Prions

Prion diseases have long fascinated biologists, because of the unusual nature of the infectious agent. Recently, prion diseases have become a major news story because of the emergence of the bovine (cow) prion disease BSE, which can be transmitted to humans as the disease vCJD.

Introduction

Prions are infectious agents that long defied some of our basic ideas of biology. They appear to behave like other infectious organisms, yet they lack any of the most fundamental features of organisms. In particular, they lack any genetic material (DNA or RNA). Over time, work on prions has suggested that the "infectious agent" is actually a misfolded protein -- which causes a normal cellular protein to change its shape to the misfolded form.

Prion diseases and prions are so unusual and so fascinating that they have been the subject of two Nobel prizes in Physiology or Medicine. In 1976 Carleton Gajdusek shared the Nobel prize for his work showing that the human disease kuru was similar to the well known sheep disease scrapie. In 1997 Stanley Prusiner, at UCSF, was the sole recipient of the prize; Prusiner was responsible for developing the modern prion model.

As diseases, prion diseases are quite rare and difficult to transmit. But they are also quite scary, because they are progressive neurodegenerative diseases, with no cure or treatment. They also have the mystique of being strange, due to the poor understanding of what prions are and how they work.

The prion disease most in the news is BSE (bovine spongiform encephalopathy), often called mad-cow disease. It is rather likely that the BSE agent can be transmitted to humans, and cause vCJD (variant Creutzfeldt-Jakob disease). The number of known vCJD cases in humans is under 200, but there are so many unknowns, including a possible incubation period of many many years, that this mysterious disease strikes fear -- at least much uncertainty.
As we learn more about prion diseases, a new part of the story is emerging. It is possible that a number of neurodegenerative diseases long considered quite distinct may share some underlying features. These include Alzheimer's disease, Parkinson's disease, Huntington disease, and the prion diseases. The common thread may be that all involve misfolded proteins. The reason for the misfolding and the details of the disease development vary, and there is no implication here that all of these are infectious. In fact, not all prion diseases are infectious.

Prion diseases

Prion diseases are typically slowly developing neurodegenerative diseases. The classic prion diseases are found in mammals. However, prion-type phenomena have been found in yeast, as discussed below. Thus we should be open to the possibility of finding prion phenomena, good or bad, that are different from the neurodegenerative diseases that we usually discuss.

Here are some of the more common prion diseases you are likely to hear about. In general, these diseases are fairly specific to one type of animal, so they are listed by animal.

Sheep

- Scrapie is the "classic" prion disease and the subject of most early work on this type of disease. Sheep are not very good lab animals, so progress was slow. Scrapie has been adapted to small lab animals, including mice and hamsters; much lab work is done with mouse scrapie or hamster scrapie.

Cattle

- BSE (bovine spongiform encephalopathy) is the big one in the news

Humans

- Kuru
- CJD (Creutzfeldt-Jakob Disease)
- vCJD (variant Creutzfeldt-Jakob Disease). This is a distinct disease from CJD; it is almost certainly caused by the agent that causes BSE in cattle.
- Less common but reasonably well-characterized prion diseases in humans include: FFI (fatal familial insomnia) and GSS (Gerstmann-Straussler-Scheinker syndrome)

Elk and deer

- CWD (chronic wasting disease)
The prion: the infectious agent

Some prion disease appear to be infectious. That is, one can isolate something from an infected individual, give it to another individual and that individual will get the disease and make more of the infectious material. This is the behavior one expects for an infectious agent, such as a virus or bacterium. (Microbiologists would say that the prion infectious agent satisfies Koch’s postulates, a set of groundrules used to show that one has an infectious agent.)

So what kind of an infectious agent is it? This is the step at which the biologists get very fascinated with the prion. The properties of the infectious agent do not correspond to those of any known agent. In particular...

* The prion agent is not inactivated by a wide range of treatments that should inactivate viruses or bacteria.
* The prion agent, so far as we can tell, contains no nucleic acid -- no genome.

