Novel Prion Strain as Cause of Chronic Wasting Disease in a Moose, Finland

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Glenn Telling, the director of the Prion Research Center at Colorado State University. We'll be discussing a new prion strain as a cause of chronic wasting disease in a Finland moose.

Welcome, Dr. Telling.

[Glenn Telling] Hi Sarah, how are you?

[Sarah Gregory] Doing well, thank you. Prions are terrible. Tell us what prion diseases are.

[Glenn Telling] You're absolutely right, prions are pretty bad news. Prion stands for "proteinaceous infectious agent", and this was a term that was coined by Stan Prusiner, who received the Nobel Prize for this work some decades ago, now. But prion diseases are transmissible, in other words "infectious", diseases that cause neurodegeneration, fatal and incurable, in both humans and animals. And they have some features that are similar to other human neurodegenerative diseases like Alzheimer's disease, Parkinson's, and so on. These tend to be diseases of old age, and they're caused by an infectious agent which is not a virus or bacteria but is instead an infectious protein. And this protein is expressed by the host, either human beings or animals, that get this disease.

And during disease, somehow this normal protein (largely expressed in the central nervous system) changes its shape or its conformation into a pathogenic form, which can then induce the conformation or change in additional host-encoded normal prion protein. And somehow this abnormal prion protein that has this bad conformation that's infectious also kills neurons, leading ultimately to neurodegeneration in older age, typically. But in some examples of human neurodegenerative disease, the age of onset can be much, much younger. And this—I'm talking particularly about a variant form of Creutzfeldt-Jakob disease (vCJD) which is related to exposure to Mad Cow Disease prions. So there's a lot going on with these diseases, a lot of very unusual features, and as you say, not very pleasant diseases to acquire.

[Sarah Gregory] So you mentioned different kinds. Tell us what the different kinds are and who they affect or what they affect.

[Glenn Telling] Yeah. So the human diseases are actually very interesting and unique in biology in that they can manifest either as (as I've already mentioned) infectious diseases. And an example of that is this disease that I've already mentioned as well (variant CJD), which was acquired by exposure to Mad Cow Disease or BSE prions. Other forms of human prion disease can be sporadic. In other words, they arise out of, really, nowhere with no obvious etiology (they're spontaneous diseases). And the third flavor is genetic. In other words, they're caused by autosomal dominantly inherited mutations in the coding sequence for the host...this host-encoded prion protein I mentioned before.

So the most common form of human prion disease is called Creutzfeldt-Jakob disease. This is...most usually manifests as a sporadic disease, but there can be also inherited forms caused by these pathogenic mutations and also this variant form, which I mentioned already, which is associated with infection by BSE prions (Mad Cow Disease). And then in humans, there are a

constellation of related diseases in different species. The archetypal prion disease that we've known about for a couple hundred years now is called scrapie (this is a disease of sheep). It's called scrapie because farmers noticed the animals would incessantly scrape their fleece against gate posts and other farm structures and scrape their wool off. And this is because they have this persistent itching or pruritus. Again, an inevitably fatal disease.

The disease that people have maybe heard about in most recent years is this disease Mad Cow Disease or bovine spongiform encephalopathy. And this was first discovered in the UK, and the cause was discovered as being feeding prion-contaminated protein supplements to cattle in farming situations. And then, these prions go into the human food chain and cause this disease variant Creutzfeldt-Jakob disease. And in recent decades, a relatively new disease called chronic wasting disease has also emerged. This was first discovered or reported on in the 1980s as a similar disease in deer and elk (similar to Mad Cow Disease), a wasting disease in these animals. And this is a very interesting disease. It was first identified in captive facilities in northern Colorado, and it then spread to wild animals. So it's the only known prion disease that we know about right now that affects both captive and also wild animals. And it's spreading at an alarming rate in North America; it's highly contagious. And in recent decades (recent years), it has also been diagnosed in other countries, in particular South Korea, and most recently in Northern Europe (these countries include Sweden, Norway, and Finland).

[Sarah Gregory] These neurodegenerative symptoms...what are they? Obviously, it ends up being fatal. But along the way, what do we see?

