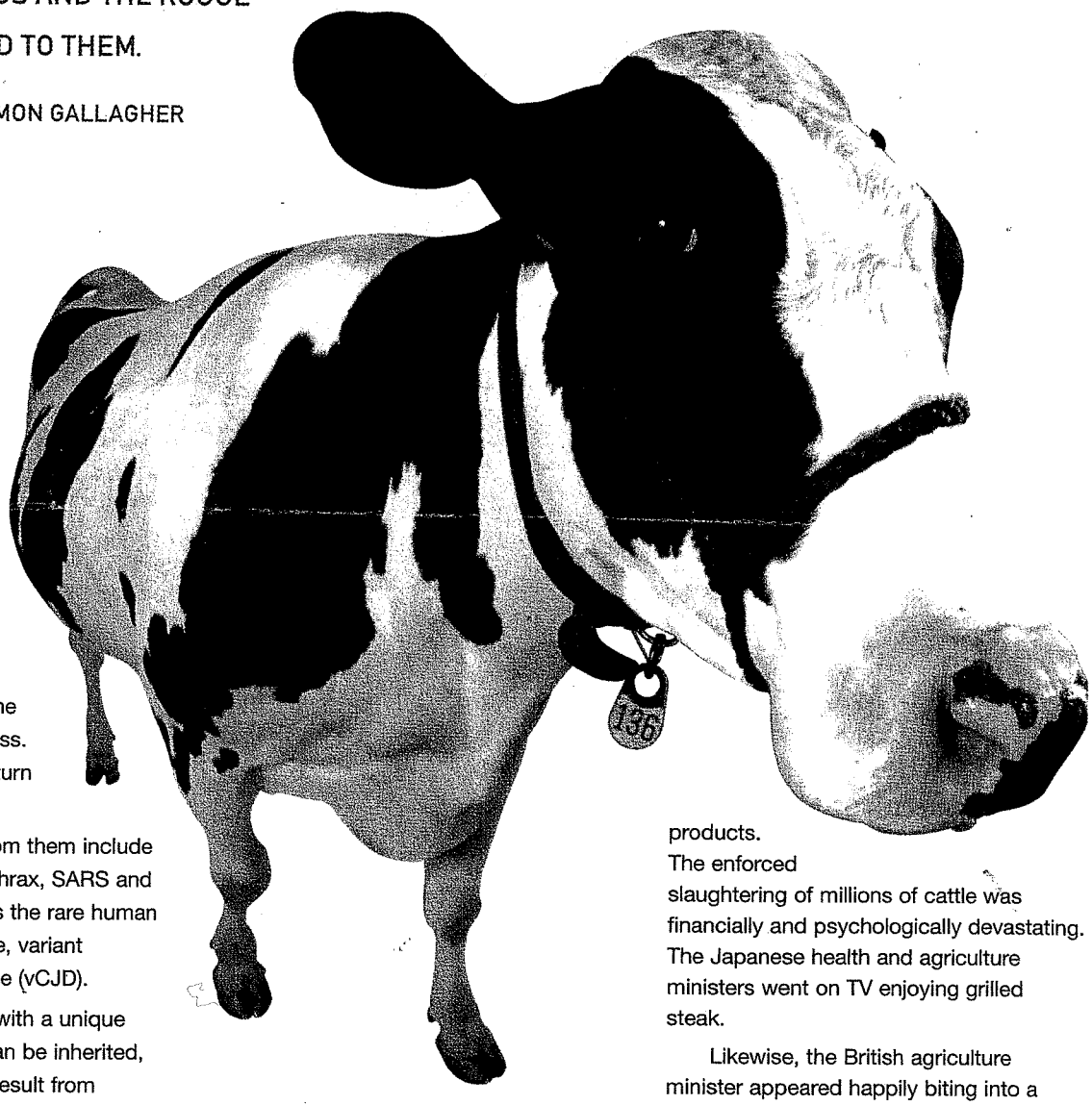
Suzanne
Regards George

BRAINS UNDER SIEGE

THE HUMAN FORM OF MAD COW DISEASE IS NO STRANGER TO HEADLINES AROUND THE WORLD. **GEORGE BIRO** LOOKS AT THE UNIQUE GROUP OF BRAIN-WASTING DISEASES TO WHICH IT BELONGS AND THE ROGUE PROTEINS LINKED TO THEM.

