Prions

"There is no conceivable risk of BSE (Mad Cow Disease) being transmitted from cows to people."

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Minister of State for Health
Her Majesty's Government
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Introduction

What are prions? The name prion was coined in 1981 by Dr. Stanley Prusiner to identify the agents that cause a novel type of fatal brain diseases. Bovine spongiform encephalopathy (BSE or mad cow disease), sheep scrapie and Creutzfeldt-Jakob disease (CJD) of humans are examples of prion diseases. A prion has been defined as "small proteinaceous infectious particles which resist inactivation by procedures that modify nucleic acids". The discovery that proteins alone can transmit an infectious disease has come as a considerable surprise to the scientific community. The "protein-only" hypothesis is a controversial hypothesis that describes what prions are and how they reproduce.

The nature of the diseases

"Scrapie" is the old Scottish shepherds' name for a disease of their sheep which has been known for several centuries. It is the original example of a group of diseases, known as the "transmissible spongiform encephalopathies" (TSE), sometimes known as the "prion" diseases. The diseases include Creutzfeldt Jakob disease (CJD) in humans and bovine spongiform encephalopathy (BSE) or "mad cow disease." They affect the brain, disrupting or destroying neurons in large numbers, which inevitably leads to the death of the infected animal.

What is the protein-only hypothesis?

There are three main features of the protein-only hypothesis. The first is that the active component in prions is an abnormal protein called prion protein (abbreviated PrP). Normal animal cells make a form of PrP that is called cellular PrP (abbreviated PrPC). Animals infected with prions make abnormal PrP. In scrapie, abnormal PrP is called PrPSc. other words, PrPSc converts PrPC into PrPSc.

Prions do not contain a nucleic acid

J.S. Griffith first proposed the protein-only theory in 1967 to explain how prions could replicate if they were made of protein but did not contain nucleic acids. He did this fifteen years before the discovery of PrPSc and PrPC. Many have called the theory
heretical because it describes replication of a pathogenic agent without a nucleic acid genome. (Genes are made of nucleic acids. The nucleic acids store and transmit genetic information in all known organisms.) In fact, the hypothesis is based upon known properties of proteins with the added wrinkle that a protein molecule folded in an abnormal way can alter the folding of another protein molecule and thereby change its biological properties. To quote from J.S. Griffith's 1967 paper, "the occurrence of a protein agent would not necessarily be embarrassing although it would be most interesting."

In many respects the diseases are unusual. For example there is a long period, the incubation period, after an animal is infected before signs of the disease can be detected. The incubation period is controlled by a gene of the infected animal which makes a protein called PrP. There is no apparent reaction to infection in the animal - no immune response. And most notably, the cause of the disease, the "infective agent" has unusual properties. These unusual properties have prompted much speculation and debate about what the "infective agent" is, and how it works. Despite its unusual properties, is it like other infectious particles, (i.e. viruses), is it a bit different from other infectious agents, or is it completely different from any other infectious particle, even perhaps have biological properties which have never been described before? This question has been debated for three decades and still has not been resolved.

The debate revolves around two issues: Firstly, is a nucleic acid (DNA or RNA) a part of the agent which determines what the agent does. If there is one, why can we not find it? If there is no nucleic acid, how are agent properties specified? Secondly, PrP (sometimes called prion protein) , is associated with the agent somehow - but what does it do? This debate matters because no life form, including any virus, has been found which does not have nucleic acid as the molecule which encodes the chemical information for its existence. There is no model which we can use to compare the T.S.E. agent, if it does not have a nucleic acid.

Do "prions" exist? The word "prion" is used in different ways. It is used to describe the TSE group of diseases but it is also associated with the "protein-only" hypothesis discussed below. I find it helpful not to use the word prion to describe the diseases, to avoid confusion with the hypothesis. The word is also used to describe the infective agent and I think nowadays it is generally accepted that by "prion" scientists mean a PrP-protein-only agent, without nucleic acid or other molecule encoding the agent's information. Until we know better what the structure of the agent is and whether it has a nucleic acid or not, I find it helpful to use the word "agent". Until a nucleic acid is found or a mechanism for protein-only replication demonstrated, prion is most usefully used to describe the protein-only hypothesis.