[Glenn Telling] Well, in humans these diseases have a very long incubation time. In other words, if it's an infectious disease like these diseases as I mentioned are transmissible, the time between the actual exposure event and the onset of clinical signs or symptoms in humans can be very long, lasting many years or even decades. I also point out there's another very rare form of human prion disease called kuru, which was a disease of a linguistic group in Papua New Guinea called the Fore people. And this example of human prion disease, it was spread by a form of ritualistic cannibalism where the brains of the elders of the tribe are eaten as an act of mourning. And this was actually the leading cause of death amongst these people during the peak of this disease, which was recognized in the 1950s. So this is another example of a transmissible human prion disease, albeit under very unusual and rare situations.

But this is what I mean by the time between the actual exposure event when, for example, people were consuming these brains—for example, young people who were exposed to these prions during these ceremonies—in several instances, it has taken decades for these individuals to actually develop clinical signs. Now when those clinical signs develop in all of these human prion diseases, the clinical phase tends to be very short. It's defined by cognitive decline. Also, in many examples of human prion diseases, there's a lack of...a bit of physical coordination, and these affected individuals also have trouble with their balance and walking. And these clinical signs and symptoms, once manifest, tend to get worse progressively over a very short period of time (typically about six to 12 months). And this is very short compared to other human neurodegenerative diseases like Alzheimer's, where the clinical phase can last many, many years. So once the onset of disease is manifested, it tends to be very, very rapid. And so this is how clinicians can distinguish this disease in humans from other more common human neurodegenerative diseases.

I've already mentioned how scrapie looks. These animals tend to manifest with signs of itching or pruritus, and they scrape themselves against walls and gate posts. But ultimately, they lack coordination, they become recumbent, and inevitably die. And the same kind of thing happens with Mad Cow Disease and chronic wasting disease. The clinical signs are subtly different between these diseases and between species, but the basic clinical picture tends to be very similar—a long disease incubation time, and then a rapid development of increasingly more severe clinical signs in these affected animals.

[Sarah Gregory] I actually knew someone personally who got the spontaneous kind, and it was diagnosis to death in six months, and truly one of the most horrifying things I've ever seen.

So how do people get sick from infections from prions? I mean, spontaneous like you said, and eating meat with the disease (cow) in the UK. But there's cervids here in North America, and they also carry a type of prion. Could people get it from eating, say, hunted deer or moose or elk?

[Glenn Telling] Yeah. The prion disease that you mentioned in the US is the one that I've already mentioned (chronic wasting disease), and this is a disease of concern because it's spreading so rapidly, and it appears to be the most contagious prion disease that we know about. The possibility of people acquiring this disease via exposure to infected materials from these animals is unproven at the moment, but certainly a possibility. And the reason we're particularly concerned about that possibility is that it's already happened in the case of Mad Cow Disease or BSE (bovine spongiform encephalopathy), which when those animal prions from cattle got into the human food chain, individuals developed this new form of Creutzfeldt-Jakob disease called variant CJD. And this was predominantly in young adults and teenagers, and this is how clinicians in the UK particularly knew that it was related to...it's different from sporadic CJD, which tends to have an onset late in life. These affected individuals were much, much younger (an average onset of around about 30 years of age).

And so it became pretty clear during that time that this was a result of exposure to BSE prions in the food chain. So because this has happened already (we call this zoonotic transmission), the possibility of this happening with chronic wasting disease is not remote, but it's still unproven and it's something that the authorities here in the US are aware about and concerned about, in particular since this disease is so contagious and so efficiently transmitting amongst these cervids in North America.

[Sarah Gregory] So potentially eating it could cause it, but what about just casual contact, like touching an animal that has it? I'm thinking of those farmers with their scrapie sheep or hunters.

[Glenn Telling] Yeah. What I would say is that there's no evidence that casual contact with infected animals has caused disease. That's not to say that it couldn't happen (that the possibility is not there), but we just have no evidence of it. And so, it appears to be a remote means of transmission. I think the thought is that if people are going to be acquiring a novel form of human prion disease as a result of interacting with these infected deer or elk, it's most likely going to be the result of consuming these prions or by some other means. So for example, in traditional Asian medicinal practices, elk antler velvet is used as a treatment for some conditions.

And so the thought is that, for example, if materials from infected elk that was somehow subclinically infected, but from which these preparations were made and then exposed to humans, so that could be, for example, another route of transmission. But like I said, there's no documented evidence (epidemiologic evidence) right now or clinical evidence that this disease

has transmitted from deer or elk to human beings. But like I said, also the authorities here and more globally are also aware of this possibility happening. And so they're on the lookout for it.