Now, prion infectious material is not easy to handle, and early experiments showing these properties were subject to challenge. However, further work continued to support these properties. Thus it seemed that the prion agent was not an ordinary agent. In fact, it almost seemed that the prion agent was a self-replicating protein. The problem is that "a self-replicating protein" does not fit with our modern understanding of proteins. "A self-replicating protein" would be a major violation of the "Central Dogma", which says that only nucleic acids can "self-replicate". This is why biologists have been fascinated by the prion agent. If it really did what it seemed to do, it would reveal a major weakness in our understanding of genes and proteins.

Two major developments have served to bring some clarity to the nature of the prion agent. We discuss these in the following two sections. At that point, we will present the current working model for the nature of the prion agent -- a model which is now widely accepted, yet has still not been clearly shown to be correct.

The prion gene

At some point the gene that codes for the prion protein was found. Where? In the host. That is, the prion gene -- the gene for the prion protein -- is a normal host gene. When a sheep gets a prion disease (scrapie), the sheep’s own gene for the prion protein codes for any new prion protein that is produced.

A direct test showing the importance of the host prion gene for the prion disease came with mice, where it is "easy" to delete a specific gene. Mice lacking the gene for the prion protein cannot be infected with prions. (The method used to make such a "knockout mouse" is discussed briefly on the BITN page Agricultural biotechnology (GM foods) and Gene therapy - Introduction.)

Finding the prion gene solves one problem in the prion mystery. The protein does not truly self-replicate. It is coded for by a gene, a normal gene -- in fact, by a host gene. Thus the feature of the prion model which most seriously challenged our common understanding of genes and proteins is no longer a problem. Attention now turns to the question of how this host protein turns "toxic", and how its toxic form can be infectious.
So what is the normal purpose of this prion gene in your cells? The work with the mice lacking that gene (above) gave a clue: Those mice appeared quite normal. That is, it seemed that the prion gene has no normal role -- that it is non-essential. However, this may not be the complete story. The prion gene is highly conserved among mammals, which suggests it is there for a reason. And there are reports of subtle differences between mice with and without the normal prion gene. In particular, there is evidence that the normal prion protein is involved in regulation of sleep. (Interestingly, one prion disease in humans involves abnormal sleep.) Thus at this point we really do not know what the normal prion protein is for, and it is even possible that it is unnecessary. We will return to this point when we discuss Genetic susceptibility -- and resistance -- to prions.

A paper published in November 2007 offers evidence for a role for the normal form of the prion protein. They suggest that it is involved in immune responses; specifically, they show that the normal prion protein acts to control endogenous retroviruses. It will be interesting to see how this finding holds up, and what its implications are. The paper is: M Lotscher et al, Induced Prion Protein Controls Immune-Activated Retroviruses in the Mouse Spleen. PLoS ONE 2(11): e1158, 11/7/07. The paper is free online at: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0001158.

Shadoo. New work is leading to a new view on the role of the prion gene. Another gene that is related to the prion gene has been found; it is called Shadoo. The key result is that loss of both Shadoo and the prion gene is lethal, while loss of either one alone is not. This suggests that we have two related proteins with overlapping function; either one can compensate for the other -- though perhaps imperfectly. This finding will open up new approaches to studying prion function. The new paper is: R Young et al, The prion or the related Shadoo protein is required for early mouse embryogenesis. FEBS Letters 583:3296-3300, 9/14/09.

A tentative model

From the work described above -- and of course much more -- a tentative model for the prion began to develop. At this point, the model is that the toxic protein is an altered form of a normal cellular protein. Extensive data has failed to show any difference in the composition of the two forms. And some data has shown that the two forms are different folded forms -- called "conformations". That is, the normal prion protein folds up to a certain 3D structure, whereas the toxic prion protein folds up differently. Then, says the model, the toxic form can cause the normal form to refold into the toxic form.

