ТРЖКҮ	This is Exactly Right.
Erin Welsh	Typically, one day in middle age the sufferer finds that he has begun to sweat. A look in the mirror will show that his pupils have shrunk to pinpricks and he is holding his head in an odd, stiff way. Constipation is common, the women suddenly enter menopause, and the men become impotent. The sufferer begins to have trouble sleeping and tries compensating with a nap in the afternoon but to no avail. His blood pressure and pulse have become elevated and his body is in overdrive. Over the ensuing months, he tries desperately to sleep, sometimes closing his eyes but never succeeding in falling into more than a light stupor. Their exhaustion is immense, beyond comprehension.
	Once the sufferer can no longer sleep, a downward progression ensues as he loses his ability to walk or balance. Perhaps most tragic, the ability to think remains intact, sufferers know what is happening. At first they can talk about it and even write down their thoughts. After a few more months, some lose this level of functioning. Once their bodies shut down, only the desperate look in their eyes shows that they know what is going on. But others can talk and reason until the end. In the terminal phase, usually about 15 months after the disease has begun, they fall into a state of exhaustion resembling a coma and die.
ТРЖКҮ	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	God.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's a bad one.
Erin Welsh	Yeah. Do you wanna hear what that is?
Erin Allmann Updyke	Yeah.
Erin Welsh	So that is a case of fatal familial insomnia which is a prion disease, welcome to prions everyone. And that is an excerpt from the book 'The Family Who Couldn't Sleep' by D. T. Max which is all about prions.
Erin Allmann Updyke	Wow.
Erin Welsh	Yes.
Erin Allmann Updyke	Hi.
Erin Welsh	Hi. I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	Yeah. Today we're talking about prions.
Erin Welsh	This is a big one and we've said that before.

Erin Allmann Updyke	(laughs) We say that almost every time.
Erin Welsh	Yeah. But it's always true.
Erin Allmann Updyke	It is, yeah. We haven't really covered any baby diseases yet.
Erin Welsh	Before we get into the nitty gritty of these many different diseases, what time is it?
Erin Allmann Updyke	It's quarantini time!
Erin Welsh	What are we drinking today?
Erin Allmann Updyke	Well this week we're drinking the Chronically Wasted. (laughs) Because one of the prion diseases is chronic wasting disease.
Erin Welsh	It has milk, naturally, bourbon, naturally, coffee, naturally. No, just because those things taste good together. And then a little bit of cinnamon and nutmeg.
Erin Allmann Updyke	And you just shake it all up and then strain it into a glass. And as always this season, we'll also be posting this recipe along with our placeborita, the non alcoholic version of our quarantinis on all of our social media accounts and our website. So check it out there.
Erin Welsh	Excellent. Okay, prions. I have read so much about the history, about the whatever, but I really avoided the biology and understanding exactly what's going on. So please enlighten me.
ТРЖКҮ	(transition theme)
TPWKY Erin Allmann Updyke	(transition theme) So prions are a pathogen unlike any that we've ever looked at before and unlike anything that we'll ever look at again, which is kind of thrilling.
TPWKY Erin Allmann Updyke Erin Welsh	(transition theme) So prions are a pathogen unlike any that we've ever looked at before and unlike anything that we'll ever look at again, which is kind of thrilling. It really is.
TPWKY Erin Allmann Updyke Erin Allmann Updyke	(transition theme) So prions are a pathogen unlike any that we've ever looked at before and unlike anything that we'll ever look at again, which is kind of thrilling. It really is. So every other infectious disease that we've discussed so far and that we'll ever discuss again has been either a virus or a bacterium or a protozoan, in the future we'll probably do a bunch of worms. But even at their most basic, all of these infectious diseases are some kind of "organism" which I'm putting in quotes because some people don't call viruses organisms. But at a bare minimum, even viruses. They've got either RNA or DNA and protein and the genetic material is required because basically that's the only way that an organism can reproduce. The DNA or the RNA serve as templates to actually make the protein. And so then they also serve as the template that's replicated to make a new version of that organism. So for anything to be considered even close to alive and for sure to be able to reproduce, it has to have either DNA or RNA. Except for prions.
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TPWKY Erin Allmann Updyke Frin Welsh Erin Welsh Erin Welsh Erin Welsh Erin Welsh	(transition theme) So prions are a pathogen unlike any that we've ever looked at before and unlike anything that we'll ever look at again, which is kind of thrilling. It really is. So every other infectious disease that we've discussed so far and that we'll ever discuss again has been either a virus or a bacterium or a protozoan, in the future we'll probably do a bunch of worms. But even at their most basic, all of these infectious diseases are some kind of "organism" which I'm putting in quotes because some people don't call viruses organisms. But at a bare minimum, even viruses. They've got either RNA or DNA and protein and the genetic material is required because basically that's the only way that an organism can reproduce. The DNA or the RNA serve as templates to actually make the protein. And so then they also serve as the template that's replicated to make a new version of that organism. So for anything to be considered even close to alive and for sure to be able to reproduce, it has to have either DNA or RNA. Except for prions. Prions. I'm excited. So prions are just protein. No nucleic acids, no genetic material, no DNA, no RNA, just protein. The word 'prion' literally comes from 'proteinaceous infectious particle'. What? So creative! (laughs) It's so amazing to me because there's no biological incentive.

Erin Allmann Updyke	Oh my god, you're so right.
Erin Welsh	I don't get it, I don't get it. How? Why?
Erin Allmann Updyke	Okay, I'm gonna try and answer those two questions.
Erin Welsh	Okay.
Erin Allmann Updyke	As you can imagine, you are not the only person to feel like this, like what, how, why? And I can't wait to hear the story of how just mind blown scientists must have been when they finally were accepting that this was just a protein. There's nothing like it. Okay, so here's how it goes. We're gonna talk about proteins for a minute. Imagine that a protein is basically a rope, okay. There are lots of different material that you can use to make rope and there's lots of different lengths to which you can cut that rope, just like protein. In our body we have lots and lots of different types of proteins, they're all made up of different amino acids, and they're all different lengths and sizes and they all have different functions. And a large part of how that function is determined is how they're folded. Or if you're imagining our protein rope, how they're knotted, okay. So think of how many different ways you can tie a knot. There are thousands, hundreds probably.
Erin Welsh	(laughs)
Erin Allmann Updyke	(laughs) And if you think of all of the different types of materials of rope, some of them are gonna be better at holding certain knots than others.
Erin Welsh	Oh!
Erin Allmann Updyke	So proteins Yeah, right? This is a good analogy. I didn't come up with it, Brett did. So different materials of rope or different types of proteins are only going to be stable and therefore functional in certain confirmations, certain knots. With me so far?
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Great. So in the case of prion diseases, there's this single protein, this single rope, it's called PrP which just means, get ready for the creativity here-
Erin Welsh	Prion protein?
Erin Allmann Updyke	Prion protein! No joke. So this protein is in your body. It's in your body, it's in my body, it's in everyone's who's listening body, it's a cell membrane protein which means it's found in the walls of your cells, in a whole bunch of different cells, especially in our neurons. And we're not entirely clear what this protein does exactly, we don't know it's exact function, we think it has to do with neuronal communication and the transport of stuff inside and outside the cell. That doesn't really matter right now for my purposes. The thing that matters is that this protein is normal most of the time and when it's in its normal state, its normal knot, it's benign. It doesn't cause any disease. But for some reason if it unknots itself and then re-knots itself in an abnormal way, it can begin to cause disease. And here's the scary part: when it interacts with other normal proteins in your body, it can cause them to change shape and then those newly misfolded proteins interact with other normal proteins and cause them to change shape. And then Do you see where I'm going with this?
Erin Welsh	It's a domino effect of terrifying misfolded proteins.