[Sarah Gregory] Okay. That raises another question for me here. You know elk antlers that drop off are sold as dog chews, and I have a couple and my dogs chewed them (haven't in recent years). Could that be a potential source of infection for dogs?

[Glenn Telling] It's unlikely. However, as scientists we can never say without absolute certainty that something is or isn't possible. With respect to dogs, there's no documented evidence of any kind of prion disease occurring in dogs. And that's an unusual feature of dogs. It's thought that maybe something at the molecular level of the constitution of the dog prion protein may make it resistant to this conversion that I talked about earlier. So with respect to dogs specifically, they appear to be one of those species that is particularly resistant to these prion diseases. And so to answer your question specifically, it's highly unlikely that dogs that are chewing these antlers or gnawing their teeth on it would be susceptible, at least based on what we know right now.

[Sarah Gregory] Yeah, that's interesting about dogs.

So how do animals get it? I mean, sheep, moose...how are they getting it in the first place?

[Glenn Telling] Yeah, that's a really interesting and important question. With Mad Cow Disease (with BSE), it's very clear how these animals got it. They got it because they were actually fed in industrial settings and farming situations with protein supplements called 'meat-and-bone meal' that were derived from the so-called 'rendering process'. There were two products from the rendering process: either tallow, which historically has been used to make candles, and then protein that's left over from this. And somebody got the bright idea that we could recycle this and feed it back to animals and we could make some money out of it.

But anyway, by doing so, these animals acquired this prion disease called Mad Cow Disease. And it's thought that there were low levels initially of prions that had been put into this mix of dead downer animals, if you like (they're called downer cattle), and that there was low level infection in the population. Then by refeeding this material back to animals, it amplified in the population. So in other words, it became increasingly more likely that these animals, as more and more animals got infected, the chances of them getting infected by refed their protein materials, if you like, over time led to increasing numbers of infected animals.

In the case of chronic wasting disease, there's no evidence for a foodborne etiology. In other words, these captive animals or animals in the wild are not being fed contaminated protein supplements. And so, you are absolutely right. The question is, how are these animals getting this disease so efficiently by contagious transmission? And with chronic wasting disease in North America, we know that this disease is peripheralized in infected animals. In other words, it's not just the central nervous system that's infected, but also peripheral tissues such as tissues in the lymphatic system are also infected (they replicate these infectious agents). And because of this peripheralization, these prions are shed from these infected animals during a very long pre-clinical phase into the environment from urine, from feces, possibly from contact between animals through saliva. And as a result of this shedding into the environment, these prions are disseminated onto soil and plants and so on.

And the other unusual feature about these infectious agents is that they're extraordinarily resistant. They persist for long, long periods of time in contaminated environments. What that

means is that it increases the likelihood of the chances for other animals that come along much later to acquire infection as a result of consuming these prions. So we think that this is a major route of transmission of these prions in wild animals. And of course, animals die in the environment, their carcasses rot, and that would be another means of how these prions might be contaminating the environment. So the actual resistance of these incredibly stable infectious proteins in the environment, the resistance natural degradation is another feature that helps in their very unique epidemiology.

[Sarah Gregory] And there are no vaccines for this for animals or humans, is that right?

[Glenn Telling] Yeah. There are no vaccines in this. The response of the host to infection with this infectious agent is also a unique aspect of these diseases. Because this protein is a host-encoded protein, the immune system of animals and humans sees it, even during the infected state, as immunologically self. And so, antibodies are not raised against this protein during the infection. And so because of that, development of vaccines against these infectious agents, unlike conventional pathogens, has been an extremely difficult challenge. And in fact, there are currently no good options for treatment in any of these animal or human prion diseases, including the lack of an effective vaccine strategy.

[Sarah Gregory] Let's talk about your article. Your article is about chronic wasting disease in a moose that was found in Finland. How were you alerted to this moose being sick in the first place?

