’s Society, and Jean Gaffin, former director of the National Association for Hospices and Palliative Care.

**CJD Cluster?**

The government revealed that experts from the CJD Surveillance Unit, The London School of Hygiene and Tropical Medicine, the Public Health Laboratory Service, the Ministry of Agriculture, the Department of Health and the local health authority joined an investigation into an apparent cluster of five cases of vCJD in Leicestershire.

The Guardian and other national newspapers (14.7.00) reported that ministers have been told that such a high number of cases in one area is unlikely to occur by chance. Lord Hunt told the House of Lords that these cases would have been exposed to the infective agent before current effective control measures were in place.

Investigations have centred on the village of Queniborough. Dr Phillip Monk, consultant in infectious diseases at Leicestershire Health Authority, reported that, amongst the investigations in the area, are plans to examine tonsil and appendix tissue removed from patients in Leicestershire. The anonymous survey would give doctors an idea of how many cases there could be.

Another area of study involved asking the residents of Queniborough for their help. Thirty-two questions were asked, including what they ate when they were a child and for any information about long closed abattoirs and other meat suppliers.
Debate on BSE

The Guardian (9.6.00) reported that scientists were preparing to launch a national debate on whether people who have been infected with the human form of BSE should be told they have the incurable disease.

CJD Surveillance Unit

The National CJD Surveillance Unit in Edinburgh has appointed Gordon McLean as national CJD care co-ordinator. Gordon qualified as a registered general nurse in 1992 and, prior to being appointed at the Unit, worked in continuing care centre for people with HIV/Aids. Gordon primarily focused on caring for individuals in the terminal stages, and their carers. He has completed courses devoted to caring for the dying and palliative care.

CJD guidelines for health workers

The Department of Health has issued CJD guidelines for health workers. These guidelines were issued to all doctors in the ‘Chief Medical Officer’s Update’ Friday 25 August 2000. The guidelines can be downloaded from the Department of Health’s website on www.doh.gov.uk/cjdguidance.htm. The CJD Support Network was instrumental in persuading the DoH to produce the guidelines.

CJD Guidelines for social workers

The Association of Directors of Social Services (ADSS) in November 1998 distributed CJD Guidelines for Social Workers to directors of social services. A copy of these guidelines can be obtained from the CJD Support Network.

CJD Voice

CJD Voice, an American Internet CJD support group, held a very successful conference on the disease in Miami in July 2000 which attracted researchers from all over America and Europe.

CJD and school dinners

Infected baby food and school meals could have helped to cause vCJD in young people, fears Professor Will. It was reported widely in the media that Professor Robert Will, director of the government’s CJD Surveillance Unit, indicated that the use of mechanically extracted meat in baby food and children’s favourites such as hamburgers and sausages in the 1980s could be at the root of the transmission. ‘One possible explanation for the age distribution is that young people tend to eat these products more than the adult population,’ said Professor Will.

The Network in America

Gillian Turner from the Network, with Dr Paul Brown from the National Institutes of Health, Bethesda, Maryland USA and Elaine Sproat, whose mother died from classical CJD, jointly presented an education session on CJD at the World Alzheimer’s Congress 2000 in Washington DC. The three-week congress attracted 5,000 delegates from 50 countries.

Food Standards Agency

Clive Evers and John Williams represented the Network at a meeting of the Food Standards Agency at Westminster Central Hall on 18 July 2000. It was a large meeting with as many people on the committee/stakeholder group as in the public audience. Sir John Krebs chaired the meeting. Thirty-nine questions are to be addressed by the Agency as agreed by the stakeholder group, five of which relate specifically to humans.

1. What is the likely future incidence of vCJD in humans?
2. What are the uncertainties and assumptions?
3. How effective are the food chain controls (relating to cattle, sheep/goats, pigs and other farmed livestock) in removing the possible fear?
4. What impact on vCJD in humans would there be if the controls were changed and would it be acceptable?
5. What additional knowledge will refine or test these predictions and assessments and on what timescale?

The meeting concluded that it was necessary to be suitably cautious. It gave no indication that it was going to recommend any loosening of the existing controls, but gave pointers to the possibility of this happening sometime in the future after further evidence is obtained from experiments.

A follow up meeting held on the 14 September discussed the draft report drawn up by the panel after the first meeting. An amended report is to be presented to the stakeholder group at a meeting on 9 October in York.
Hospices and community palliative care services are extending their help to patients with illnesses other than cancer and at any time following diagnosis. These days, help and support is provided to patients and families with any illness which is progressive and incurable. CJD thus falls into this category.

So what sort of help can hospices or palliative care services provide? Help is available for the psychological, physical and practical problems caused by the illness with the overall aim of maximising quality of life for however long the illness runs. Such help may be necessary at any time after the diagnosis, not just in the final few days or weeks.

