Susan Manfull: 00:00:00 <Silence> Untangling Pandas and Pans is a podcast about two little known medical disorders characterized by the sudden and dramatic onset of symptoms such as obsessions and compulsions, vocal or motor ticks, and restricted eating behaviors, and a whole host of other symptoms following a strep or other bacterial or viral infection. I have the privilege of interviewing some of the top researchers and clinicians in this rapidly growing area, known by various names such as immune mediated neuropsychiatric disorders, infection associated neuro immune disorders, and autoimmune encephalitis, or simply pandas and pans. My name is Dr. Susan Manfield. I am a social psychologist, the executive director of the Alex Manfield Fund, and the mother of Alex Manfield, who died at 26 years old due to Pandos a disorder, my husband and I knew next to nothing about, certainly not that our daughter could die from it.

William Manfull: 00:01:18 This is episode 10 of untangling pandas and pans recorded December 6th, 2024.

Susan Manfull: 00:01:27 Dr. Harris, let's get started. And actually, let's get started with the question of what would you like me to call you during this interview?

Dr. Brent Harri...: 00:01:37 You're welcome to call me Brent. I'm a first name type person, and, and I answered about Dr. Harris and Brent, but my preference is usually Brent.

Susan Manfull: 00:01:44 Okay, Brent. Good. Alright, well, I, I'm gonna start off with some really basic stuff. What is neuropathology?

Dr. Brent Harri...: 00:01:55 Neuropathology? So, I kind of went to medical school being very interested in neuroscience, and as I went through I had done an mdph during my training. So I wanted to get trained as both a scientist and a clinician. Always fascinated about the brain, and we can talk a little bit about that. But I decided in my very last year of a seven year MD PhD program to do neuropathology. And neuropathologists are the physicians who study the brain under the microscope at the molecular level and run the laboratories that make the diagnoses that are, are so important. So, pathology bad things that happen to the body and diseases, neuro being the brain and the, the central nervous system and the peripheral nervous system. And so we are the doctors who help to make the diagnoses of peripheral and central nervous system disorders, all different kinds of things.

Susan Manfull: 00:02:58 So it's not always looking at postmortem tissue, correct?

Dr. Brent Harri...: 00:03:05 That is correct. Yeah. Neuropathologists have a, a, a very, it's a very narrow field, but it is a field that, that actually has a, a wide variety of things that we do in a, a given day. And so

neuropathologists and there are not a lot of us out here. It's a fairly small specialty, maybe three or 400 in the United States at most. Every medical school has one or two or three neuropathologists, and there are a few more that are not associated with medical schools. But in a given day most neuropathologists are working with surgeons. They may be working with other doctors in the hospital if there is an autopsy. They're often doing teaching of medical students and residents and fellows. And then they often have laboratories and are doing research in, into neurologic disease.

Susan Manfull: 00:03:59 I tend to associate the neuropathology with postmortem brain tissue. But as you were talking, I realized that that's not at all the case. Certainly sounds like a deal that will be growing in the future. What, what do you think

Dr. Brent Harri...: 00:04:17 That's a that's an interesting question. You know, I think it's been fairly stable in the last 50 years or so. We certainly have more and more people with neurologic diseases emerging as, as our populations are becoming older. And there always will be a need for understanding these diseases at the neuropathological level. But whether or not it will be an increasing or decreasing subspecialty is kind of hard to say. In many ways neuropathology is certainly not a moneymaker for medical institutions. <Laugh>, I guess it's because we don't have lots of biopsies, so other areas of pathology certainly help institutions and, and have different types of work. And I think that's why neuropathologists do a variety of different things, because we don't have lots of brain biopsies that we're working on at any given time. We don't have lots of autopsies. The auto autopsy rate is decreasing in this country. But the need for brain banks, which I know we'll talk about today is, is certainly increasing. And there's plenty of work to do for Neuropathologists for those that are find it an interesting field.

Susan Manfull: 00:05:43 I know that you said that you decided to go into neuropathology in your last year of medical school. Were there any particular reasons that you went into that when you were, for example?

Dr. Brent Harri...: 00:05:58 Yeah. Yeah. I I was always interested in science as a kid. I had a dad who has been and still is at the NIH and is cancer researcher there. So I remember as a kid going with him to his laboratory. And one of my early remembrances was much easier to get on the campus of NIH than it is now, unfortunately. But I remember running around and the fields and then going in with him, and he took me to an electron microscope, which is this big giant microscope, a lot of tubes coming into it, and it gives off this weird sort of science fiction greenish light. And he said, come here, look at this. And, and I came over and, and it is a a

microscope that allows you to see at a very, very high resolution cell organelles.

