Opinion

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Mad Cows and Prions: Some Background for Bioethicists

By David Elder

The newspapers are full of stories on Britain's 'mad cow' epidemic and its possible spread to humans. We read of a mysterious new kind of infectious agent, the 'prion'. What is its nature? And what implications might the affair have for bioethics? In this article I will try to give accessible answers to these questions, so far as the answers are known at the time of writing (in July 1996).

Prions - Nature's Domino Effect

The 'prion' theory invokes a new kind of infectious agent, distinct from both bacterial germs and viruses. Bacteria are living cells, viruses are not; but both contain *genes* - hereditary blueprints for reproduction. Genes are made of *nucleic acid,* usually the famous double helix of DNA (some viruses use its relative RNA). But prions astonishingly seem to be able to multiply without carrying any genetic material. They are apparently made up of *protein* alone.

Proteins are the molecular machinery of the cell. Chemically they are long chain-like molecules, but they fold up in complex ways to perform their biological roles. Proteins can do most things in the cell, but they cannot make more protein; only genes (nucleic acid) can direct this. So a protein would not normally be an infectious agent. But one particular protein in the brain, the 'prion' protein, has an unusual property. If it becomes folded up incorrectly, it can *transmit* this misfolding to normal molecules of the protein. This 'domino' effect explains how a prion protein can act as an infectious agent. It was a radical departure from conventional molecular biology, and at first many scientists were sceptical; some are still unconvinced. But most researchers now take the prion theory seriously.

When the prion protein misfolds, the consequences are grave - behavioural problems like dementia, and ultimately death. The brain becomes full of sponge-like holes - the medical term 'spongiform encephalopathy' refers to this. Sadly, there is no known cure. The symptoms take years and even decades to appear; so monitoring the spread of a prion disease, and obtaining rapid answers to vital questions about it, are frustratingly difficult.

In humans, prions have proved to be at the bottom of a rare and formerly obscure disorder called Creutzfeldt-Jakob disease (CJD). The reasons why prion protein misfolds in CJD are complex and not fully understood. In some cases dominant mutations in the gene encoding the prion protein cause the problem. These cases run in families; they constitute about 10-15% of the total victims. But most cases do not run in families, and we usually do not know what triggered the misfolding in these patients.

In a few instances, prion infection tragically occurred from medical accidents - for example, when pituitary extracts from cadavers with undiagnosed CJD were used to supply growth hormone to cure dwarfism. Fortunately, we can now provide the hormone safely from genetically engineered microbes. Infection also occurred in a part of New Guinea where 'kuru', a disease looking very like CJD, was spread by cannibalism in mourning rituals. When the practice was stopped, this avenue of infection was also closed off.

The 'Mad Cow' Affair

Now prion diseases are also known in animals. In particular, sheep have a condition called 'scrapie' (so called because afflicted animals itch and scrape off their coat). It is spread when sheep eat prion-infected foetal membranes. But humans have long been eating sheep without any obvious outbreaks following.

However, several decades ago the farming industry began to recycle the unused parts of animal carcasses into meat and bonemeal supplements for livestock. In Britain there was a further fateful change in the early 1980s. The processors had been using strong solvent and heat treatments to extract tallow (animal fat) as a by-product. These treatments were now reduced. In hindsight, these vigorous processes would have been destroying the sheep scrapie prion - an agent which unfortunately is exceptionally resistant to normal sterilisation procedures.

In the mid-1980s an outbreak of a scrapie-like disease occurred in British cows. This was 'bovine spongiform encephalopathy', BSE or mad cow disease. Research and inquiries followed. It was concluded that scrapie had crossed the species barrier from sheep offal into cattle. Recycling of cow offal had then aggravated the problem. Countermeasures were taken: in particular, recycling of offal in ruminants was banned in 1988; but the authorities stopped short of total slaughter of all stock which might have been affected. The key question remained unanswered: could the 'mad cow' prion also infect humans?

There is now reason to fear that this may have occurred. In March 1996 British authorities reported an apparently new form of prion disease, resembling CJD but with distinctive features. For example, CJD is mostly a disease of the elderly; the new disease strikes at much earlier ages. Some ten cases have been confirmed to date (for perspective, there are about 40 cases of standard CJD in Britain each year). The 'mad cow' prion seems to be the obvious suspect. But absolute confirmation of this is still not available. Even if we were sure of the link, we could not predict how many people would ultimately succumb to this slow-developing disease. We can only hope that the problem does not escalate, or that research finds a way to combat the prion - a drug designed to inhibit the misfolding of the prion protein is one possibility.

Lessons From The Affair

The British government and regulatory authorities have met with heavy criticism over the affair. It is alleged that they have been too close to the farm lobby; selective in their response to (and release of) their scientific advice; lax in setting and enforcing

countermeasures; encouraging under-reporting of 'mad cow' by failing to fully compensate farmers for destroying infected animals; and so on. At least some of these criticisms seem to warrant attention. In fairness to the authorities, it is easier to be wise after this event; prion diseases were obscure and poorly understood until recently. But on the other hand, it does pay to err on the side of (reasonable) caution. One could especially question whether feeding sheep offal to cattle was ever a good idea. Sheep were known to harbour scrapie at an appreciable frequency; and although scrapie had not previously crossed the species barrier freely, there was no cure in reserve in case it did. And if Britain had slaughtered all cattle at risk from 'mad cow' (hard decision though this was), recrimination would have been reduced.

At the very least, there are some obvious general lessons for the future here. We should take care with activities which might risk infection across the species barrier. One such area is of special relevance to bioethicists. Modern biotechnology is using or contemplating transplants of animal organs into humans in several contexts. We use pig heart valves to replace defective human ones. We plan to use whole pig hearts and other organs, genetically engineered to minimise immune rejection, to ease the shortage of human transplant donors. We are considering using monkey bone marrow transplants to revive immune systems depleted by AIDS. I have no fundamental ethical objections to any of these humanitarian projects. But we must beware of infection by disease agents from the animal donor - a special concern with patients who will be immunologically depressed from the transplant procedure, the disease or both. The work should not be banned; but bioethicists involved in interspecies transplantation assessments should advise that this concern be carefully scrutinised by independent specialists on an ongoing basis.