That proteins may have more than one stable or useful conformation is well within our common understanding of biochemistry. Proteins are flexible, and shape changes are part of their normal function and regulation. Proteins commonly interact with each other, and of course cause conformational shifts when they do so. Nevertheless, the specifics of the prion model -- that one form causes the other form to refold "in its own image" -- is novel.
Yeast prions

Yeast? How did we get from neurodegenerative diseases to yeast? Well, it is a complicated story, so just a few notes here with some highlights. Yeast biologists had noticed that certain novel properties did not show normal inheritance. After some sleuthing, they showed that the behavior was very much like that of the postulated prion of mammals. The novel property was due to an altered folding of a normal protein, and the abnormal protein could induce abnormal folding of normal molecules.

So what the yeast work did was to establish a simple model system for one key aspect of the prion story. The basic idea of a protein inducing a shape change in its brethren, causing a new cellular property to occur, could be experimented with rather easily in the yeast system. This induced shape change is the heart of the prion model, and so these yeast proteins became known as yeast prions.

It is important to stress that the yeast work did not prove what mammalian prions are. What is important is that the yeast prions provided a model; they showed that proteins could do what was proposed in the mammalian system. The yeast work progressed rapidly because yeast prions are relatively easy to work with. It remained to be seen how much the yeast prion model actually fit the mammalian prions. As we shall see below, the answer is that the basics of yeast prions do carry over to the mammalian prions.

Genetic susceptibility -- and resistance -- to prions

There are two broad reasons why some organisms might be more/less resistant to getting prion diseases, for genetic reasons. One would be "general" -- that something in the general genetic nature of the organism affects some aspect of the prion disease. The other is more specific: since the prion protein is now known to be coded by a host gene, variations in this gene might cause variations in disease.

So far as I know, there is no evidence yet for "general" genetic factors that affect prion disease in animals. One might expect that some will be found at some point, so we should not make much of this point, one way or the other. (In yeast, a chaperone protein is essential for the prion effect; hence its gene would be such a general genetic factor. I suspect that such factors will be found in animals.)

On the other hand, there is abundant evidence that variations in the prion gene affect prion disease.

The most dramatic example is that absence of the prion gene makes the animal resistant to the disease. This was noted above, as evidence for the key role of the host prion gene.
It was also noted that the animals that lack the prion gene seemed quite normal. Thus one might wonder whether a practical way to combat prion disease, at least with farm animals, would be to breed them to lack the prion gene. In fact, work is being done along this line. Whether it proves useful remains to be seen.

In December 2006 it was announced that researchers had finally succeeded in making cows that lack the prion gene. Preliminary evidence suggests that these cows are indeed resistant to prion diseases, but more definitive work is in progress. The cows also appear to be quite normal so far. The paper is J A Richt et al, Production of cattle lacking prion protein. Nature Biotechnology 25:132, 1/07. Online: http://www.nature.com/nbtjournal/v2...s/nbt1271.html. (Access beyond the abstract is probably restricted to subscribers.) A news story: "Mad Cow Breakthrough? Genetically Modified Cattle Are Prion Free"; January 1, 2007. It is at http://www.sciencedaily.com/releases/2007/01/070101103354.htm.

Could this approach be extended to humans? Well, the common approaches used to make genetic variants of farm or lab animals are not applicable to humans -- at least at this point. However, one might also wonder whether a drug targeted at reducing activity of the prion gene would help. Again, this is under investigation, but it is not an easy problem (partly because it is difficult to get drugs to the brain).

There are natural variations ("polymorphisms") found in the prion gene in humans. The frequency of prion diseases is different for people with different versions of the prion gene. Thus it seems that some versions of the prion protein are more likely to convert to the disease state than other versions.

Transmission and other "causes" of prion diseases

Most of our attention has been focused on the idea that prion diseases are "transmissible" (or infectious, at least in a general sense of the word). That is why we are concerned about BSE; it seems that the BSE prion can be transmitted to humans (albeit probably inefficiently). However, we also now understand that the prion protein itself is a normal part of the body. So can it somehow cause a "disease" -- without any "transmission"? Yes, indeed.