Palliative care can be provided in a variety of different settings, not just in a hospice. The majority of patients prefer to be at home if at all possible cared for by their GP and district nurse. They can be visited by palliative care (Macmillan) nurses or specialist doctors who provide specialist support to professionals and family alike. Close communication with other health professionals – for example, specialist nurses in CJD, occupational therapists, speech therapists, social workers – is also very important so that patients can receive truly holistic support for every aspect of their illness.

There may be circumstances where it is proving too difficult for the patient to remain at home all the time. Hospices may be able to provide day care or respite admissions periodically so that families can recharge their batteries and continue to look after their loved ones at home. Occasionally, particularly difficult physical or psychological symptoms may be helped by a short admission to the hospice where assessment and monitoring first-hand leads to resolution of the problem. If time is short and it is proving too difficult for the patient to be nursed at home, admission for terminal care can also be considered.

The days when all patients admitted to a hospice never came out again are over. Palliative care services can hopefully provide extra help and support over and above that available through the health service to make life for patients and their families more bearable. Further information about your local hospices and palliative care services is available from the Hospice Information Service, telephone 020 8778 9252, website: www.hospiceinformation.co.uk
Are vaccines the cause of vCJD?

Professor Bob Will, Director, National CJD Surveillance Unit, Scotland

There is now compelling evidence that variant CJD is caused by the BSE agent, but the route of transmission of infection has not been established. Although the most likely theory is that infection occurred through the past consumption of high levels of BSE infection in human food, other possibilities must be carefully considered. One theory is that variant CJD was caused by infection from vaccines contaminated with BSE.

Some vaccines were manufactured in the UK using in the production process tissues or blood components from British cattle. Vaccines are usually given by injection, which is more efficient at transmitting infection in prion diseases than infection given by mouth. However it is very unlikely that vaccines can be the cause of variant CJD. The dose of infection, as well as the route of exposure, is a critical factor in whether or not prion diseases can be transmitted. The material from cattle used in the production of routine childhood vaccines almost certainly contained no significant infectivity even if taken from an infected animal and the amount of this material in the final dosage of vaccine was very small. Taking these and other factors into account, a recent calculation from a meeting of the FDA in the United States suggested that for viral vaccines produced in the UK between 1985 and 1988 were used outside the UK and that not a single vaccine-associated case of BSE had been identified.
Transmissible spongiform encephalopathy (TSE)

Dr Paul Brown, M D, National Institutes of Health, Bethesda, Maryland USA.

Scientific beginnings
A round the middle of the nineteenth century, vets in England, France, and Germany initiated the scientific study of scrapie, a fatal disease spreading amongst sheep.

French vets finally succeeded in 1936 in transmitting scrapie to healthy sheep (confirmed at the same time in England). The transmissible nature of scrapie was established beyond any doubt.

The 1940s and 1950s yielded the observation that infectivity survived a dose of ionizing radiation that was incompatible with the biologic integrity of nucleic acid. This observation later led to the idea that the agent might consist only of protein.

The human connection
In 1959 scrapie was proposed by an American to be analogous to a neurological disorder of humans called kuru, found only in Papua New Guinea. Experiments to detect an infectious agent in kuru were extended in 1963 to include the observation of inoculated chimpanzees, which two years later developed the disease. In the meantime, a study of kuru had suggested a resemblance to Creutzfeldt-Jakob disease (CJD). CJD was duly inoculated into chimpanzees, and transmitted disease within 12-14 months.

An unexpected twist
In the early 1980s, it was discovered that brain tissue could be purified to the point that only a single protein (called PrP or 'prion protein') remained associated with the infectivity. To the surprise of everyone, this protein was encoded by a normal host gene, and not by a foreign invader. All that we have since learned has suggested a self-replicating protein as the core of the infectious agent. Many further studies have since been undertaken to determine the precise basis of infectivity in transmissible spongiform encephalopathy (TSE), and to find some means to protect both humans and animals from becoming infected.

Successes...
We have learned that PrP is not distinguished from other proteins by any unique structural features, and that its primary structure is identical in both normal and disease state. However, in diseased individuals its three-dimensional structure is altered, changing from a ‘floppy’ soluble to a ‘stiff’ insoluble amyloid. We have also learned that, although the only cells that are visibly abnormal occur within the nervous system, the infectious agent is also present in many visceral organs. The major pathway after oral infections involves the tonsils, intestinal lymphatic tissues and spleen, from which it spreads along nerves the spinal cord and brain.

After identifying the gene that encodes PrP, more than two dozen different mutations were identified as responsible for the familial form of CJD, Gerstmann-Straussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). All are transmissible in the laboratory. These mutations suggest with near certainty that during a single lifetime the normal protein will transform itself into an abnormal configuration. Once transformed, the altered protein leads to the generation of amyloid with the property of self-replication. This, at least, is the theory.