[Glenn Telling] Yeah. I talked a lot about chronic wasting disease in North America and its emergence and its highly contagious transmission. And now there are about 30 US states that have reported infection in either wild or captive animals, and also three or perhaps four provinces in Canada. So it has been known about in North America for a long time. And in 2016, this disease was reported, diagnosed in a moose...actually, sorry, in a reindeer initially in Norway. And so, this was extraordinarily interesting, alarming, important, for the first time CWD was detected in Europe. And you can imagine with all the problems and fury over Mad Cow Disease in Europe that the advent of a new prion disease in Europe was a major cause for additional concern. So that happened in 2016. And then after that, additional cases in reindeer started to be diagnosed in Norway, and also cases in moose (a handful of moose were also diagnosed with prion disease). And over the years as surveillance was increased in these Nordic countries, additional cases were diagnosed in moose from not only Norway, but also Finland and Sweden.

[Sarah Gregory] When you investigated it, what were you looking for?

[Glenn Telling] When we heard about this new case of chronic wasting disease that was emergent in Norway, we immediately contacted our collaborator Sylvie Benestad, who is a veterinary pathologist and molecular biologist who works in Norway and who was involved in identifying these initial cases. And we collaborated with her because the question was ‘where did this new form (this emergent form) of CWD come from? Is it related to what we became aware of as being established in North America? Was it related to CWD from North America or was it an entirely new form of disease in moose and reindeer in Norway?’ So in order to address this very important question, we collaborated with Sylvie, we received samples from these infected animals from her, and we started to do experiments on these prions (these new emergent prions in moose and reindeer from Norway) and we asked, "Are there properties similar to or different from the prions that we've been studying for some years in North America?". And by asking this question, it gave us some information (or we hoped would give us some information) about the

etiology or the origin of this disease and as to whether or not it was related to North American CWD or something different.

[Sarah Gregory] Tell us about how the investigation was done on the moose in Finland. What kind of samples were collected and how were they collected?

[Glenn Telling] So brain samples and samples from lymphoid tissue samples were collected. And the reason that those tissues were collected is because, as I've mentioned several times already, these prion diseases are diseases of the central nervous system that manifest in brain tissue (we can detect it in brain tissue in diseased animals). But very often, these diseases also peripheralize and affect other tissues including tissues from lymphoid tissues and also sometimes muscle. And so, that's why Sylvie, our collaborators in Norway and Finland, sent us materials from brain and the lymphoid tissues as well. And we used those tissues as a means of investigating the prions that were in those animals that died from this disease. And the approach that we took was to use genetically engineered mice. And there's a long history of using so-called 'transgenic mice' in the study of prion diseases.

What we found (my lab found and others have also found) is that by expressing the gene for the prion protein from different species in mice, usually in the absence of the endogenous mouse prion protein, that by expressing PRP (the prion protein)—I'll refer to it as PRP; that's the shortened term of it—from these species, that we could infect those mice with prions from those different species. In other words, expression of the normal form from deer rendered those animals susceptible to prions from deer and moose and elk. And the same thing is true from...we could also engineer mice to express the human prion protein and also render those animals susceptible to human prions.

So with these models in hand, and also more refined models where we produced so-called 'knock-in' or 'gene-targeted' mice where we expressed the protein from deer or elk under the precise control of the endogenous mouse protein, which is a much more accurate and effective model for transmitting these prions, we found that the samples from Finland and Norway (that we're talking about now) produced disease that was very different from samples from North America. In other words, we call this "differences in the strain properties of the agent"—the strain of agent causing disease in moose from Finland is very different from the strain of agent causing disease in North America. So what that tells us is that this disease that emerged in Norway and Finland is not because of accidental exportation of subclinically affected animals. And this has happened in other situations, like the reason why South Korea has CWD is because animals from North America that were subclinically infected (and people didn't realize this) were transported to South Korea and once they were there, they manifested with chronic wasting disease and spread it to other animals in that situation. That's not how this happened; that's not how these newly emergent cases in Norway and Finland happened. They're not related to North American CWD, so there must be other explanations to account for how these prions are manifesting in Norway, Finland, and Sweden.

[Sarah Gregory] Was there anything in this that surprised you?