Several prion diseases are known in humans. The most common is Creutzfeldt-Jakob Disease -- the original CJD. It occurs at a frequency of about one in a million, per year -- thus making it a rare disease, but certainly not unknown. It seems likely that it is due to a random event of the normal prion protein misfolding into the disease form. It is conceivable that some event triggers the disease event, but so far there is no evidence on the matter. This "background", apparently spontaneous, CJD is sometimes known as "sporadic CJD", or sCJD".

In a very few cases prion diseases have been found to run in families. Modern analyses of such families shows that the family carries a mutant form of the prion gene. Apparently, the mutation increases the chance of the disease form of the prion forming.

Thus we have three broad "causes" of prion disease:

- Transmission: acquiring a defective prion from the outside;
- Spontaneous or sporadic: one's own prion protein turning to the disease form;
• Genetics: having a higher chance of one's own prion protein turning to the disease form.

All of these causes of prion disease can be accounted for in the current version of the prion model.

**Routes of Prion Transmission**

We have said that prions can be transmitted from one infected animal to another. What are the routes of transmission?

In common discussion, we are often talking about oral transmission. vCJD is transmitted to humans by eating infected beef -- meat from cows carrying BSE. Further, it is likely that BSE was transmitted from cow to cow by feeding the cows material containing products from infected cows. Kuru was transmitted from human to human by ritual cannibalism -- eating the brains of infected people.

However, oral transmission is only one possible route. In fact, oral transmission is not particularly efficient, and is not well understood. Generally, proteins ingested orally are degraded. Somehow, the stable toxic prion manages to survive the usual digestion process -- at least at some low level.

In laboratory work, transmission is often accomplished by direct injection into the brain. This is probably the most efficient transmission known. It might seem irrelevant to the real world, but unfortunately that is not entirely true. There are known cases where prion disease has been transmitted on surgical instruments, or by use of infected tissues. These cases are extremely rare, but they are clear, and they do help in understanding the transmission process. CJD transmitted by medical procedures is known as iatrogenic CJD.

It used to be thought that the risk of prion transmission was associated only with nervous system tissue. However, this seems to be an over-simplification. As work continues, it seems that other tissues -- including body fluids such as blood or saliva -- can transmit prions, at least in some cases.

**How do prions cause disease? Relevance of prion diseases to other protein-folding diseases.**

The short answer is that we do not know.

An interesting story is emerging, however. It is now clear that there are several neurodegenerative diseases of higher animals, including humans, which share a common feature: production of an aggregate of insoluble proteins in the affected cells. These diseases include Alzheimer disease, Huntington disease, and Parkinson disease, as well as the prion diseases. How the altered protein that produces the aggregate is made varies with the disease. Only the prion diseases appear to involve a transmissible protein. Now, there is no assurance that all of these protein aggregates cause damage the same way, but at least the broad issue of the effects of these excessive aggregating proteins is being studied in several systems.
There is some evidence that Alzheimer disease can be transmitted by direct injection of the disease form of the protein into the brain. The work was done in model systems in mice. To my knowledge, there is no evidence for transmission of Alzheimer, or any of the other non-prion protein-folding diseases, by "ordinary" means.

The paper showing transmission of Alzheimer disease in the mouse model is: M Meyer-Luehmann et al, Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host. Science 313:1781, 9/22/06. It is free online at: http://www.sciencemag.org/content/313/5794/1781.abstract.

One theme that is beginning to develop is that it may well not be the aggregate itself that causes disease, but rather something about the high level of the protein. A variation of this is the possibility that a very early stage of aggregation is the toxic agent. For example, an aggregate of only a few protein molecules -- called an oligomer -- may still be soluble, and able to cause damage; in contrast, the more prominent large aggregates may be more side effects than important in their own right. A consequence of this model is that effort to disaggregate the large aggregates may be misguided; doing that may create more of the smaller and more toxic oligomers.