PHOTOGRAPHER: EAMON GALLAGHER



We humans have benefited in many ways from animals. We farm them, we keep them as companions and we experiment on them in the quest for medical progress. But sometimes animals turn back to bite us.

Diseases to come from them include tuberculosis, plague, anthrax, SARS and bird flu. And then there is the rare human form of mad cow disease, variant Creutzfeldt-Jakob disease (vCJD).

The latter is classed with a unique group of diseases that can be inherited, occur spontaneously or result from infection, the transmissible spongiform encephalopathies. These fatal brain-wasting conditions, as the name suggests, leave brain tissue riddled with holes and looking like a sponge.

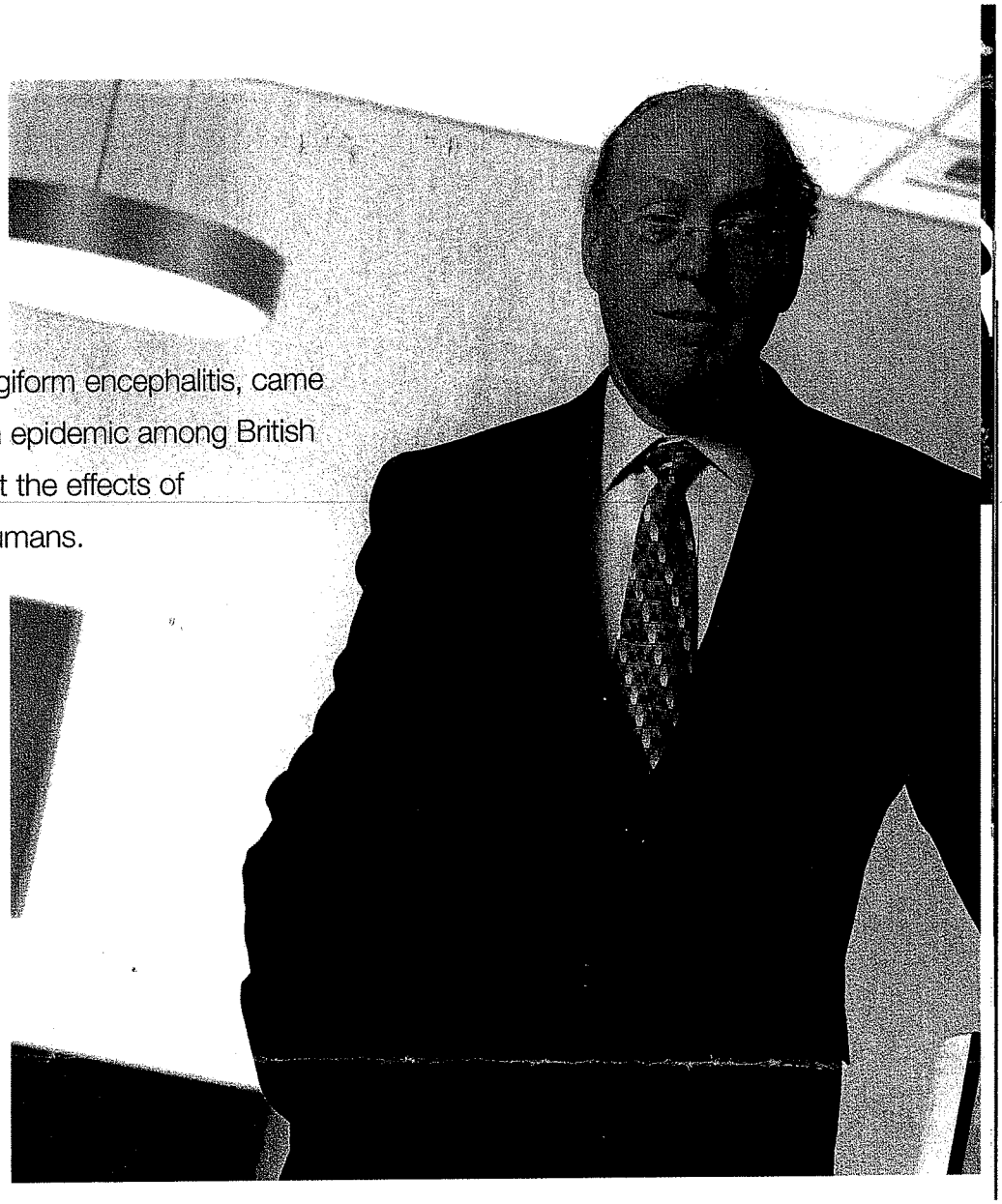
Mad cow disease, or bovine spongiform encephalitis, came to public attention as a result of an epidemic among British cattle in the 1980s and fears about the effects of contaminated beef products on humans.