Erin Allmann Updyke That's exactly what it is. And it's outrageous. It's similar in some ways to how a virus or a bacterium will get into your body and replicate and grow in number but in this case, it's just a misfolded version of a protein that's already in your body. And in its normal form, it's not a big deal but if it comes into contact with a misfolded version, it becomes misfolded and that's how it replicates. And exactly how this happens to begin with, we don't know. Erin Welsh I'm just struggling... Erin Allmann Updyke Struggling for words right now? Erin Welsh I'm struggling for words because it sounds like it's from a sci-fi book. Erin Allmann Updyke Yeah, it totally does. Erin Welsh And it's outside of this paradigm of infection or disease or proteins that we have been taught throughout school, throughout life, whatever. (laughs) Erin Allmann Updyke Yeah, we kinda mentioned this at the beginning but there are a lot of different names for prion diseases. But the thing that I did not realize until starting to research for this episode is that all of these different diseases that you've probably heard of are all caused by misfolding of the same protein. The same one, that PrP protein, it's not tons of different proteins in a cow vs a sheep vs a human, it's the same one! Erin Welsh How? How? How? How? Erin Allmann Updyke Great question. (laughs) Honestly I did not know that at all. Now the thing is each of these misfoldings, these different knots in the rope, they're slightly different versions. So they kind of refer to them as different strains the way that we would call different strains of ebolavirus, it's the same virus but there are multiple strains. It's similar in this except that again, it's just a protein. But they're all misfolded in slightly different ways. So these different variants of the misfolding of the prion protein, they cause different diseases that were named by and classified by their incubation period which varies really widely and the actual neuropathology, so the way that they affect your brain and the symptoms that they cause are actually a little different in each version of prion disease, even though it's the same misfolded protein. So what I'm gonna do is go through the different human diseases and I am gonna focus on human diseases but we can talk about some of the other mammal diseases too because they're also really interesting. Erin Welsh Don't worry, I'll get there. Erin Allmann Updyke Oh good! (laughs) So we'll go through the different human ones. But first I just want to talk to you about what they all have in common. So the other name for prion diseases is transmissible spongiform encephalopathy. Erin Welsh Which is a mouthful.

Erin Allmann Updyke	So what does that mean? It means this. 'Transmissible' just tells us that this is an infectious disease, meaning it can be passed from one person to another or in some cases from one mammal to another. 'Encephalopathy' just means it affects your brain, and 'spongiform' tells us how it affects your brain. It actually causes spongiform changes, so your brain becomes holey like a sponge. And importantly, these holes that happen, it happens without any inflammation. So inflammation is a response of our body, it's a natural response to either tissue damage or the presence of some kind of nonself like bacteria or viruses. But in this case with prions, your body doesn't react to the prion proteins or to the damage they cause with normal inflammatory responses. So you have neurons and other brain cells actively dying, leaving gaping holes, empty space in their place with no white blood cell invasion, no activation of the inflammatory cascade or anything like that.
	So that's what they have in common. Let's talk briefly about the different variants of this disease. Okay so the first one, since we touched on it briefly in our firsthand account, is fatal familial insomnia. Now this is a weird one. It's super, super, super rare, like very rare. But it causes insomnia, that's one of the major symptoms. It also causes speech and physical coordination problems and dementia. This one is not necessarily infectious but it is familial, so it's actually transmitted genetically and it's autosomal dominant which means that if one of your parents has it, you have a 50% chance of getting it as well.
Frin Wolch	Like Huntington's
Erin Allmann Updyke	Exactly, just like Huntington's. (laughs) So it's a weird one. Okay, the next one. We're just gonna blow through these. The next one is called GSS, Gerstmann-Sträussler-Scheinker syndrome. Was that good?
Erin Welsh	Okay. I don't know.
Erin Allmann Updyke	I don't know either, I don't speak German. This is another weird one. It's also familial, so just like fatal familial insomnia, it doesn't cause insomnia though. Instead what happens is you first start with dysarthria which means difficulty speaking, so you might not be able to talk. And then you'll get what's called ataxia which means you can't coordinate your body movements, so you might have tremors, you might have an unsteady, wobbling gait. And then you'll progress to dementia, memory loss, visual disturbances, and eventually death.
Erin Welsh	That sounds like it's going to be the common thread and I know that it is, but
Erin Allmann Updyke	Other thing that I didn't mention that ties all these things together is that they are 100% fatal.
Erin Welsh	Cool.
Erin Allmann Updyke	Yeah.
Erin Welsh	So that's our second this season.
Erin Allmann Updyke	Yeah, well i mean rabies was like almost 100%.
Erin Welsh	(laughs)
Erin Allmann Updyke	At least you can treat it if you catch it early.
Erin Welsh	You optimist.

Erin Allmann Updyke	Yeah. We've gotta have one. (laughs)
Erin Welsh	Yeah.
Erin Allmann Updyke	Now let's get into the diseases that you've probably heard more about. kuru, have you heard of it?
Erin Welsh	Oh yeah.
Erin Allmann Updyke	Well I know you have. Listeners, have you? Tell us. kuru is a disease that is transmissible and it's believed to have been transmitted to people from the consumption of deceased family members during burial rituals, which I'm guessing you're gonna talk a lot more about, Erin.
Erin Welsh	Oh yeah.
Erin Allmann Updyke	I avoided the history of this. What I do know is that this was one of the early prion diseases that people sort of found out about, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	And one of the first ways that we figured out that this was actually a transmissible disease and how people actually got it from eating meat that had been contaminated with prion proteins. So for this one, the symptoms start often with body tremors, so all over body tremors, and then bursts of laughter which I find so interesting and scary.
Erin Welsh	Yeah.
Erin Allmann Updyke	Because what it was described as people would become very depressed, which is understandable, but then they would have these bursts of uncontrollable laughter that they just could stop.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. Then you would also get that same ataxia, so tremors combined with a wobbly gait and just not being able to coordinate your body movements. And then in the later stages, you can actually get ulcerations, so open wounds like on various places of your body that lead to secondary infection.
Frin Welsh	Oh
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Erin Allmann Updyke	Yeah. And so actually one of the major causes of death in kuru is pneumonia or another secondary infection, not necessarily the prion proteins itself.
Erin Welsh	Interesting, I didn't know that.

Erin Allmann Updyke	Yeah. And then we have the most famous, or should I say actually the two most famous probably forms of prion disease in humans, Creutzfeldt-Jakob disease, also variant Creutzfeldt-Jakob disease. There's actually more than two forms, but these two forms are very distinct. So let's talk about the classic first. Classic CJD is sporadic. This is not what you get from eating cow meat that's been contaminated, this is not mad cow. So Creutzfeldt-Jakob disease is a prion disease that we don't know why or how it happens. We think maybe it's just age-related random mutations. Who knows? You can get them from things like corneal transplants, there have been several documented cases of people who've received corneal transplants from someone who had died from Creutzfeldt-Jakob disease who then got Creutzfeldt-Jakob disease and died from the cornea transplant. And also dura mater transplants. Dura mater is the outer layer of your brain meninges, so like the tissue that covers your brain essentially.
Erin Welsh	Okay.
Erin Allmann Updyke	Sometimes you might do a graft of that from one person to another in the case of some extreme trauma. And if that person died from Creutzfeldt-Jakob then you will also. So this type of CJD is characterized by a rapidly progressive dementia and memory loss, those are the first two things that tend to happen. And then you'll get personality changes, hallucinations
Frin Welsh	So when you say rapidly progressive, what's the timeframe we're looking at?
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Erin Allmann Updyke	So most of the time, that was something I didn't mention about all of these diseases, but they all have very different durations of illness. So fatal familial insomnia, the average age at death is 50 and the average duration of illness, so from the time you start showing symptoms until you die is 18 months for FFI.
Frin Welsh	Okay
	Ondy.
Erin Allmann Updyke	For Gerstmann-Sträussler-Scheinker, GSS, the median age of death, it's really variable because it's such a small population but the duration of illness is anywhere from 3 months to 13 years with an average of 5 years.
Frin Welsh	Oh my god.
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Erin Allmann Updyke	Yeah, it's a very long progressing disease. kuru, the duration of illness is only about 12 months but they think that the incubation period could be as long as 50 years. That's the time from when you first get exposed to prions until they build up in enough number in your brain to actually start causing disease. But with Creutzfeldt-Jakob, classic CJD, the median age of death is 60 but the duration of illness is only 4-6 months. So once you start showing symptoms, you're probably dead within 5 months.
Erin Welsh	Holy cow.
Erin Allmann Updyke	The longest that's been documented that somebody has survived after starting to show symptoms is about 2 years with classic CJD.
Erin Welsh	Okay. Wow.