New work with Alzheimer disease has yielded some interesting clues. The work involved purifying different forms of the Alzheimer protein, and injecting them into rat brains. A key result was that the soluble dimer of the protein was most active. In particular, the monomer was not active, and insoluble plaque material was not active. This provides direct support for the idea that a small soluble form is the active form, not the more readily observed plaque material. Of course, this result is for this disease and this model system; its generality remains to be seen. The system also allows them to begin to see how the active protein causes disease.


Treatment of prion diseases

The short answer is that there is no treatment or cure available.

As understanding of the prion improves, there is work on trying to find agents that might interfere with either the formation of the "bad" form or with its action, or possibly even "dissolve" preexisting prion material. There is some interesting work, and even some anecdotal promising results. But so far, proper testing has not validated any treatment.

Testing an agent against prion disease in humans is very difficult. For one thing, such diseases are quite rare. Further, much of the lab work suggests that treatment would be most effective very early in the course of the disease; however,
Some work on developing treatments for prion diseases...

Congo red derivatives. Congo red is a dye that binds to prion proteins. It is used to detect prions, but it is too toxic to be used therapeutically. Here they explore some derivatives of Congo red, with two interesting results. One is that they develop a compound that is effective in clearing cultured cells of prions, and seems worth testing in animal models. Second, comparison of the compounds suggests that a key property is that the effective compounds allow degradation of the prion protein. More specifically, the drug may keep the prion from inhibiting the protein-degrading machinery -- the proteasome. A news story about this work is: Congo dye derivatives free proteosome [sic] to rid cells of prions, Microbe 2:524, 11/07. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at [http://forms.asm.org/microbe/index.asp?bid=54023](http://forms.asm.org/microbe/index.asp?bid=54023). The paper itself is: S Webb et al, Mechanistic insights into the cure of prion disease by novel antiprion compounds. Journal of Virology 81:10729-41, 10/07. Free online at: [http://jvi.asm.org/cgi/content/abstract/81/19/10729](http://jvi.asm.org/cgi/content/abstract/81/19/10729).

RNAi treatment. RNAi stands for RNA interference; the idea is to make a short RNA molecule that can bind to the mRNA (messenger RNA) for a gene, and interfere with its function. An interesting article made news in December 2006. In the new work, they used RNAi to reduce production of the prion protein. They demonstrated the principle using mouse cells in lab culture. Then, using a viral vector to deliver the gene for the RNAi, they showed an effect in a mouse model system. Emphasize that this result -- certainly very interesting -- is a clue that needs to be followed up. The logic is good, but the effect is fairly modest at this point -- and all the work is with mice. The world of drug development is littered with good ideas that showed promise in an animal system, then did not work in humans. Nevertheless, this is an interesting item, and the Commentary article shown below is a good overview of the field (including other treatment options being tried) as well as the particular work. The Commentary: Q Kong, RNAi: a novel strategy for the treatment of prion diseases. Journal of Clinical Investigation 116(12):3101, 12/06. It is free online at: [http://www.jci.org/articles/view/30663](http://www.jci.org/articles/view/30663). The Commentary links to the research article. This item is also briefly noted under the BITN topic RNAi (RNA interference or silencing).

Reversal. The symptoms of a prion disease can be reversed if continued prion replication is prevented, according to work reported in February 2007. The work was done in mice, using a genetic trick that would not be applicable to humans. Nevertheless, the work offers some hope, a "proof of principle." It is likely that such treatment would be most effective early in the disease, thus raising the problem of early diagnosis. The paper is G R Mallucci et al, Targeting cellular prion protein reverses early cognitive deficits and neurophysiological dysfunction in prion-infected mice, Neuron 53:325, 2/1/07. A news story about the work: "Scientists 'reverse' vCJD signs. Prion diseases affect the brain. Symptoms of prion diseases, such as the human form of mad cow disease vCJD, can be reversed, a study of mice suggests." February 1, 2007. [http://news.bbc.co.uk/2/hi/health/6314877.stm](http://news.bbc.co.uk/2/hi/health/6314877.stm).