[Glenn Telling] Yes. The most surprising aspect of this study, in particular looking at the case of CWD from Finland, is that not only that it was different from North American CWD, but also that the strain of the agent causing disease in this moose from Finland, whereas it had some characteristics that were related to previously identified strains from Norway, nonetheless these Finnish moose prions had characteristics that were subtly different. So what that tells us (and this

is the most surprising aspect of this study) is that whereas the disease in North America that affects moose, elk, and deer has a fairly consistent profile, in other words, the strain characteristics of the agent in North American CWD are pretty much invariant (that's not to say that different strains don't exist), but there's a well-known, well-described, stable picture in CWD in North America to the extent that we've looked—and we've now looked at many different cases of CWD that is emerging in Norway and Finland and also Sweden (although we haven't published these results)—every time we look, the outcome of these experiments are subtly different.

And what that tells us is that there's an abundance of different strains emerging in these Nordic countries (Norway and Finland and also Sweden) that are not only different to what we...the picture that we find in North America, but also different from each other. And the unusual aspect of this is that it's only been since 2016 that we've realized that these cases emerged in these Nordic countries, and yet already there's an abundance of different strains—I would imagine at least half a dozen that we've characterized so far, and some of which we've published on—all of which are very different. So the profile of strains in these countries where CWD is emergent is surprisingly diverse and different from the relatively stable profile of strains that we recognize in North America.

[Sarah Gregory] So one of the important aspects of all of this is that these prions are increasing and are emerging, and they are spreading, and rapidly. Why all of a sudden?

[Glenn Telling] Well, that's one of the $64,000 questions. With BSE, it was fairly...that the cause-and-effect aspects of that disease became fairly clear pretty quickly of what the causes and effects were. In other words, we discovered rapidly that the reason these animals were getting Mad Cow Disease is because they were being fed contaminated meat-and-bone meal protein supplements. And once that was discovered and that practice was no longer put in place, the disease...it took some years, but the disease naturally (or as a result of that, rather) declined in these cattle populations.

Since the etiology of chronic wasting disease both in North America and emerging forms in Nordic countries isn't related to these animals being fed contaminated food stuff…these are wild animals, right? It does beg this very important question, "Where did it come from?". And unfortunately right now, we don't have a lot of very good answers, but there are two possibilities. One is that these newly emergent forms in Norway, Sweden, and Finland could be caused by interspecies transmission of prions—in other words, prions that are already existing in other species. For example, I mentioned scrapie in sheep has been around for hundreds of years. Is it possible that that could be the origin of this disease and somehow it has spread from infected sheep (or even cattle) to these wild animals (moose and reindeer). That's one possibility. There's no evidence for that right now, but it is certainly a possibility that we're entertaining.

The other possibility is that I've mentioned already that at least in humans, sporadic or spontaneous forms of prion disease are the most common forms, so it could be that the etiology of these newly emergent forms is somehow related to sporadic disease that we know about in human diseases. In other words, spontaneously in these animals, particularly as we think as they get older and older, the chances of them converting the normal prion protein to the abnormal infectious form increases, and this is how these animals spontaneously develop this disease. Obviously once this infectious conformation has been produced, it rapidly...well, not rapidly, but certainly inexorably converts additional normal protein into the abnormal form (infectious form),

and it is game over for those animals. And it also leads to the possibility that these animals could be shedding these infectious prions and thereby adding to the contagious properties of this disease. But right now, it's too early to say definitively how these new emergent diseases...how they originated in Norway and Finland. But those are the two possibilities that we're entertaining—either transmission of a preexisting disease from a different species, or spontaneous conversion in these animals as they age.

[Sarah Gregory] So you've been talking about a previous study you did in these Norway moose, and now you've recently done this study about this Finnish moose. Was there anything that stands out as a difference in the two studies for what's happening?

[Glenn Telling] There's nothing that stands out with respect to difference except for subtly different differences in the properties of the strains in the moose from Finland compared to several different moose in Norway. I mention that certain features of these strains are related. But there are also subtle differences between them, indicating that they rose independently. But beyond that, the kinds of approaches that we used to ask these questions and to discover these issues...the approaches that we used were very similar. In other words, using these genetically modified mice that we made, most particularly the more precise models that we call 'knock-in' or 'gene targeted' mice, by assessing the transmission properties of these newly emergent prions and comparing them with preexisting North American prions, we could very precisely ascertain whether they had similar or different properties. In other words, the strain properties of the infectious agent we could characterized using these models. And that approach we used in both studies of Norway and Finland CWD.

[Sarah Gregory] Let's talk about how big a public health concern this really is. Is it a big public health concern or is it still very rare? And what are the implications for the future?