Erin Allmann Updyke	Yeah so very rapidly progressive. You'll also end up with hallucinations, myoclonus which means muscle spasms, and then late in the disease you can have things like ataxia, again that wobbly gait so we're seeing some overlap with symptoms, speech impairment. Again here the cause of death tends to be pneumonia which I find very interesting, especially that it can happen that rapidly.
Erin Welsh	Well and also I don't understand the mechanism behind, like this is a neurological disorder primarily.
Erin Allmann Updyke	Tell me about it. Yeah.
Erin Welsh	So how? How?
Erin Allmann Updyke	Well if it's affecting the parts of your brain that cause you to breathe normally and if you're not breathing normally, you're not coughing up normally or if it's even just affecting all of the functions of your organs, right, everything is controlled by your brain. It's maybe impairing more of our unconscious functions than it is our conscious functions.
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Erin weisn	Окау.
Erin Allmann Updyke	And then the last human prion disease that we need to talk about is variant Creutzfeldt-Jakob. This is the one associated with mad cow. So this is the one, which I'm sure you'll talk about the outbreak that started it all-
Erin Welsh	Don't you know it.
Erin Allmann Updyke	Where a bunch of people became infected presumably after eating contaminated cow meat, beef, that those cows had died from mad cow also known as bovine spongiform encephalopathy or BSE. So that is the form of prion disease that happens in cows and if you eat a cow that's died from that, you will get vCJD. Very different from classic CJD, the median age of death is 30 or under.
Frin Welsh	Veah
	16411.
Erin Allmann Updyke	So these were young who are affected. And the median duration of illness is 13-14 months so it's a longer duration of disease.
Erin Welsh	Possibly because it came from a cow?
Erin Allmann Updyke	Yeah, yeah. So it presents in a way that's much more similar to kuru.
Erin Welsh	Okay.

Erin Allmann Updyke	And that's part of the reason that they were able to make that link between vCJD and kuru both being transmitted by consuming prion-infected meats because they do present very similarly. With vCJD, it's a hard acronym to say, you present not so much with dementia and memory loss like with classic Creutzfeldt-Jakob but with other psychiatric and behavioral symptoms and also very classically with very painful, what's called dysesthesias which means nerve pain and like your nerves are firing in ways that is very painful and not under your control. So maybe you'll have hands cramping and things like that. Yeah. You don't get as much of the ataxias and things with vCJD as you do with some of the other diseases. But you do die just like with all the others. And one of the scary things about vCJD is that it is believed that it can also be transmitted by blood products. So that means likeblood products. (laughs) What's another way to say that?
Erin Welsh	Serum?
Erin Allmann Updyke	Serum, yeah. If you give blood-
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Erin Weish	Blood transfusions.
Erin Allmann Updyke	Blood transfusions, that's what I'm trying to say. Whereas there isn't really evidence that other forms of this disease can be transmitted in that way.
Erin Welsh	Oh.
Erin Allmann Updyke	Yeah. So while you can get CJD from corneal grafts or dural grafts or things where you're actually coming in contact with neuronal surfaces, there isn't evidence that you can get it from blood products. But with vCJD you can potentially transmit that because you do find prion proteins in the peripheral blood, not just in the nervous system.
Erin Welsh	That's very strange.
Erin Allmann Updyke	Yes. Yeah. And the other thing that's similar between kuru and vCJD is that you get more deposition of the actual prion proteins into plaques which means that these misfold proteins aggregate, clump together, and deposit into your brain in a similar way that you get aggregates in something like Alzheimer's. And also we have no idea how long the incubation period is for these two diseases, these are the most sort of transmissible of the transmissible spongiform encephalopathies in humans and we don't know how long ago some people were infected. It could be in some cases it seems to be a matter of months, in other cases it could be 20, 30, 40 years. So a lot of people think that there are going to be more and more cases of vCJD down the line from people who were exposed back in the 90s.
	That's didfilling.
Erin Allmann Updyke	It's alarming and probably the most alarming thing about prions is that we can't do anything about them. So there's no treatment.
Frin Welch	Is it because it's a protein that's in your body and so by attacking that protein you're liable to
	attack other proteins that you actually need and function?

Erin Allmann Updyke	It's part of it, yeah. But I mean cancer cells are also your body cells but we have ways that we can kill those. The reason it's so hard to deal with prions is because most of the drugs that we use to target diseases, infectious diseases and things like cancers, target DNA. So they target reproduction in the way that we know reproduction happens. We don't know why this protein becomes misfolded and we don't know how it causes other proteins to become misfolded. So we don't know how to target it. And because we don't know exactly what the PrP protein does normally, it makes it even harder to actually find ways to try and stop it from misfolding or make it go back to it's normal confirmation. Yeah.
Erin Welsh	Is there at least promising work on stuff like how it's analogous to Alzheimer's? Or is that telling us anything more about these other neurodegenerative diseases?
Erin Allmann Updyke	It's a good question, we'll talk a little bit more about it in the sort of current events section. There's definitely a lot of parallels especially in terms of understanding how proteins fold and why they misfold in certain ways. These don't tend to be misfolded at least from what I read, they don't tend to be misfolded in the same ways that Alzheimer's proteins are misfolded so it's not the same confirmations that cause Alzheimer's plaques, if that makes sense.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	But yeah. We don't have a lot currently and they're also just really hard to get rid of. If your meat becomes contaminated, there's not much that you can really do about it because proteins don't degrade as easily as DNA or RNA, so the ways that we normally use to sterilize things don't always work on prions. They're not impossible to kill, though. People who are like, 'You can't ever kill a prion!' Like that's not true, it just takes a lot higher heat, it takes things that denature proteins rather than things that denature DNA and RNA. So it's different techniques, it is possible though, it's not impossible.
Erin Welsh	Right.
Erin Allmann Updyke	Yeah, how was that? That was prions.
Erin Welsh	Very scary introduction to prions.
Erin Allmann Updyke	Yeah. And we didn't even talk about scrapie or BSE or chronic wasting disease which I think is actually the scariest one. So Erin, tell me what is up with these prions, how did they get here, and why should I be so afraid of them?
Erin Welsh	(laughs) I think that last question you're gonna have to answer.
Erin Allmann Updyke	Okay.
Erin Welsh	Actually I think that last question you just answered.
Erin Allmann Updyke	Oh okay, well then just tell me how they got here and what's going on with them.
Erin Welsh	Okay, happy to do that.
ТРЖКҮ	(transition)
Erin Welsh	I'm warning you now. The history of prions is a huge one.

Erin Allmann Updyke	Yes!
Erin Welsh	In part because it's not really just one disease, like you just talked about. Each prion disease has its own detective story and each contributes to the story of prions as a whole.
Erin Allmann Updyke	Yes.
Erin Welsh	And that story is going to take us all over the world, from the pastures of Spain to the highlands of Papua New Guinea, from the grocery stores of Britain to the forests of North America. And we're gonna meet some rather interesting people along the way who will show us that changing people's minds can be exceptionally hard, especially when ego and glory seem to be driving you more than a quest for truth. Let's get started. Even though the word 'prion' was only invented a few decades ago, the history of prion diseases stretches back much farther, probably hundreds of thousands of years.
Erin Allmann Updyke	Whoa.
Erin Welsh	But before I get to that, let's try to track when prion diseases first became known to modern humans. There are many early references to a prion-like condition that have been put forth as evidence for the disease being present at a certain time or place. Hippocrates may have mentioned it, there's strong support that Shakespeare refers to it in MacBeth-
Erin Allmann Updyke	What?
Erin Welsh	Yeah. (laughs) I didn't read it but a lot of things were like, 'Oh yeah, MacBeth, blah blah blah.'
Erin Allmann Updyke	What?
Erin Welsh	I should probably find that line. And it was probably around during those times. But let's get down to when it first started making big waves. Between the 18th and 19th centuries in Europe, human population was on the rise and that meant figuring out ways to make more food, to make more clothing, housing, etc to support the growing populace. And one way that people maximized efficiency and productivity was through selective breeding which wouldn't actually go by that name for almost 100 years when Darwin would discuss it in his books. But the concept of breeding plants or animals to select for certain desired traits was known and one of the biggest developers of selective breeding was a dude named Robert Bakewell who applied it to sheep and in doing so changed the course of history.
Erin Allmann Updyke	Oh. Always the Bakewells with the sheep.
Erin Welsh	(laughs) What is the fastest way to get the traits that you want in a sheep?
Erin Allmann Updyke	(laughs) I don't have the slightest idea.
Erin Welsh	Okay, well you would breed the sheep who already look the closest to your ideal image.
Erin Allmann Updyke	Okay, that makes sense.
Erin Welsh	Bakewell started doing what was known as in-and-in breeding.