My opinion/advice about BSE risks

At the top of the page, I cautioned that my background is not medical, and that my purpose here is not medical advice. I have been interested in the prion story long before BSE -- long before the word prion or the name Prusiner became known. Prions are fascinating.
Nevertheless, having gotten this far, I do want to state how I evaluate the current BSE situation in the United States. I will try to give my reasons, so you can analyze those, not just take my bottom line. From my understanding, I think there is a very low risk of getting vCJD from eating beef. There are several considerations that go into reaching this conclusion. Each of these reasons has limitations, but overall, I see little reason to be concerned.

Reasons to not worry too much about BSE-infected beef:

- There is no reason to believe that there is any significant number of BSE-infected cows in the US. Of course, one limitation of this is that rather few are tested, so one can be somewhat leery of the actual data. However, there is almost no evidence of any cows with signs of disease, and steps to prevent transmission of BSE have been in place for several years. Remember that the BSE-cow in the news (Jan 2004) was born before key steps to break transmission were put into place. This cow has re-focused attention on the subject, and additional measures to reduce BSE transmission have been implemented.

- Acquiring the disease from an infected animal requires eating tissue that contains the prion. To the best of our knowledge, this is largely brain and nervous system tissue. These are parts that do not commonly enter the human food chain. Muscle, the part of the cow most commonly eaten, has little or no prion.

- Transmission of the agent from cows to humans is probably not very efficient. In Great Britain, which had a huge number of BSE-infected cows, fewer than 200 people have developed vCJD. Of course, we do not know whether more will develop it later; after all, this is a type of disease with a notoriously long latent period. However, the accumulating evidence is showing no signs of a major increase -- at least so far.

External Links

- Book: Warwick Anderson, The Collectors of Lost Souls -- Turning kuru scientists into whitemen. Johns Hopkins University Press, 2008. ISBN 978-0-8018-9040-6. Kuru is a neurodegenerative disorder, a spongiform encephalopathy rather like what we refer to as mad cow disease (or BSE or CJD). It was the first large cluster of this type of disease, which was endemic to the Fore tribe of New Guinea. This book is the story of kuru, and the work of scientists in the late 1950s to learn about this unusual disease. In particular, it is the story of Carleton Gajdusek, who received the Nobel prize for showing that kuru was transmitted by ritual cannibalism among the Fore. Later work would lead to the understanding of the transmittable agent as a prion -- and to another Nobel prize, to Stan Prusiner. The book is the story of disease, but also of culture: the culture of the Fore, and the culture of the scientists. For example, there is a discussion of the nature of cannibalism, including a comparison with the doctors' practice of doing an autopsy and collecting brains. Much is made of the competition between various groups studying the Fore, and of changing styles in science in the US. It is interesting that, despite all the dedicated efforts to figure out kuru, what really made the difference was a casual comment by a veterinarian -- which Gajdusek was wise enough to follow. The book concludes on an inevitable down note, with Gajdusek's fall, and imprisonment. But that is part of the story, and it is handled gracefully. Author Anderson is a doctor and science historian, so he understands the content, and he writes well. All in all, this is an enjoyable book at multiple levels.

- Book: P Yam, The Pathological Protein: Mad cow, chronic wasting, and other deadly prion diseases. Copernicus, 2003. ISBN 0-387-95508-9. An excellent overview of the prion story, for the general audience, from a science journalist. This book presents the range of prion diseases, in animals and humans, and the relationships between them. It develops our current understanding of what prions are and how they work, with a good consideration of uncertainties in the story. A good place to start, if you want to know what prions are about; probably a good overview for many scientists, as it brings together a lot of information into one fairly short and very readable book.