[Glenn Telling] Well, public health is always being asked to be concerned about emerging diseases, and we've just gone through two years of this with COVID. So to some degree, these issues are driven by resources and prioritization. With respect to COVID, we're not talking about something that is going to be on the same scale of infection and global coverage. Again, the $64,000 question is...although the fact that these are contagious diseases that are spreading unchecked for which there are no cure in wild animals, have very significant implications for wildlife management and deer populations and cervid populations in general (certainly in North America). And now with the emergence of this disease in Europe, the same concerns apply there.

With respect to public health, it's all about whether or not hunters and other people who are exposed to these prions are likely to develop a novel neurodegenerative disease as a result of that exposure, either by consuming prions in animals that they've hunted or by some other means. And as I've mentioned already, there's no epidemiologic evidence that that has happened yet. However, what I would say is that it would take quite a long time for the evidence to manifest unequivocally because, as I've already mentioned, the incubation time of these diseases tends to be very, very long, lasting years or even decades. When you factor onto...that's within a species, right? Under optimal circumstances, when you factor in an interspecies transmission from deer or elk with CWD to human beings that may be consuming this material or be exposed by other means, what we know from other prion diseases is that that interspecies transmission adds another layer of difficulty, if you like, for the prion to infect. So it would take rather a long time (decades) for this disease to be manifested in human beings after it being present in cervid populations.

And some would argue that this is a newly emergent disease, and it may be too early right now to have any definitive conclusions about human beings and their susceptibility to this disease, and it may take many more years for this to be manifest. But as I said before, these are issues that public health authorities, certainly in the US and I would imagine in Europe, are taking very seriously because we know it has already happened—it has happened in the case of BSE (Mad Cow Disease). So the zoonotic transmission of these newly emergent strains of prion in deer and elk is certainly a possibility that we've encountered before.

[Sarah Gregory] As we've said, this is a terrible disease that once it manifests, people decline quickly with it—so, a terrible outcome and horrifying symptoms along the way once they have it or once it manifests. Is there anything people can or should be doing to protect themselves for the coming future?

[Glenn Telling] Well, I wouldn't advocate particular lifestyle changes to ensure that they don't develop human prion disease. Right now, the most common forms of human prion diseases are these sporadic forms. We don't know what triggers the spontaneous conversion of the normal prion protein into this infectious form. And so, it's very difficult to advise measures to prevent something that we don't understand the molecular basis for it happening. I mean, obviously with respect to Mad Cow Disease, I mean people took their own individual choices as to whether or not they wanted to continue to consume meats in the UK during the 90s and 2000s, but there was certainly no public health advice as to counteract that, nor are there right now currently public health advice as to avoid chronic wasting diseases except that hunters are encouraged to have their animals tested in regions where chronic wasting disease is known to be present.

So for example, in northern Colorado where I'm currently talking to you, rates of CWD tend to be quite high, and the wildlife authorities here encourage hunters to drop off the heads of hunted animals to get them tested for presence of prions in the brains, and then once those test results are back, they can make their choices about their decisions about whether or not they wish to consume those animals. Obviously, that tends to be difficult at the timeline between submitting, hunting, and then submitting materials for testing and getting those test results back...I don't know what the exact timeline is, but there's certainly going to be some timeline. And certainly hunters are encouraged not to expose themselves to brain materials or consume brain materials. They're encouraged to wear gloves when they're dealing with these animals (dressing them and so on). So on that level, there are public health awareness and advice for people who are certainly dealing with CWD (chronic wasting disease), hunters in particular, and how to maybe mitigate their levels of exposure. But beyond that, there are no alarm bells ringing right now.

[Sarah Gregory] So Dr. Telling, tell us how you got to be the director of the Prion Research Center in Colorado, how you came to be in Colorado, and what you enjoy most about this job.