Erin Allmann Updyke	Uh oh.
Erin Welsh	Yeah. Which means mating parents with offspring, offspring with each other, really Game of Thrones type stuff.
Erin Allmann Updyke	I was gonna say just like England. (laughs) Back in the day.
Erin Welsh	(laughs) The royals. This practice wasn't really done because it was common knowledge among farmers that inbred animals tended to have more hereditary defects. But the results that Bakewell had gotten in a really short amount of time were too impressive to ignore and soon enough Bakewell was studding out his best rams and farmers everywhere started their own in- and-in breeding practices. In those years, the relatedness of those sheep sharply increased as you might expect. And things were about to get a whole lot more related.
Erin Allmann Updyke	Uh oh.
Erin Welsh	English sheep weren't known for their fleece unlike the Spanish merino breed.
Erin Allmann Updyke	Your favorite sheep, I believe.
Erin Welsh	(laughs) Merino wool is one of my absolutely favorite things on earth.
Erin Allmann Updyke	Yeah I know, I know.
Erin Welsh	So anyway yeah. So a guy named Banks decided to turn a profit by shipping a handful of Spanish merino sheep to farmers all over England where they were bred in-and-in even more so they could get that nice fleece. By the end of the 1700s, A) most of England's sheep were intensively inbred, and B) the inbreeding was not in pockets but rather all over, it was the only way you could maintain sheep. Then a few sheep started acting strange. They seemed to have an itch they could not scratch enough.
Erin Allmann Updyke	Ugh.
Erin Welsh	They would rub their heads and their rumps on posts, on trees, on rocks, on fences, on anything to try to get some kind of relief. But this was a one direction disease. The sheep never recovered from their itch and in later stages staggered around until they suddenly dropped dead. Soon this phenomenon was all over England and Scotland, earning various names along the way such as 'rubbers' and 'yeukie pine', 'the frenzies', 'the giddies', 'scratchy', 'shrewcroft', 'turn sick', 'the dizzies'.
Erin Allmann Updyke	Just 'the disease'? That's not creative.
Erin Welsh	(laughs) No, the dizzies. Like getting dizzy.
Erin Allmann Updyke	Oh the dizzies! (laughs) I was like I'm sorry, prion is now officially the least creative group of people. We're just gonna call this one 'the disease'.
Erin Welsh	I kind of like it. It's like 'the band'.
Erin Allmann Updyke	Yeah.

Erin Welsh	Just classic. 'The shaking', 'the mad staggers' which might be my favorite.
Erin Allmann Updyke	Yeah.
Erin Welsh	The goggles', and finally the one that stuck with it: 'scrapie'.
Erin Allmann Updyke	Scrapie.
Erin Welsh	Everywhere sheep were dropping by the dozens, hundreds, and no one knew what was causing it. Hypotheses of course abounded. It was the air, it was a maggot, it was too much sex, it was not enough sex. It turned out that it had previously been described by Spanish shepherds decades before but this outbreak probably wasn't caused by the import of those sheep, just a matter of high sheep density and a lack of scrapie resistance in the inbred sheep. No real progress would be made for years on what the actual cause of scrapie was but solving that mystery lost a little bit of its urgency as scrapie-resistant sheep breeds began to take over.
Erin Allmann Updyke	Wow.
Erin Welsh	Let's say goodbye for now to our beautiful merino sheep in England and travel to Papua New Guinea in the 1950s, which was at the time partially under Australian rule. The Australians in charge didn't really know a lot about the islands cultures, ecology, etc but they were looking to change that. In particular they wanted to know who was living in the dense rainforest of the highlands, to "make contact" - I'm saying that in air quotes - rather than conquer.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. Anyway. One of the groups that was contacted was called the Fore. Right away those making the contact noticed a couple of strange things. For one, there weren't many women around but there were a lot of unmarried men. And after spending a bit more time with them, they noticed a mysterious illness that was circulating, resulting in a high number of deaths. Those afflicted, mostly women, would shiver and jerk uncontrollably for weeks, occasionally hit, as you mentioned, by this involuntary hysterical laughter. And then this would continue until they died. The Fore called it 'shaking' or kuru and it was devastating villages. Seeing this, the Australians decided to send for a doctor to investigate what exactly was going on. The doctor, a man named Vincent Zigas, interviews sufferers and took many samples to send off for analysis. But no one could find anything in the blood or serum or even brain samples he sent. No bacterium, no virus, no fungus, no worm, nothing. Nothing.
	Enter Carleton Gajdusek. I wanna pause here and warn anyone who is listening that I'm going to talk a bit about Gajdusek's criminal history which includes his conviction as a child molester. So if you don't wanna hear about that, fast forward about 2.5 minutes. Let me give you a little bit of background on this piece of work. Gajdusek was a convicted child molester and self-proclaimed pedophile. He was also a Nobel Prize winning pediatrician.
Erin Allmann Updyke	I'm sorry, what?
Erin Welsh	Oh yeah. Yep. Medically Gajdusek was fascinated by rare, incurable diseases. Personally he was interested in so-called "non western sexuality" particularly as it related to children.
Erin Allmann Updyke	Ew. I hate this already.

Erin Welsh	Yeah he's a despicable human being. He was not well liked by many of his colleagues or liked at all and some would refer to him as inhuman and just short of a sociopath. Along the path of his research were scattered the remains of former collaborations and friendships. At the same time, Gajdusek was widely admired by his academic peers for his drive, ambition, and intelligence.
Frin Allmann Undyke	Hap
	050.
Erin Welsh	And many of these peers would later beg leniency from the judge for Gajdusek's sentencing for child molestation. Quote: "Carleton was a complicated man,' his peers would say. Or something along the lines of 'No, he wasn't perfect, but he was a genius' which seemed to excuse his behavior as a child molester as the cost of conducting important medical research."
Erin Allmann Updyke	Oh my god.
Erin Welsh	Or they would take a stance of cultural relativism. If pedophilia was practiced in a certain culture then it was okay if Gajdusek sought out those cultures as his hunting ground.
Erin Allmann Updyke	Ew!
Erin Welsh	Yeah. That was part of his defense.
Erin Allmann Updyke	Ugh.
Erin Welsh	The reason that I'm spending so much time talking about who Gajdusek was is because I am extremely frustrated with the fact that his molestations, his crimes are so often relegated to a footnote when discussing him or his research.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's so frustrating to me when I read an entire book about prions. 'The Family Who Couldn't Sleep' discusses it in depth but Stanley Prusiner's book very briefly mentions this and it is so appalling.
Erin Allmann Updyke	Cause then it just almost excuses it, like we can just ignore that piece of history.
Erin Welsh	Exactly. So now that you know who Gajdusek was, let's get back to Papua New Guinea in the 1950s. Gajdusek was always on the hunt for new diseases and new, in his words, "uncivilized" places to explore. When he was in Australia looking for his next adventure, he learned about this mysterious illness that was devastating the Fore. This could be the medical find of the century and he wanted to be a part of it, not just a part of it, the whole of it. He shouldered his way into the investigation and took it over, irritating many people along the way who started to wonder if he had a medical degree at all.
Frin Allmann Linduka	Wow
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Erin Welsh	Yeah. Once in Papua New Guinea, he took samples and more samples and tracked cases as the numbers climbed every month. In June of 1947 he had recorded over 200 deaths and these deaths followed a strange pattern. It appeared that for every one male struck by kuru, up to 14 females were sick with the disease. And still the origin of this disease or even its pathology had yet to be figured out. But slowly the pieces were falling into place. First, a researcher working in one of the labs to which Gajdusek had sent victims' brains noticed strange deformities in some nerve cells and these deformities reminded him of a disease he had just seen in a textbook: Creutzfeldt-Jakob disease.
Erin Allmann Updyke	Oh.
Erin Welsh	Yeah. Anxious to make similar headway on the source of the disease, Gajdusek's supervisor told him he wanted to assemble a team of anthropologists, epidemiologist, physicians, etc. But Gajdusek refused. Couldn't they understand? He was the team.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Yeah. But he wouldn't end up actually solving that riddle even though he would later claim to have known about the disease's origin all along.
Erin Allmann Updyke	Oh cool. Yeah no I knew about it, I just didn't tell you guys. What?
Erin Welsh	Yeah he said it was too obvious to publish.
Erin Allmann Updyke	Oh my god.
Erin Welsh	(laughs) Yeah.
Erin Allmann Updyke	I don't know that I've ever hated a person that we've talked about on this podcast more. (laughs)
Erin Welsh	Yeah I despise him. No, the origin of the disease would actually be uncovered by anthropologist Shirley Lindenbaum and medical researcher Michael Alpers.
Erin Allmann Updyke	Yeah, Shirley!
Erin Welsh	(laughs)
Erin Allmann Updyke	And Michael too.
Erin Welsh	They did the careful, methodical work that Gajdusek never had the time for, like drawing family trees and tracing relationships. And more importantly they listened to the Fore. Since the disease was relatively new to Fore, dating back only 40 or 50 years, whatever had caused it was probably new as well. And while numerous people had noted their observations of cannibalism practiced by the Fore, what they didn't know was what these two researchers would learn by listening. Cannibalism had only been adopted by the Fore about 50 years prior.
Erin Allmann Updyke	Aha!