- BSE and vCJD News. http://www.cidrap.umn.edu/cidrap/content/other/bse/index.html. From CIDRAP; I also list CIDRAP as a good general source of information on Emerging diseases.
• Chronic wasting disease (CWD). [http://wildlifedisease.nbii.gov/disease...agemode=submit](http://wildlifedisease.nbii.gov/disease...agemode=submit). From the National Biological Information Infrastructure (NBII). CWD is a prion disease of deer and elk, which is becoming a serious problem in the US. The implications for human health are unclear. So far, there is no evidence for transmission to humans (e.g., deer hunters), but it is hard to make a strong argument that there is no risk.

• Bovine Spongiform Encephalopathy (BSE). From the USDA FAS (Foreign Agricultural Service). "This page provides sources of information on the effects of BSE on trade. Provided are links to related documents such as regulations, reports, and press briefings, as well as main BSE pages for various government and organization sites." [http://www.fas.usda.gov/dlp/BSE/bse.html](http://www.fas.usda.gov/dlp/BSE/bse.html). This page may be too technical for most use, but is a great source when you want information about governmental regulations.

• S Seethaler, In the face of uncertainty -- Batty bovines and empty blood banks. (Also titled: What do mad cows have to do with my blood? Connecting the dots: Batty bovines, empty blood banks, and groceries for a song.) Berkeley Science Review, Spring 2003, p 40. BSR is a free publication by UC Berkeley graduate students, usually highlighting work from Berkeley. This article is available online at [http://sciencereview.berkeley.edu/article=perspective](http://sciencereview.berkeley.edu/article=perspective). It focuses on the new restriction that those who have spent much time in England cannot be blood donors. At the time this came out, there was almost no evidence that prions can be transmitted by blood; however, more recent evidence has increased the concern a bit. In part, the article is based on discussion with Dr Kate O'Neill, Professor of Environmental Science, Policy and Management.

• Nobel prize sites:
  • Prusiner’s page, at UCSF: Molecular Biological, Genetic and Protein Structural Studies of Prion Disease. [http://www.neuroscience.ucsf.edu/neu.../prusiner.html](http://www.neuroscience.ucsf.edu/neu.../prusiner.html).

Miscellaneous; updates

• Killer chickens - follow-up (December 9, 2009).
• Is Alzheimer's disease transmissible? (February 4, 2011).

A new type of prion disease. A feature of the prion protein is that it is anchored to the cell membrane. In fact, it has been shown that the anchor is necessary for the usual prion disease process. Here they extend that work, with lab mice, and show that a mutant form of the prion protein that is not anchored can cause a distinct type of disease. The paper is: B Chesebro et al, Fatal Transmissible Amyloid Encephalopathy: A New Type of Prion Disease Associated with Lack of Prion Protein Membrane Anchoring. *PLoS Pathogens* 6(3): e1000800, 3/10.

The CWD risk. Is CWD a risk to those who eat deer? A new paper makes a contribution to the story, though once again without a definitive answer to the real question. What they do is to test two types of monkeys for susceptibility to CWD. One type turns out to be susceptible, whereas the other is not. The one that is not is closer to humans. This may be interesting, but proves nothing about what could happen in humans. However, it also remains true that there is no epidemiological evidence suggesting that any transmission has occurred. Further, laboratory work has shown no signs of CWD transmission to human cells. Here is a news story about this work, from the NIH... Species Barrier May Protect Macaques from Chronic Wasting Disease, July 29, 2009: [http://www.nih.gov/news/health/jul2009/...aid-29.htm](http://www.nih.gov/news/health/jul2009/...aid-29.htm). The paper is: B Race et al, Susceptibilities of Nonhuman Primates to Chronic Wasting Disease. Emerging Infectious Diseases 15(9):1366, 9/09.