**Supporting evidence**

The prion protein (PrPSc) fulfills all the necessary criteria to be the active component of the infectious particle. First, infectious prions isolated from brain tissue contain PrPSc. A process called purification removes molecules that are not part of the prion. The purity of a prion preparation is judged by how much infectivity is present for each gram of protein.
or nucleic acid. PrPSc is the only protein found in the best-purified preparations. Scientists have looked in these preparations for specific nucleic acids (e.g., virus genes) but have not found one despite searching for more than 30 years. Thus, the only molecule identified in the infectious particle is PrPSc. PrPSc is involved in all known prion diseases. In some cases, PrPSc molecules have a normal sequence but an abnormal conformation. In other cases, a change in the PrP gene sequence (mutation) causes PrP to fold incorrectly.

All mammals appear to have prion protein genes and the gene sequences are similar, but not identical, in related species. Differences in the PrP amino acid sequence play an important role in determining whether prions from one species can infect hosts of another species. This behavior is difficult to explain if prions are not made of prion protein.

PrPSc molecules can bind to PrPC molecules in the test tube and convert them to the abnormal (PrPSc) conformation. The sequences of the PrPSc and PrPC molecules must be similar for the conversion to work, and thus the behavior of the PrP molecules in the test tube parallels the behavior of prions in nature.

Sometimes prions from different cases of prion disease vary in the way they affect the brain, giving rise to different prion strains. The variation in strain behavior correlates with differences in the conformation of their PrP molecules. Prions isolated from certain new cases of CJD in the United Kingdom that are thought to be caused by BSE prions show unique strain characteristics. Those prions have a PrP conformation that is similar to that of the PrP molecule from BSE prions, but different from that in conventional CJD prions or scrapie prions.

**Conclusion**

The protein-only hypothesis remains controversial because it breaks new conceptual ground. Those who have worked in this field under other paradigms (like the virus or virino hypotheses) are reluctant to accept this new paradigm. Scientists from other fields are more receptive to this hypothesis, however, and thus it has gained broad support. This hypothesis best explains all of the observations about these agents and the diseases they cause. If at some point it fails to do so, the hypothesis will need to be revised or rejected in favor of a better hypothesis. That is the nature of science.
Creutzfeldt-Jakob disease (CJD)

In 1920, two Austrian doctors called H.G.Creutzfeldt and A.Jakob first described a disease which in many respects is similar to Alzheimer's disease:

Looking at the victims brains under the microscope, they saw that many of the normal brain cells had died, causing the development of many tiny holes, too small to be seen by the naked eye, and a mesh of fine fibres. The appearance of the brain tissue resembled a microscopic sponge, and the expression "spongiform encephalopathy" was used to describe the disease. At first, sufferers of Creutzfeldt-Jakob disease (CJD) are usually unaware that anything is wrong. Often there are subtle symptoms such as lapses of memory for daily events, and sometimes mood changes. Increasing apathy and loss of interest in normal daily and social activities is common. At this point, straightforward tasks that were previously simple become progressively more difficult for the sufferer. Early in the disease, the illness is frequently disregarded by friends, relatives and the sufferers themselves as the results of stress, being 'run down' or as mild depression.

Within weeks of the onset of the disease, other less easily discounted symptoms begin to appear. Neurological signs such as loss of balance, hesitancy in walking, deteriorating vision (sometimes including terrifying hallucinations), slurring and slowing of speech are common. After this, sufferers decline rapidly, becoming incontinent and experiencing involuntary, jerky movements of the limbs (known as myoclonus). Most patients slip into a comatose state without the ability to speak or move. Fortunately, the very apathy and loss of mental functions which CJD causes seems to protect victims from awareness of their fate. People affected by CJD usually die within 6 months of the onset of the disease. Only in 10% of cases does the disease run a more prolonged course of, for example, 2-5 years.

There is no known cure for CJD nor is there any treatment which can halt the progress of the disease.

References – information above taken from the following sources
http://www-micro.msb.le.ac.uk/Tutorials/cow/cow1.html
http://www.pbs.org/wgbh/nova/madcow/prions.html