Erin Welsh	Yeah. Timelines lining up. This wasn't revenge cannibalism, eating their enemies, the Fore used cannibalism to honor and mourn their dead loved ones. And this practice seemed to be at the root of the kuru epidemic. It explained the recent emergence of the disease and the skewed sex ratio. And when the Fore stopped practicing cannibalism at the insistence of some missionaries, the disease started its decline. This was a controversial explanation for many reasons but if this was an infectious disease it was unlike any that had been described. The years long, decades long incubation period, the absence of any detectable virus or bacterium. It was bizarre. Around 1960, Gajdusek returned to the U.S. to work on kuru in a lab setting when he was contacted by a scrapie researcher named William Hadlow who had seen an exhibit on kuru in a museum that included pictures of brain tissue showing the damage.
Erin Allmann Updyke	Oh!
Erin Welsh	Hadlow thought that kuru looked strikingly similar to scrapie, so he published this observation and also wrote to Gajdusek directly. Earlier I left off with scrapie in the early 1800s but the disease hadn't disappeared. Occasional outbreaks still occurred in sheep all over Europe and it showed up in American sheep in 1947, so it was still getting a lot of research attention. The biggest development with scrapie though came about when it was shown to be transmissible after thousands of sheep developed the disease after being given a vaccine for louping ill.
Erin Allmann Updyke	For what?
Erin Welsh	Louping ill. It's a tick-borne illness. (laughs)
Erin Allmann Updyke	What a ridiculous name!
Erin Welsh	We'll cover it someday.
Erin Allmann Updyke	Yeah, yeah. Good.
Erin Welsh	The vaccine had been prepared from sheep brains that had been treated with formalin which should kill pretty much all living things.
Erin Allmann Updyke	It sure should.
Erin Welsh	But not prions.
Erin Allmann Updyke	Okay, also people don't get scared of vaccines because of this because we don't make vaccines from brains for humans, okay.
Erin Welsh	No we don't.
Erin Allmann Updyke	So relax.
Erin Welsh	This also showed that there could be a very long period from exposure to development of symptoms, just like kuru. The note from Hadlow gave Gajdusek the idea to see whether kuru could also be transmitted. He set about acquiring chimpanzees, other primates, mice, hamsters, basically whatever he could get his hands on to inject with tissue from kuru victims. He left someone else in charge of doing the actual work and went to go explore new places. Within 21 months, which is an eternity in the lab, a chimpanzee named Georgette started showing signs of the disease.

Erin Allmann Updyke	Wow. I never thought about how difficult it would be to do research on prions in the lab because of how long the incubation period is.
Erin Welsh	It's really difficult and I think very emotionally taxing.
Erin Allmann Updyke	Yeah.
Erin Welsh	And also it's a gamble.
Erin Allmann Updyke	Right.
Erin Welsh	Yeah.
Erin Allmann Updyke	Man.
Erin Welsh	One by one, the rest of the chimps developed what looked like kuru and died.
Erin Allmann Updyke	Ugh, poor babies.
Erin Welsh	I know. Georgette. The damage to their brains looked incredibly similar to that of kuru, scrapie, and Creutzfeldt-Jakob sufferers and Gajdusek ordered more injections, not just with kuru but with tissue from other neurodegenerative diseases as well. These experiments showed that kuru, scrapie, and Creutzfeldt-Jakob could all be transmitted. He published his results and hypothesized that these three diseases were all caused by the same thing: a slow virus. A vague explanation that he didn't really expand on.
Erin Allmann Updyke	(laughs)
Erin Welsh	For this and for his description of kuru he would be awarded the Nobel Prize in 1976.
Erin Allmann Updyke	Jeez.
Erin Welsh	Yeah. A decision that baffled many including me.
Erin Allmann Updyke	Can they take it away? Like does that ever get taken away?
Erin Welsh	That's a great question. I don't know, we should look into that.
Erin Allmann Updyke	We should look into it.
Erin Welsh	Meanwhile plenty of other researchers were hard at work on these diseases, such as Tikvah Alper who demonstrated that even radiation could not destroy the scrapie particle.
Erin Allmann Updyke	Whoa.
Erin Welsh	I also have to say she sounds amazing. So she refused to accept a royal 60th wedding anniversary greeting from the queen because it was addressed to her and her husband under his name even though she didn't take his last name.

Erin Allmann Updyke	Oh my god, I feel so strongly about Whenever we get a letter that's addressed to Mr. And Mrs. Brett Updyke I throw it at him and I'm like, 'This is for you!' Which like, it's not his fault but (laughs)
Erin Welsh	(laughs)
Erin Allmann Updyke	Oh my god, I feel that so strongly.
Erin Welsh	She's awesome. Another big discovery was that there seemed to be multiple strains of scrapie judging by the different patterns of disease. But still, what was the agent? Where was the virus? How could it survive being irradiated, desiccated, cooked? Researchers could isolate the protein coat of this mysterious virus that supposedly existed but they couldn't detect any nucleic acids.
Erin Allmann Updyke	I am getting so excited. I'm sorry, I'm getting so excited.
Erin Welsh	No that's okay. Could it actually be just a protein causing these diseases?
Erin Allmann Updyke	Could it?
Erin Welsh	Most researchers gave a firm 'no' but a handful were more open minded and largely ignored. Tikvah Alper was in this open minded and largely ignored category.
Erin Allmann Updyke	l love her.
Erin Welsh	A British mathematician actually named J. S. Griffith published a paper proposing several different mechanisms by which it could be a protein but it doesn't really gain a lot of traction. And the scrapie/kuru/Creutzfeldt-Jakob/slow virus field was about to gain a new member who would give prions their name and earn a little notoriety for himself. Meet Stanley Prusiner, MD. With a background in neurology and biochemistry, Prusiner's career trajectory became a whole lot more focused when he saw his first Creutzfeldt-Jakob patient in 1972. This was a problem he knew he wanted to work on. He collaborated with the scrapie researcher William Hadlow and began attempting to purify the scrapie particle. Having that isolated agent was super important because you could do experiments directly on it to see how it would react. For instance, Prusiner and his group showed that the particle did not lose its infectivity when treated with chemicals that destroyed proteins.
Erin Allmann Updyke	Bom-bom-bom!
Erin Welsh	With this purified particle you could also design an antibody test for it which really sped up diagnosis.
Erin Allmann Updyke	Yeah.
Erin Welsh	Previously you would have had to inject a lab animal with tissue from a person or a sheep or whatever and then wait for signs of disease for confirmation which can take at least a year.
Erin Allmann Updyke	Oh wow.