In late 1984, a farmer in Essex, England, became worried about a Friesian cow that was losing weight, drooling and threatening other cows. Six weeks later the animal was unco-ordinated; a week after that it was dead. Two years later, the UK Veterinary Board reported that BSE was spreading alarmingly, not only in Britain but also in many other countries.

Around the world, frightened people questioned the safety of British beef products.
The enforced slaughtering of millions of cattle was financially and psychologically devastating. The Japanese health and agriculture ministers went on TV enjoying grilled steak.

Likewise, the British agriculture minister appeared happily biting into a burger. Sydney University neurologist John Watson was in London with his family at the time. As fans of Yes Minister, they took this gesture as an omen and at once forswore all beef!

About a decade after mad cow disease came its terrifying aftermath in humans: the variant form of CJD blamed on consumption of beef products contaminated by central nervous system tissue from affected animals. (CJD itself was not a new human disease).



Professor Colin Masters blames the spread of BSE in the UK on the practice of adding animal protein to feed, allowing the infection to pass from animal to animal.

Mad cow disease, or bovine spongiform encephalitis, came to public attention as a result of an epidemic among British cattle in the 1980s and fears about the effects of contaminated beef products on humans.

By striking contrast with classic CJD, patients with vCJD are much younger. Sixty per cent present with psychiatric symptoms. Soon they get gait disturbance, slurred speech or tremor, progressing to involuntary movements, lack of co-ordination or dementia.

This newest type of human CJD mostly affected people thought to have eaten infectious bovine brain-spinal cord tissues added for flavour and bulk to hamburgers, pies, stock cubes, consommes, sausages, pates and baby food.

Measures were taken to prevent infectious material reaching the food supply, including a worldwide export ban placed on British beef in 1996. Since 1995, there have been 161 cases of vCJD in Britain, three of which were the result of transmission between humans by blood transfusion.

Melbourne University pathology professor Colin Masters blamed the spread of BSE in the UK on the common practice of supplementing ruminant feeds with protein from bovine meat-and-bone meal produced from heads and offal after slaughter. This allowed the infection to pass from animal to animal.

He also pointed to deficiencies in the British government's response: "The repeated warnings of medical scientific advice were not adequately managed or communicated to the general public," he said.