00:06:52 And he pointed out mitochondria and he pointed out endoplasmic reticulum and all these cool structures. And, and I loved it. I loved it. I went to college though, and I was dead set against not going into science. 'cause I didn't wanna do the same thing my dad did. You know, we often want to do something different. But I I, after my freshman year, I came home and I actually did a rotation at the NIH not in my dad's lab, but in another cancer lab. Fell in love with it and kind of changed my major sophomore year to biology. And, and very much enjoyed my science undergraduate career. And then when I was finding time to decide what area I wanted to go into after college, I really wasn't sure if I wanted to be a scientist or a clinician.

00:07:42 And so I spent a couple of years doing a master's degree in biochemistry to kind of flesh out that interest and decided I really wanted to be trained in both. I wanted to be a clinician. I wanted to be able to take care of patients. I wanted to understand human disease, but I also really wanted to focus as a PhD scientist on a particular area. And I decided the neuroscience neurosciences were very different than cancer. This was in the eighties. And I thought a little bit about infectious disease because we had just discovered HIV and aids, and I said, oh, that would be a super fascinating area. And, and so that combination of, of immunology and and infectious disease almost caught my interest. And then I said, oh, they'll have aids, you know, cured in the next 10 years.

00:08:39 I'm gonna go into something that there's so many things we don't know about still that I can study for 50 or 60 years. And the neurosciences, you know, caught my interest the most. So in medical school, I did the standard MD-PhD where you start your first couple of years of med school, you learn about all different kinds of diseases and how to diagnose things and how to treat things. But then I started my PhD and it was molecular neuroscience and studying GABA receptors and glutamate receptors, which are the two most common kinds of receptors we have in our neurons in the brain. And from that, I knew I was going to do a neuroscience related clinical career. I did some rotations after that in neurosurgery, loved neurosurgery, the things that neurosurgeons can do. Amazing. I actually was kind of interested in psychiatry for a little while because of the overlap of glutamate and GABA receptors.

00:09:38 And my PhD was in pharmacology neuropharmacology. So I thought a lot about psychiatry. But back at that point, this was in the nineties now, still was a kind of trial and error and not as much known about the molecular biology of, of psychiatry. I

think if I was thinking about it again, I might have made that decision differently. But and then I, I kind of settled on neurology which was really the treatment of, of disease neurologic disease. Again, we didn't have a huge number of treatments back then but, but in my last year, and I, and I loved all of those areas. My wife said, you're not doing neurosurgery. You've been a student for too long. I had two little kids at the time, and she was right. That neurosurgery was not, not the best match, but I did a rotation in neuropathology thinking that it would be helpful for my neurology residency, which I was kind of planning on.

00:10:39 And I loved it. And neuropathology is at the interface of science and medicine. And so I enjoyed learning about the nuts and bolts of how to do neuropathology and how we serve as consultants for the neurosurgeons and the neurologists and other doctors in the hospital. And went full force you know, to pursue that that combined kind of degree. So in the past, it used to be neurologists would become specialized in neuropathology. So but then nowadays mostly it's pathologists that do general pathology and then do a fellowship in neuropathology. And that's, that's the direction that I went. I guess my earliest that I kind of knew and got interested in, in the brain was in the seventies. I loved movies in the seventies, and my favorite, favorite favorite actors and directors were the Mel Brooks movies. And my favorite of those was Young Frankenstein, which you know, to a a teenage guy, had a little bit of bodiness to it and had these amazingly episodes of understanding the brain and, and how you could transfer a brain into, you know, a potential other body. And then with electricity, get it to work in, in the Frankenstein monster. So, you know you know, both, both Mary Shelley's Frankenstein book I read but then, you know, I love the, you know, the, the Mel Brooks movie, young Frankenstein.

Susan Manfull: 00:12:17 Yeah. <laugh>. I I wonder how many other students found their interest in neuropathology or neuroscience watching that movie. So we, we know your interest in, in young Frankenstein and cases like Phineas Gage and the corpus callosum splitting. Can you tell us how you ended up at Georgetown as the director of the, the Brain Bank?

Dr. Brent Harri...: 00:12:44 Yeah, sure. Well, I did my MD PhD training at Georgetown, so I knew about Georgetown from, as a student. But there were no neuropathology training programs in Washington DC back then. And so when I was applying for programs I was working with my wife who really wanted to go to business school, and she looked at a number of different business schools, and she had been very patient while I was an MD-PhD student. So I said, all right, you can kind of pick, you know, the next place we go as

long as they have a really good strong neuropathology training program. So she got into a number of programs, she's a very smart cookie, and we made the decision together as a young family to go out to California. And, and I started my residency at, at Stanford, and she started business school out there.