Erin Welsh	Yeah. The field of prion research as it would soon be known seems to have been filled with egos, with Prusiner's perhaps the largest.
Erin Allmann Updyke	Wow, I'm shocked.
Erin Welsh	Yeah to say that he was not well liked by most of the field is probably understating it. Prusiner was fiercely driven, often combative, selfish with his findings, and obsessed with getting credit.
Erin Allmann Updyke	God.
Erin Welsh	He painted himself as a martyr and fighting the good fight against conventional thought. And part of the reason that I say this is because it was how he was written about in the prion book that I read which I understand is going to be It's a story right, it comes from a certain angle, it's biased. But I also read the book that he wrote, his memoir, and this comes through very strongly in that as well.
Erin Allmann Updyke	(laughs) Oh yeah.
Erin Welsh	Anyway Prusiner really did advance this field and one way he did that was to give it its name. When he started working in this area, kuru, scrapie, and Creutzfeldt-Jakob were all still generally referred to by the term given to it by Gajdusek: slow virus. Prusiner didn't like this name, it wasn't really accurate since no virus had been found, so he set about trying to think of a new one. He came up with 'prion' for proteinaceous infectious particle.
Erin Allmann Updyke	So creative. Props.
Erin Welsh	This wasn't a popular move in the field. First of all, he was criticized for making it sound like his own name.
Erin Allmann Updyke	Oh.
Erin Welsh	Secondly, it dodged the question of what this particle actually was. Was a prion a protein? A virus? Or just a particle?
Frin Allmann Undyke	(laughs) lust a particle man Belax
Erin Welsh	(laughs) Despite the disdain for this word, it worked. The press loved it and it rolled right off the tongue. But Prusiner still needed to get more evidence for the protein-only hypothesis to show that a protein could be infectious. He had to synthesize a protein and then introduce it to an animal.
Erin Allmann Updyke	Oh I'm so excited about this part cause I read a little bit about it in the biology and I can't wait to hear more about it.
Erin Welsh	Oh man I hope that I give you enough of what you're looking for. I'm not sure. So a problem arose when they had purified this protein only to find out that it was just an ordinary protein produced by the own host.
Erin Allmann Updyke	Yeah. Can you imagine how bizarre that must have been? You're like, 'No we really think we've got it, it's this thing.' What?

Erin Welsh	Yeah! It called into question the entire concept of an infectious protein.
Erin Allmann Updyke	Oh man.
Erin Welsh	Especially when he in collaboration with other labs found the location of this gene that produced the prion and he found that it was highly conserved across so many animal species indicating that it was probably super important to keep.
Erin Allmann Updyke	Right! It's this gene that like all these mammals have, that's why you get prion diseases in so many different mammals.
Erin Welsh	Yeah. It must've just been like well this was a wild goose chase, how were we so wrong?
Erin Allmann Updyke	Right, where do we go from here? Where did they go? Erin!
Erin Welsh	(laughs) Okay so if the only function of this gene was to produce a protein that killed the animal, why would it still be around? How could it still be around?
Erin Allmann Updyke	It couldn't.
Erin Welsh	Prusiner had an answer for that too, the same one that the mathematician Griffith had proposed years earlier. A protein could have two forms, one that was normal and the other that was disease-causing.
Erin Allmann Updyke	I'm sorry, this is the first time that people realized that proteins could misfold was because of prions?
Erin Welsh	I don't know.
Erin Allmann Updyke	But that is so cool.
Erin Welsh	Yeah. I think so. I think it is because at this point this was still just a concept, it had not been observed or demonstrated that proteins could do this.
Erin Allmann Updyke	Wow. Oh my gosh.
Erin Welsh	There needed to be an experiment.
Erin Allmann Updyke	Yeah!
Erin Welsh	And there actually kind of was one that nature had already set up. So like you talked about, some prion diseases can be inherited like Creutzfeldt-Jakob disease and GSS, and those diseases show that there were mutations in the prion gene leading to a state of disease. So Prusiner created mice with mutations in this gene. He observed them getting sick, killed them, and then took the infectious prions from them and injected them into mice that didn't have the mutation.
Erin Allmann Updyke	And?
Erin Welsh	Those got sick and yeah, so you could see easily how a protein could be normal or infectious.

Erin Allmann Updyke	Oh my gracious.
Erin Welsh	But there still remained the mystery of the sporadic case.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Creutzfeldt-Jakob, like you said, could be infectious as had been demonstrated, it could be inherited as it often was, but sometimes it would just appear randomly.
Erin Allmann Updyke	Yeah.
Erin Welsh	The sporadic form of the disease was a bit harder to explain. If someone had a normal non- disease-causing form of the prion gene, how could the disease suddenly develop? Prusiner once again had an answer: confirmational influence. This doesn't fully explain it really but this is basically the concept of the domino effect of one misfolded protein causing all the other ones it came into contact with to readjust themselves. But this completed the three components of infectious, familial, and sporadic to create this unified prion protein-only hypothesis.
Erin Allmann Updyke	I mean it still doesn't explain how the first one becomes misfolded sporadically in a person.
Erin Welsh	Unless it's just probability.
Erin Allmann Updyke	Right, exactly, yeah. Cause then if just randomly it might get misfoldedyeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	But oh man.
Erin Welsh	Yeah. I know that we keep saying this but prions are super bizarre and it's no surprise that they remained such a mystery for so long and it's really it's more incredible that some of their secrets have been revealed at all, I feel.
Erin Allmann Updyke	Yeah.
Erin Welsh	I'm also presenting this research as though it was accepted as a fact as it happened but in reality it was and continues to be debated.
Erin Allmann Updyke	Yeah.
Erin Welsh	There are still researchers who firmly believe that there's the tiny virus hiding out that will one day be uncovered.
Erin Allmann Updyke	Yeah.
Erin Welsh	But Prusiner was awarded the Nobel Prize for a new biological principle of infection in 1997. When you hear the word 'prion', what's the first disease that comes to your mind?

Erin Welsh	Of course, of course it is. Mad cow disease reared its ugly head in the late 1980s in Britain and flashed across headlines for years. It awakened the public to tragic failures in agricultural and public health oversight, it resulted in the deaths of hundreds of people and almost a million cattle, and it showed how much we still don't know about prions. It started at least in the 1970s. Normally docile cows started acting aggressively and had trouble walking. Death was always the outcome. Like scrapie-infected sheep, when you stroked a cow's back it would uncontrollably nibble and lip smack, but the connection between scrapie and this new disease wouldn't be made until 1986.
Erin Allmann Updyke	Wow.
1 /	
Erin Welsh	A veterinary pathologist checks out some brains of a cow that had been acting like it had scrapie according to another vet. Sure enough, this brain looks like scrapie in a cow. And scrapie in a cow is huge news. Initially the authorities weren't that worried about the human risk. Scrapie had never been shown to be transmitted from sheep to human but this might not follow that same pattern. One worrying finding was that it had jumped species. A nyala - I don't know if I'm saying that right - which is an antelope-like animal in a local zoo had died of a scrapie-like disease.
Erin Allmann Updyke	Oh.
Erin Welsh	Bovine spongiform encephalopathy, which is the mouthful of a name given to the disease, started appearing all over England and the hunt was on for the common exposure, though quietly of course. Mustn't worry the public.
Erin Allmann Updyke	(laughs) That was good. That's a good line.
Erin Welsh	(laughs) The Ministry of Agriculture, Fisheries, and Food was housed under one roof bureaucratically speaking and they were in charge of both the, as the name suggests, the agricultural sector and human food safety which kind of seems like an inherent conflict of interest. They could either keep the mad cow meat out of the human food supply and
	economically devastate the farmers or keep it in and potentially expose millions of humans to an incurable disease. The silence about the potential danger to humans didn't last long, nor did the original name. It was soon dubbed 'mad cow disease'. Much more memorable.
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Erin Allmann Updyke	What? Cake?
Erin Welsh	Cake in parlor.
Erin Allmann Updyke	(British accent) Like we're having cake in the parlor, dear? That was bad.
Erin Welsh	Precisely!
	Olimi
Erin Alimann Updyke	Окау.
Erin Welsh	Cake was a high protein concentrate that farmers would give to cows who were milking in parlor. So 'in parlor' means milking.
Erin Allmann Updyke	Oh, this is cows eating cake in the parlor, not humans.
Erin Welsh	Yeah, where was it coming from in the cows.
Erin Allmann Updyke	Got it.
, ,	
Erin Welsh	The protein in this cake didn't come from soy.
Erin Allmann Updyke	Oh no! Oh no.
Erin Welsh	It generally came from farm animals that couldn't be sold to the human market.
Erin Allmann Updyke	Yeah.
Erin Welsh	Just bits grounded up and molded into a cake.
Erin Allmann Updyke	I'm sorry. I'm thinking about my dog food right now.
Erin Welsh	Yeah.
Erin Allmann Updyke	Gross, man.
Erin Welsh	This explained how the disease was showing up all over the country and how the nyala had gotten sick. The zoo had recently switched from soy to meat pellets.
Frin Allmann Lindyke	Oh my gosh Guys cows are not carnivores
entry initialiti opuyke	
Erin Welsh	Nope. But once they start being fed it, they don't do well without it.
Erin Allmann Updyke	They go mad for it?
Erin Welsh	They go mad for it. (laughs) Nerd alert.
Frin Allmann Unduka	(laughs) Yeah, puched my glasses up
спи Ашпани ориуке	(ומעקווס) וכמון, אימופע וווץ צומספט עא.