[Glenn Telling] So this goes back to my career as a graduate student. I was interested in studying the molecular biology of infectious diseases back in those days when I was doing my PhD at Carnegie Mellon University. And in those days, I was studying human adenoviruses and then I was deciding what I was going to do for the next phase of my career and my postdoctoral training, and this was during the time when Stan Prusiner and the prion hypothesis was really emergent during the 80s. And this is a radical proposal, right? How could a protein be infectious? How could this infectious agent lack a nucleic acid? And so, the unusual features...that unusual feature, the unusual properties or the replicated properties) of this infectious protein that is produced by the actual host itself and some of these, as I've talked about, unusual diseases like

kuru and Mad Cow Disease...it just really piqued my imagination. And I was fortunate enough to be accepted into Stan Prusiner's lab as a postdoctoral fellow, and I stayed there for some eight years and then went back to the UK during...at the height of the BSE (Mad Cow Disease) crisis, worked for a couple of years there for the Medical Research Council. And then, I did a tenure for about 12 years at the University of Kentucky at the Alzheimer's Disease Research Center there. The reason for that relationship with the Alzheimer's Center is because, as I've mentioned, these are (at least the human forms are) neurodegenerative diseases of humans that bear resemblances to Alzheimer's disease and other conditions of humans. And then with the advent of the emergence of CWD over the decades, I began to collaborate with folks out here, most particularly Ed Hoover, who was using natural infected deer to study the pathogenesis of CWD, and our approaches using transgenic mouse modeling and molecular biology approaches really complemented his approach.

And so, we collaborated quite closely. And then an opportunity arose in about 2011 for the establishment of an actual center here at Colorado State University. And the reason for that is because chronic wasting disease was first discovered here by the late Beth Williams, who was I think a graduate student at CSU. So there's a rich history of prion disease research, most particularly CWD research, here at CSU. And so, when the opportunity arose to...for me to move and establish a center with the clinical mass of researchers here, I really jumped at the opportunity. So I've been here since 2011. There's a group of researchers here that study different aspects of prion disease. It's a very active center. It's internationally recognized as one of the places globally where this kind of work can be done, ranging from studies in both the natural animal host using specialized facilities where deer can be infected and studied, down to these transgenic mouse models and gene targeted mouse models that I told you about here, to more in vitro approaches to studying prion diseases. And that's how this started. I've been here since 2011, and the research center is thriving. And we collaborate internationally, as I mentioned, with many, many different people working on CWD and other prion diseases.

What I like most about research and prion disease is that it involves on a continual basis thinking outside the box. The mechanism of pathogenesis for these agents (these proteinaceous infectious agents), we're only just beginning to decipher. And even with all the work that's happened since I first joined this field in the early 90s, the work with Stan Prusiner and other groups globally, there are still many gray areas and even black boxes as to how this happens, you know? What is the actual mechanism of conversion of the normal to the abnormal prion protein conformation? What's the normal function of the host-encoded prion protein? How the strains work? How is inflammation propagated in a stable way from generation to generation in the absence of a nucleic acid? These sorts of questions still are largely unresolved, and it's this that really keeps me interested in moving forward. And of course, as we've mentioned many times here, these are inevitably fatal diseases that are new diseases and different species are being recognized all the time. And ultimately, we need to understand how this disease works so that we can generate cures for these horrible diseases that affect families. It's not as common as diseases like Alzheimer's or Parkinson's disease, but certainly, as you've already alluded to, families that are affected by this disease are devastated by it. There are no cures. It's a really terrible disease.

And the final thing that I would say also is that by studying these relatively rare diseases, the mechanism of how this protein acts to be an infectious protein, it has really informed us about the mechanism of pathogenesis of these other more common neurodegenerative conditions like Alzheimer's and Parkinson's disease, because the proteins that are involved in those diseases

(most specifically tau, a-beta, and alpha-synuclein) have properties that are very analogous or comparable to the properties of the prion protein. In other words, conformational changes of this host-encoded normal form of the protein in these diseases is also a feature. So we've learned that from prion diseases as well. So it's not just studying these diseases because this is a completely novel form of information transfer and pathogenesis at the protein level, it's not only the desire to do something clinically about these devastating diseases, but it's also the fact that it informs more generally about common mechanisms or pathogenesis of a number of different, more common human neurodegenerative diseases, and possibly other diseases like cancer and so on.

[Sarah Gregory] Thank you so much for taking the time out of your important work to talk to me today, Dr. Telling.

[Glenn Telling] Well, it has been a real pleasure talking to you. And I hope your listeners enjoy it. Thank you very much.

[Sarah Gregory] And thanks for joining me out there. You can read the February 2023 article, Novel Prion Strain as Cause of Chronic Wasting Disease in a Moose, Finland, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.