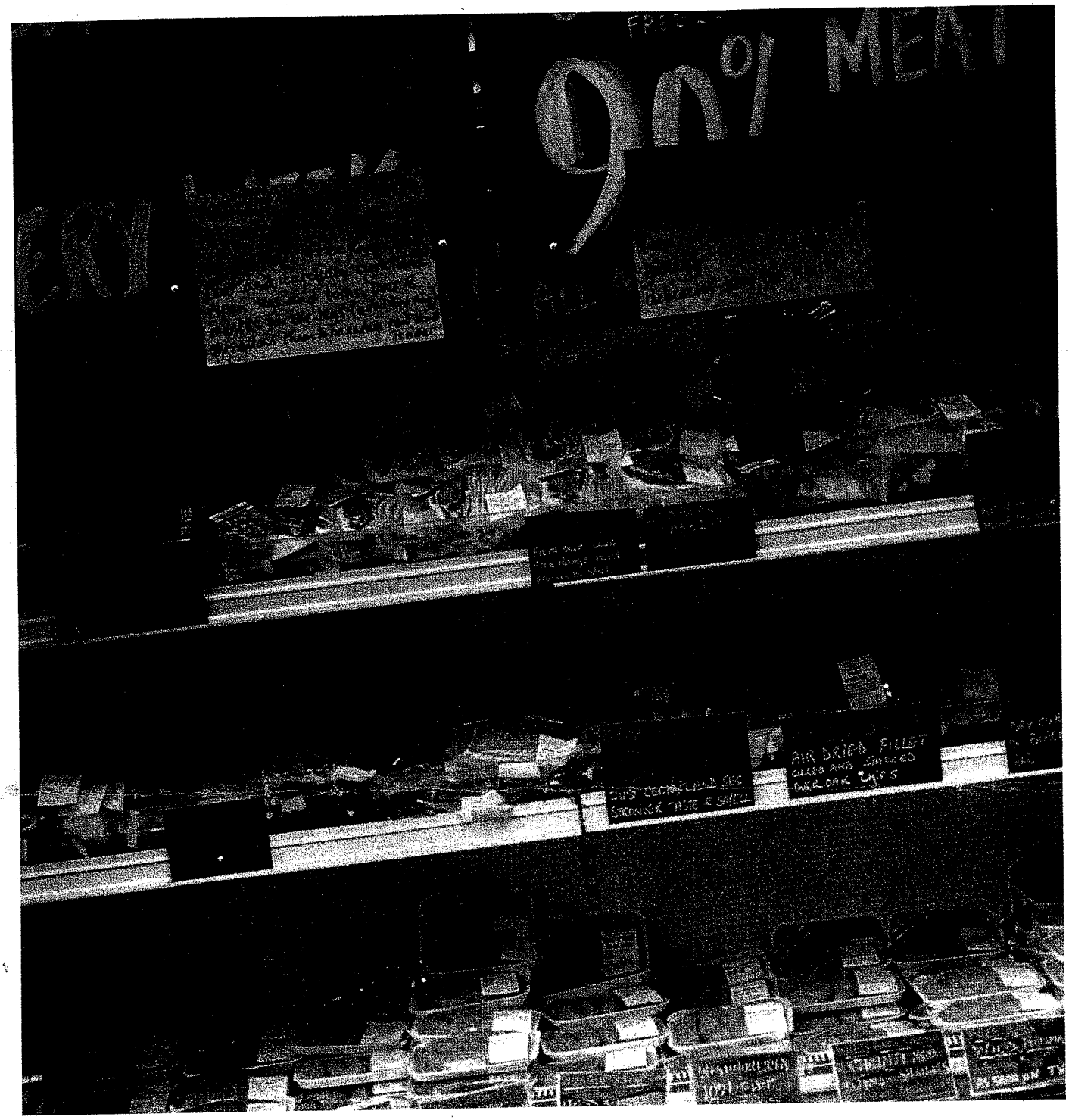
Australia has imported cats and cheetahs with mad cat disease, but no cattle have so far had BSE and no one has had vCJD.

Dementia-stricken Graham died of an inherited form of CJD. Several of his relatives had died in similar ways. Last October, medical writer Jennifer Cooke, author of *Cannibals, Cows and the CJD Catastrophe*, wrote an account dealing with his three daughters: Mandy, 36, Susan, 44, and Lisa, 38. In July 2005, all three asked to have the DNA blood test for the gene that had killed their father the year before. Eight weeks later, they went to Prince of Wales Hospital in Sydney for the results. Two, (who both have children), did have the genetic mutation, while one did not.