Molecular manipulation has shown that mice with no PrP are totally resistant to infection and disease, thus opening the door to a consideration of genetic engineering to prevent human TSE.

... and failures
While these research studies were going on, three outbreaks of CJD tested our ability to foresee potential problems and found it wanting. A procedure developed in the mid ‘60s to extract growth hormone from pituitary glands led to large-scale distribution to hormone-deficient patients. Glands were obtained from cadavers at autopsy, and were pooled in batches of up to 10,000. In 1985, CJD was reported in three US patients, leading to the immediate replacement of native hormone by a genetically engineered product. Despite this, CJD has since been responsible for over 130 hormone-related deaths, chiefly in France, Great Britain and the US, after longer and longer incubation periods (up to 30 years) from the period when native hormone was used. It is clear that even when the potential risk was appreciated (nearly ten years before the first case of CJD), most of the damage had already been done.

Almost coincident with the growth hormone-CJD outbreak, contaminated dura mater (brain tissue) grafts were also discovered to have caused iatrogenic CJD. Since 1988, more than 100 neurosurgical cases have died from CJD, the contamination again resulting from inadequate donor screening criteria and batch-pooling of cadaveric tissue. The lessons learned from these tragedies have prompted much more stringent regulations governing the collection and use of human-sourced biologicals.

In 1996 a ‘new variant’ of CJD (nvCJD) was recognised in young British people. This has since with near certainty been traced to the consumption of tissue from cattle infected with spongiform encephalopathy (BSE), they having in turn consumed meat and bone meal contaminated with scrapie-infected rendered sheep carcasses. It appears most likely that changes in the animal rendering process that occurred around 1980 allowed the scrapie agent to survive and infect cattle, the carcasses of which were then recycled through the rendering plants, leading to ever greater levels of cattle-adapted infectivity in meat and bone meal, and eventually producing a full-scale BSE epidemic.

An imposition in 1988 of a ruminant feed ban turned the epidemic around by 1992, but the loss of some 180,000 cattle to date has brought the British...
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livestock industry to its knees. BSE has also echoed through the tallow, gelatine, and pharmaceutical industries, all of which make use of bovine-derived products for human use. Even the blood bank community has been seriously affected by the uncertainty about infectivity in blood donations from patients incubating vCJD. There are presently 84 definite or probable cases of vCJD in the UK, and the number continues to grow at the rate of about 10 new cases per year. Whether they represent a small group of susceptible individuals, or the leading edge of a major epidemic, is still moot.

The millennium
We expect that during the early years of the 21st century, most of the remaining uncertainties will be resolved. These can be grouped into four broad categories: precise characterisation of the infectious agent; elucidation of the mechanism of agent replication; prevention or treatment of disease; and continued exploration for other candidate diseases.

Although PrP is beyond doubt a necessary component of the infectious agent, formal proof that it is by itself infectious is still lacking.

What is it about PrP amyloid (as distinct from other types of amyloid such as that of Alzheimer’s disease) that gives it the ability to replicate and transmit disease to new hosts?

The answer to this fundamental question need not inhibit research into disease prevention and therapy, which may come from a more general understanding of the process of amyloid formation. Chemical manipulation of the cellular pathways involved in PrP metabolism or interference with the protein transformation to amyloid could become viable therapeutic approaches, and efforts to arrest and even reverse amyloid accumulation in experimental models are already beginning to show promise. Similarly, manipulation of the PrP gene in familial forms of disease will become feasible when genetic engineers manage to duplicate in humans the successful results obtained in mice.

A more detailed version of this review, including references, can be found in British Medical Journal, Volume 317 (19-26 December 1998) 1688-92.

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**Monthly Creutzfeldt-Jakob disease statistics**

5 September 2000

The Department of Health issued the latest information about the numbers of known cases of Creutzfeldt-Jakob disease in the UK

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<th>familial</th>
<th>GSS</th>
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**CJD Support Network membership application**

The CJD Support Network is part of the Alzheimer’s Society. Becoming a member of the Society adds to our strength and enables you to take a full part in the decision-making process and the work of the Network.

☐ I would like to become a member and receive the Alzheimer’s Society’s monthly newsletter.

☐ I would like to become a member but **not** receive the Alzheimer’s Society’s monthly newsletter.

There is no fixed subscription, but please give generously to help our work.

☐ £8 ☐ £12 ☐ £25 ☐ £50 ☐ Other

Please make cheques payable to Alzheimer’s Society

However, if you are a carer and would appreciate free membership, please tick the box ☐

Name ____________________________ Title ____________________________

Address ____________________________________________________________

____________________________________________________________________

Postcode __________ Telephone ________________________________

I am caring for someone with CJD: ☐ at home ☐ in residential care

I am: ☐ a concerned relative/friend ☐ former carer ☐ professional ☐ interested CJDNS

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