Erin Welsh	Despite this very clear evidence of how prions could be introduced to cows through their food, it would be 8 whole years until animal protein in cow feed would be banned. The author of this book 'The Family Who Couldn't Sleep' compared it to keeping the Broad Street water pump operating for 8 years after John Snow showed it was the source of cholera.
Erin Allmann Updyke	We all know how bad that wouldn't been.
Erin Welsh	Yeah. I was like that's an analogy I can get.
Erin Allmann Updyke	Everyone listen to Episode 4 if you haven't already and then you'll get it, too. (laughs)
Erin Welsh	(laughs) Nice plug.
Erin Allmann Updyke	Thanks.
Erin Welsh	During those 8 years certain protective measures were enacted. For instance, any cows showing signs of bovine spongiform encephalopathy were to be reported and killed with full compensation. Schools banned British beef. Many people stopped eating it but other worrying things started to emerge. A cat nicknamed Mad Max was diagnosed with feline spongiform encephalopathy. I think he was Max and then he got named-
Erin Allmann Updyke	Mad Max? That's the cutest and saddest thing.
Erin Welsh	Yeah. Cows were still getting sick after mad cow meat was banned from the cow food supply. Two marmosets began showing signs of the disease after being experimentally inoculated demonstrating that the disease could be spread to primates. Big news there. And finally, tragically, human teenagers started to be diagnosed with Creutzfeldt-Jakob disease. This was not the sporadic form, this was a new variant, a cluster marked by a common exposure. Europe banned British beef. Millions of cattle were slaughtered. Estimates of the number of people who had developed this new Creutzfeldt-Jakob variant ranged from the hundreds to the millions. As of this year, 2018, only 231 cases of the disease have been reported but screenings of tissues from healthy people in the U.K. have revealed evidence of prion infection in at least 4000 people.
Erin Allmann Updyke	Wow.
Erin Welsh	So it's not really clear whether these people will eventually develop the disease cause there's still so much not known about the tipping point from infection to disease.
Erin Allmann Updyke	Right.
Erin Welsh	But because this story is still unfolding, didn't even mean to make that pun-
Erin Allmann Updyke	That was a protein joke, guys.
Erin Welsh	And because the U.K. received such an enormous dose of prions, a lot of countries have regulations against blood donations by people who live din the U.K. during the 1980s and 1990s.
Erin Allmann Updyke	Yeah.

Erin Welsh	Mad cow has also popped up elsewhere in the world including the U.S. Many mysteries remain about the mad cow disease outbreak. For instance, why England? How are cows still getting sick? Proteins are really tough things, even prion ash is apparently infectious. And why did only a handful of people get sick? The answer to that last question might be in our DNA. There is variation in susceptibility to prion diseases not just among people but also among animals, like sheep and scrapie-resistant breeds. Molecular research has shown that those who have two copies of the mutated gene are more likely to get the disease while those who have one normal and one mutated copy of the gene never get the disease but can act as a carrier. Nearly all of those who developed variant Creutzfeldt-Jakob from infected beef had two copies of this mutated gene. More recent research shows that in the Fore people, a new variation in the prion protein emerged super recently, maybe 10 generation ago, and those with this variation have resistance to kuru.
Erin Allmann Updyke	Yeah.
Erin Welsh	That's genetic evolution that's happening on a scale we can observe.
Erin Allmann Updyke	So cool.
Erin Welsh	Yeah. The final chapter, almost done, of prion history I want to cover is a short one and one that will take us back to the present, to the forests of North America where thousands of deer and elk and moose are dying of chronic wasting disease, yet another prion disease. Where did this one come from? As usual the answer isn't entirely clear but we may have a guess. In the 1960s, young biologist Gene Schoonveld decided to study starvation in mule deer in Fort Collins, Colorado. Schoonveld kept some starving deer in one pen and control deer in another pen so he could compare the two. This control pen also happened to house sheep.
Erin Allmann Updyke	Uon.
Erin Welsh	Now there isn't universal agreement on this but several people on the project say that scrapie was present in those sheep. If that were the case, scrapie could have passed from the sheep to the deer who began showing signs of disease.
Erin Allmann Updyke	Wow.
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Erin Welsh	After the experiment was over, Schoonveld released the control deer, so the ones who had been in the enclosures with the sheep, back into the wild. 10 years later researchers started noticing scrapie-like behavior and Brain damage in wild deer populations in Colorado and Wyoming. Since then it has spread every year throughout the American west, plains, and more recently the Midwest and Canada, Saskatchewan and Alberta. Chronic wasting may pose a threat to other ungulate species as well, it's been spotted in elk, moose, reindeer, etc and to other parts of the world. It's been seen in South Korea, Norway, and Finland for instance. How is it spreading? Deer aren't forced to eat deer meat and they aren't in as high of population densities as sheep. Prions are incredibly tough so it's probable that chronic wasting is transmitted among these ungulate species by direct contact via bodily fluids, indirect contact through a contaminated environment, or by a crow acting as a vector for dispersal of the prion.
Erin Allmann Updyke	Weird, A crow?
Erin Welsh	Yeah.
Frin Allmann Unduko	I don't know

Erin Welsh	Basically a crow eats a bit of This is in terms of long distance dispersal.
Erin Allmann Updyke	I don't know.
Erin Welsh	A crow eats a bit of a deer that died of chronic wasting, the prion survives the digestive journey, and then it poops it out to contaminate a different part of the forest.
Erin Allmann Updyke	Seems a little sus but sure.
Erin Welsh	Yeah. But this is still an area of very active and interesting research.
Erin Allmann Updyke	Yeah. There's people at Illinois doing cool research on chronic wasting disease.
Erin Welsh	Yeah! The whole time I was researching prions I kept getting this feeling that I was just seeing the tip of the iceberg. We obviously know so much more about prions today than 50 years ago but so much seems left to be uncovered. It truly is a new frontier of health and medical research and it's changed the way we think about infection. Like we talked about, prions don't have this biological imperative to pass down their genes. It's just a protein! And yet it is an infectious disease and one that has told us a lot about ourselves. So what I wanna know is A) what do the numbers look like today? And B) what's the latest on cures or treatments or technologies or whatever?
Erin Allmann Updyke	Yeah, okay. (laughs)
ТРЖКҮ	(transition theme)
Erin Allmann Updyke	It's interesting that you described this as a new frontier of research kind of because even in just hearing what you were just talking about with chronic wasting and what I've read about what's going on in research today, it seems like there's a lot of open territory and possibilities for research. If I wanted to keep doing research, maybe I'd switch to prions right now. But in terms of the research that's going on, it seems like and I'm probably missing a lot of it but it seems like there's kind of two main branches because there's two big areas that we still lack a lot of information on. One of those areas is focused on actually understanding the mechanism behind this pathophysiology of disease and a lot of that has to do with figuring out what this protein does in our body when it's not misfolded.
	So because we still don't entirely know what this normal protein does. It's a protein that is very abundant in neuron cell plasma membranes and there's a lot of thought that it has to do with possibly calcium channels, possibly copper, maybe bringing things into cells or pushing ions out of cells. It's not entirely clear. It does seem to be a really important protein and it makes sense that it's in such high density on your neurons since those seem to be so highly affected. But we still don't know, like there is no clear answer as to what this protein does. The other field of research is what do we do about it? We know that this disease exists so how do we treat it?
Erin Welsh	Yeah.