Mandy is active in the National CJD Support Group Network set up by the Federal Government. The network's establishment followed the deaths of Australians treated for short stature or infertility with extracts derived from human pituitary glands that were later found to be contaminated with CJD. Despite their bad news, Lisa and Mandy may still live long lives. Their grandmother tested positive for the same mutation but lived to 88.

Associate Professor John Watson recalls the case of a woman in her late 60s whose family was concerned that her speech had slowed greatly over the previous six months. Whereas she had been sociable, articulate and fluent, now she was quiet and had a poor vocabulary.

Professor Watson found her easily distracted and she failed a test of verbal fluency. Clinically, he thought she might have a fronto-temporal brain disorder. But neither neuropsychological testing nor an MRI scan supported his initial diagnosis. Testing of the brain's electrical activity with an EEG showed only non-specific changes. By the end of July, she was much worse: she was unsteady walking and had jerking of the limbs and upper trunk. MRI and EEG testing now showed widespread changes. A type of protein suggestive of CJD was present in her spinal fluid.



She became bedridden and incontinent and died only two months after first seeing a doctor. Some of her family resisted an autopsy and especially the diagnosis of CJD, but Professor Watson points out that whereas Alzheimer's disease takes years to progress, such rapid progression is typical of CJD.

Like other forms of transmissible spongiform encephalopathies, CJD, first reported in the 1920s, is experimentally transmissible to animals. The good news: CJD is very rare. The bad news: there is no diagnostic test while a patient lives; there is no treatment or cure; it is always fatal.

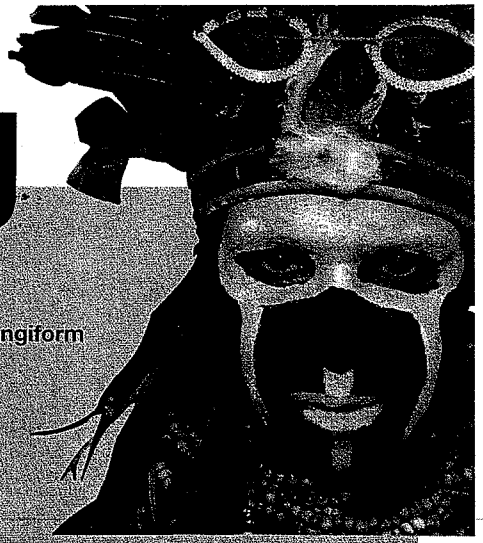
People with CJD may appear normal for up to 30 years. The eventual symptoms may include poor co-ordination and vision, slow thinking, poor concentration, memory and judgement and changed personality and behaviour. Soon there is progressive dementia, apathy, self-neglect, irritability and muscle spasms. Later, patients become bedridden and lapse into a coma.

There are four types of CJD: sporadic, genetically determined, medically transmitted and variant. Sporadic, or classical CJD, is by far the commonest form, accounting for 80 to 85 per cent of cases. Each year, about one in every million people contracts sporadic CJD. The cause is still unknown. It occurs worldwide and mainly affects people over 60. Typically, patients suffer rapidly progressive dementia, with death in a mute, almost motionless state within one year.

Genetically determined CJD also occurs worldwide, but it accounts for only about 10 per cent of cases. It is caused by an inherited mutation the nature of which determines the clinical picture. The three main types are familial CJD, Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia.

Medically transmitted CJD has affected, in rare cases, people having a

KURU



An intriguing form of transmissible spongiform encephalopathy that affected a New Guinea tribe became known to Western medicine in the 1950s. In 1953, an Australian patrol officer in the Eastern Highlands of New Guinea was startled to see a girl of the Fore tribe jerking her head violently and shaking. The Fore told him that she was a victim of sorcery and would die, just like many others.