How BSE arises. There is no consensus as to how BSE arose at the start of the BSE epidemic. It is possible that it...
arose by transmission from an animal such as a scrapie-infected sheep. It is possible that it arose by a mutation in a cow. It seems unlikely that evidence will allow us to distinguish these possible origin events. However, in 2008 scientists reported a cow in the US with BSE that rather clearly is due to a mutation in the cellular prion gene; in fact, the mutation is similar to one known to cause CJD in humans. This shows that mutations can cause BSE in cows, just as they can cause prion diseases in humans. However, it is speculation to extend the argument. The paper is: J A Richt & S M Hall, BSE Case Associated with Prion Protein Gene Mutation. PLoS Pathogens 4(9):e1000156, September 12, 2008.

How Animal Prions Cause Disease in Humans, a feature article by Suzette A. Priola. Microbe 3:568, 12/08. Microbe, the news magazine of the American Society for Microbiology, is free online; this item is at http://microbemagazine.org/index.php...red&Itemid=212. The title is a bit presumptuous, but this article is a good overview of prion diseases, with an emphasis on transmission between species. It addresses the problem of CWD -- without answering it, of course, since no answer is yet known.

Prion conversion -- in vitro. A basic tenet of the prion model is that the normal form of the prion protein is converted into the disease form. However, attempts to show this step in the lab have been fraught with difficulty. Some work was suggestive, but insufficient material was generated to allow complete testing. A breakthrough a few years ago was the development of an amplification process, to increase the amount of disease prion made in vitro. Early work with this amplification system required a crude cell extract; therefore the requirements for conversion were not defined. Now, we have work showing conversion in a clean in vitro system. The key development was to add a synthetic polyanion; a range of polymers worked. With this addition, prion conversion is now carried out in a clean system, free of other cellular materials. The role of the polyanion remains to be elucidated; it is considered likely that it serves as some kind of scaffold for protein interaction. The paper is: N R Deleault et al, Formation of native prions from minimal components in vitro. PNAS 104:9741, 6/5/07. Free online at: http://www.pnas.org/content/104/23/9741.abstract. There is a news story about this work in the Dartmouth Medical School alumni magazine, Fall 2007: A simple recipe for cerebral disaster.

Prion disease incidence (2007). The message listed here gives some statistics for vCJD and other prion diseases for 2007 and recent years. Among the useful points here: Total number of cases of vCJD is less than 200; incidence of vCJD is declining, and is small compared to sporadic CJD. Prion Disease Update 2007, from ProMED-mail. If you search their archive for the word prion, you will get the more recent updates. I also list ProMED-mail as a good general source of information on Emerging diseases.

Blood. It is now clear that prions can be transmitted by blood. The risk is probably low, since few blood donors will have defective prions. However, additional precautions have been implemented to reduce the chances of prions in the blood supply. A news story on prion transmission by blood: Fourth vCJD case linked with blood transfusion in UK (January 22, 2007). http://www.cidrap.umn.edu/cidrap/content/other/bse/news/jan2207vcjd.html. I also list CIDRAP as a good general source of information on Emerging diseases.

Foie gras. The food product foie gras consists of the enlarged livers from certain birds that have been force fed. Here they show that the product contains "amyloid" protein, and that when fed to mice in a model system, enhances amyloid diseases. The particular amyloid protein seen here is most relevant to human rheumatoid arthritis. I'd treat this as a preliminary finding for now. However, it has several possible implications that need to be explored. The simplest, of course, is whether foie gras really promotes amyloid formation and disease in humans. But beyond that, are there any significant levels of such amyloid in normal bird livers -- or in other food products? Further, although it is most likely that a particular kind of amyloid enhances further production of very similar amyloids, it is not at all certain that it is always
so. What other risks are there to be discovered? Press release from the University of Tennessee: UT Medical Researcher Determines Link between Foie Gras and Disease, June 18, 2007. [http://www.utk.edu/tntoday/2007/06/1...s-and-disease/](http://www.utk.edu/tntoday/2007/06/1...s-and-disease/). The paper is: A Solomon et al, Amyloidogenic potential of foie gras. [PNAS 104:10998, 6/26/07](http://www.pnas.org/content/104/26/10998).

**Contributors**

- Robert Bruner ([http://bbruner.org](http://bbruner.org))

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