Erin Allmann Updyke	Yeah. So at this point it doesn't seem like much of that research in that realm is out of the screening phase or maybe at best the animal models phase. So a tiny background on drug development. Any drug that gets developed, especially if it's a brand new drug and not a drug that we use for a different disease that you wanna use to treat some other disease, it goes through a lot of stages of screening. Usually it's tested in cell culture first to make sure it does the thing that you're trying to get it to do and then you screen it. You often screen a whole bunch of different compounds and you say, okay, which one of these compounds has an effect on this protein or against this pathogen? So there's a lot of papers especially form the early 2000s where they were screening hundreds or sometimes thousands of compounds to see if any of the had an effect on diminishing the accumulation of misfolded prion proteins.
Erin Welsh	Okay.
Erin Allmann Updyke	So there was at least some work that has been done so far and is I'm sure continuing to be done to try and just find compounds. Once they find those promising compounds, then you test those on animals, usually in mice but also in other animals as well to see if they're safe and if they actually work once you take them out of a cell culture and put them into a real animal. Then once you can show that a compound actually works on a disease in an animal, you have to test it on small groups of humans to make sure that it doesn't kill people or cause any other serious reactions and that's a phase 1 trial.
	And then you do a phase 2 trial which is a larger group of humans and now you wanna look at odes it actually work? Like we know it doesn't kill you, now we can ask does it actually work? Then you have to do even bigger trials. So it's a very, very long process before you actually get any sort of drug to market. And as far as I can tell, any potential drugs seem to be in the very early stages still. There are some drugs or some treatments that have been used to treat other diseases. There's an antihistamine which is super random, antihistamine is like Benadryl, it's like what you take if you have allergies or something like that.
Erin Walch	Vooh
	16411.
Erin Allmann Updyke	That in those early trials of trying to identify compounds, seemed to have effect on binding to Alzheimer's proteins, misfolded Alzheimer's proteins. Os it was suggested that perhaps it also could bind to misfolded prion proteins.
Erin Welsh	Oh.
Erin Allmann Updyke	It has been shown in cell culture also to inhibit the prion protein but I haven't found any papers that it has been tested on beyond the cell culture level. But that's a drug that already exists and has been used in humans, it's not generally used because it has a lot of side effects but you know, whenever we look at drugs we have to look at the side effects vs the disease and if you're treating something as benign as allergies, you wanna make sure you have very little side effects. But if you're treating something where the only alternative is death you might tolerate a lot more side effects. So who knows. There's another treatment called PPS which is pentosan polysulfate, it's been getting some press in trying to treat prion diseases but it has not been shown to work. So people have actually tried this in at least a couple of humans and they died, it didn't work at all.
Erin Welsh	So but it's still getting press?

Erin Allmann Updyke	It's still getting press or at least it got press, I don't know if it's still getting press. There's at least one study that suggests that it delays the progression of disease and decreases the amount of abnormal protein deposition in mice brains but you had to inject it directly into the mouse brain. So that's not likely something that's gonna be in human trials soon.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah so I don't know, it seems like there's a lot open territory and I do think that a lot of this kind of hinges on being able to figure out this protein because with a lot of other diseases, even if we don't fully understand everything about a bacterium or a virus, we know generally how they replicate, we know generally how they operate and so we can use drugs that we have to try and stop them. There are targets that we know that we can aim for but with this it's really hard. And it is like you said early on, it's a protein that's in our bodies and presumably it's an important one, you know.
Frin Welsh	Right It has to be
Erin Allmann Updyke	Yeah. In terms of numbers, the only one where you can get sort of good numbers on is classic Creutzfeldt-Jakob disease and so the majority of those cases, 85% are sporadic, about 5-15% are inherited, and overall those are at a rate of about 1-3 cases per million people per year.
Frin Welsh	Ob that's quite rare, okay
	on thit's quite fuie, okay.
Erin Allmann Updyke	Yeah, it's pretty rare. So in the U.S. for example there have been 11,000 cases reported from 1979 to 2016.
Frin Welsh	Oh wow.
Erin Allmann Updyke	Yeah. Between 180-400 cases per year. So on the CDC's website you can find a chart essentially of the number of cases that have been reported in the U.S. each year of classic CJD. And the numbers get bigger every year but it's important to keep in mind that it could be in part due to better screening and recognition, it also could be because our population size has grown a lot since 1979.
Frin Welch	Veah
Erin Allmann Updyke	So when you see 400 vs 120 it's sometimes easy to go, 'Oh my god! Its growing!' But it actually has been at a pretty constant rate.
Erin Welsh	I've also read that a lot of or at least a proportion of CJD patients have been misdiagnosed as Alzheimer's.
Erin Allmann Updyke	Absolutely, yeah. Because with CJD you present with similar symptoms. You present with rapid onset dementia, I think the difference is the onset of time and then the time to death. Alzheimer's is a very, very slow progressing disease generally, it's faster if it's earlier onset. This is what I want to end on.
Erin Welsh	Окау.

Erin Allmann Updyke

I think that chronic wasting disease is so important and I hope that, I know that there are so many people studying it but I just want them to get so much money for research because... So there has been so far no evidence that chronic wasting disease in deer can cause disease in humans. There have been at least a few studies that have looked for those links. Cause here's the thing about chronic wasting, even though we haven't yet found any evidence that chronic wasting disease in deer can cause disease in humans, it has been found at very high prevalence in deer populations, in wild deer populations rates up to 10% or 25% but in captive herds up to 80% of deer have been found to be infected.

Erin Welsh	Yeah.
Erin Allmann Updyke	And if you combine that with data from the CDC that suggests that up to 20% of people surveyed had hunted deer at some point and up to 2/3 of Americans have eaten venison-
Erin Welsh	l've eaten venison.
Erin Allmann Updyke	I've eaten venison, our neighbor hunts deer and brings them over and there's chronic wasting disease in Illinois. I find the prospect terrifying.
Erin Welsh	Yeah. Tip of the iceberg.
Erin Allmann Updyke	Tip of the iceberg. It's so interesting because it's not outside the realm of possibility, right. We know that it can happen from eating contaminated cow meat.
Erin Welsh	Right.
Erin Allmann Updyke	Because I don't think there have been any cases of humans getting any kind of prion disease from eating sheep meat infected with scrapie, is that correct?
Erin Welsh	That's what it seems to be, yes.
Erin Allmann Updyke	And so I'm curious if maybe it's because the outbreaks of variant CJD that were from mad cow disease, I wonder if it's just that the prions were in higher concentration in the cow because of the ways that the cows got infected, so then now they're in higher concentrations in humans. I don't know. I don't think anybody knows.
Erin Welsh	Right something about the folding of that particular fold, who knows?
Erin Allmann Updyke	Yeah, right. Who knows? I want to know though.
Erin Allmann Updyke Erin Welsh	Yeah, right. Who knows? I want to know though. I know, I know. Yeah and kind of in retrospect, despite that being one of the longest histories that we've ever discussed, it feels premature because it seems like there's so much more to be done and there's so much more that's going to be discovered.
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Erin Allmann Updyke Erin Welsh Erin Allmann Updyke Erin Welsh	Yeah, right. Who knows? I want to know though. I know, I know. Yeah and kind of in retrospect, despite that being one of the longest histories that we've ever discussed, it feels premature because it seems like there's so much more to be done and there's so much more that's going to be discovered. Right. Yeah. And I feel like in talking about what's currently happening it's kind of just like so many things but I don't know how to talk about any of them because they're all kind of in their infancy, like there's no 'here's the new drug' or 'we have an answer', it's all just currently being figured out which I find so exciting. Right. Yeah it's super, super cutting edge, news is happening

Erin Allmann Updyke	Yeah. Right.
Erin Welsh	Yeah.
Erin Allmann Updyke	On that note, should we share our sources?
Erin Welsh	Yeah, great idea. So I read a couple of books, one is called 'Madness and Memory' and that is by Stanley Prusiner, so that is his memoir of prion research. I also read 'The Family That Couldn't Sleep' by D. T. Max, great overview of prion history. And then I have a few articles which I will put on our sources list. And then finally if you're interested there is a documentary about Carleton Gajdusek called 'The Genius and the Boys'.
Erin Allmann Updyke	I have so many articles, they're all going to be posted on our website thispodcastwillkillyou.com under the EPISODES tab. So we post all of our sources from every single episode, this one in particular I have a lot of cool articles about the current research that's being done so if you're interested in reading more about what's going on with prion research now, definitely check that out.
Erin Welsh	Cool.
Erin Allmann Updyke	Yeah, well. Thank you everyone for listening, we couldn't make a podcast without you. Well we could but then it would be just us. It's be weird.
Erin Welsh	(laughs) It would be weird. Thanks to Bloodmobile for providing the music to this and all of our episodes.
Erin Allmann Updyke	Thanks so much.
Erin Welsh	Well on that note, wash your hands.
Trin Aller and the holes	March Children and Sam La
Erin Alimann Updyke	You filthy animals.