Their illness started slowly with unsteady gait, then shaking and uncontrolled movements. Later, victims could no longer walk or even sit up and within two years suffered a miserable death. At its peak, the kuru epidemic was killing 5 per cent of the Fore population each year.

Drs Vincent Zigas (working for the Australian government) and Carleton Gajdusek (an unconventional but brilliant American paediatrician/virologist) roughed it in New Guinea while tracking down cases and doing autopsies. What caused this disease, which was then new to Western doctors?

Specimens sent to the Walter and Eliza Hall Institute in Melbourne gave them no help. No one outside the Fore had the disease. Could it be genetic? Then William Hadlow, a veterinary pathologist, wrote to Lancet, citing similarities between kuru and scrapie, a TSE endemic in sheep in the UK for nearly 200 years.

Gajdusek had brains of kuru victims flown to the US, where extracts were injected into chimpanzees. After three years, the first chimp showed signs of kuru. The long incubation period of TSEs, sometimes decades rather than years, is a major problem for any kind of research. Likewise, asymptomatic people who may be carriers infecting others pose a public health problem.

Two anthropologists suggested the Fore tribe's ritual cannibalism of deceased relatives was the means of kuru spreading. Gajdusek continued the hunt for the agent causing kuru. His pathologist team included the still prominent Melbourne neuropathologist Professor Colin Masters. The disease, now linked to prions, all but disappeared following the end of cannibalism.

In seeking to understand the cause of TSEs, researchers have looked to proteins, the minute particles that are building blocks of every animal, including humans.

blood transfusion or treated with human pituitary growth hormone, and patients having a corneal graft or neurosurgery with contaminated instruments or implantation of human dura mater, the outermost of the membranes covering the brain and spinal cord.

In seeking to understand the cause of TSEs, researchers have looked to proteins, the minute particles that are building blocks of every animal, including humans. In the case of BSE, for example, infectious agents known as prions and made of protein accumulate within the brain of the cow and fatally damage it.

Vigorous debate once raged over what caused TSEs. For years, the popular choice was a "slow virus". The first suggestion that a rogue protein was the agent came in 1967. Fifteen years later, American neurologist Stanley Prusiner proposed abnormal prion protein as the infective agent. He won a Nobel Prize for his work.

His efforts were revolutionary, because the very concept of the prion (pronounced preeon, a composite word from protein and infectious) was then new. As well, prions lack nucleic acid, the genetic material that bacteria and viruses use to replicate.

Today the role of prions in TSEs is widely accepted. We all have the protein that prions are made of, but its structure in infectious material is different.

If some of the deformed protein of an animal infects another animal, it may induce the same protein deformity there. Transmission is easiest between animals of the same species, and in some cases, the "species barrier" may prevent transmission altogether.

Unlike most bacteria or viruses, prions are virtually unaffected by acids, alcohol, heat or radiation. Clive Harper, professor of neuropathology at Sydney University, says prion particles are almost indestructible.

TSEs are also known as "prion diseases". Some workers group them with other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, which can also cause dementia. The common theme is the intracellular accumulation of abnormally folded, insoluble, amyloid protein that destroys nerve cells and their synapses. It is their transmissibility that separates TSEs from these other neurodegenerative diseases.

The Australian National CJD Case Registry monitors all known cases. The only certain diagnosis is by autopsy. Affected or potentially affected people are excluded from donating blood or organs.

So what is being done about CJD?

Researchers are working on:

- A simple, non-invasive test to diagnose or exclude CJD in humans and animals before death.
- The mechanism of infection.
- The means by which the brain is damaged.
- A drug to control or cure CJD.

RESOURCES

CJD Support Group Network
Tel/Fax **02 98998905**
Toll Free Number **1800 052466**
email s.solvyns@cjdsupport.org.au
website www.cjdsupport.org.au