00:13:40 And I had great training and, and very fond memories of, of being out there and, and learning about these diseases in a very different way than I learned in, in medical school. And from there I actually was up in your neck of the woods and was a faculty member at Dartmouth for about eight years. Had a, had an excellent time being a, a junior pathologist and, and kind of learning the, the, the rules and, and nuts and bolts of doing neuropathology. It was great proximity to Boston. So I had good colleagues down in Boston that I could show things to and interact with. But once my kids kind of went off to college, my wife and I started thinking about a mid-career move, and Georgetown was in need of a neuropathologist, and the dean of the school there contacted me and said, you know, Brent, would you like to come down and give a talk?

00:14:40 And I said, sure, I'm happy to give a talk. I was doing a LS research at the time and, and came down and, and spoke, and they, they indicated that they really wanted to start a brain here. This was in 2009, 2010. And would I be interested in looking at a position here to be the director of neuropathology and to, to build the neuropathology department and start a brain bank. And I said that sounded like a great idea. It was very hard leaving beautiful New Hampshire and Vermont. We lived in Vermont, I worked in New Hampshire. But it was a good timing for both of us and having family down here that was aging, it was nice to come down as and be closer to them as they were aging. So it's, it's been a, a wonderful reconnecting with my alma mater. I never thought I would come back and, and be here again. We often, you know, go off in academic medicine to different places based on where there are jobs and you know, you don't always go back to where, where you trained. So it was a, a nice reunion to come back. The neurosciences had continued to, to get stronger here. And the proximity to NIH made Washington a really wonderful place to, to kind of continue my career.

Susan Manfull: 00:16:01 Can you tell us a little bit about how one starts to create a brain bank?

Dr. Brent Harri...: 00:16:07 Yeah. So brain banks are kind of like the banks that we all use, that you put things in and you take things out, and they keep those things stored and safe in that, in that bank. Brain banks are a wonderful invention that's been around for, for a while. Some are very specific to certain diseases and some are more general. But the idea is that families and individuals who want to make a

donation to science can donate either their whole bodies or they can donate individual organs like the brain when they die. And those tissues then can be examined by a neuropathologist to look for the specific diagnoses. If it's outta medical school the neuropathologist can use the material to teach junior people who are learning about these diseases. And the tissues can be retained in a number of different ways so that they are usable by a wide variety of scientific investigators around the world, actually who have in important questions that they, they want to ask.

00:17:35 So when I, when I agreed to start the brain bank at Georgetown I needed to have a little bit of, of capital. I wanted to have a buy-in from both the university, which is more the research and education side, as well as the hospital, which is more of the clinical side that would support a brain bank, and that it would serve really three constituencies or four constituencies, depending on how you look at it. It would serve families who really could benefit from having a careful neuropathological evaluation of their loved one's brain so that they had an idea of what the diagnosis was. There's still diagnoses that the, what we call the gold standard is the autopsy where you can have a pretty good clinical idea of what the disease is, but until you actually look at it under the microscope and a pathologist weighs in on the diagnosis, you don't know.

00:18:37 And so for the clinicians who took care of somebody with neurologic disease, and for the family who also took care of and loved that person with a neurologic disease this provided a, a a diagnostic report. And that was really important to me. It was really important that people learned from this process. So not just me, you know, working with a brain and making my diagnosis, but that graduate students who were studying becoming PhD neuroscientists learn about neurologic disease for humans so that they could correlate that with animal studies and cell culture and computer modeling for neurologic disease. I really wanted them to learn about the disease in humans. And, and one of the courses that I teach to grad students is called the Neurobiology of Disease in the very first session. These are for our new PhD students in neuroscience.

00:19:34 I take them down to the autopsy suite, and we look at brains, human brains. I also enjoy teaching younger people. And so every summer we have neuroscience camps where 80 or 90 high school students come from around the country, sometimes around the world. And they spend a week or two at Georgetown, and they learn about all different kinds of neurologic disease. So we do a session with them on brain banking, and, and we take them into the same laboratory that the medical students go into to see actual human brains and to have a chance to hold the human brain in their hand. These are all fully protected. We call

them fixed, so we fix them so they're not infectious in any way, and they learn about it. I teach undergraduate students at the university here, and then I have residents in pathology and neurology and neurosurgery who come to the brain examination laboratory with me and learn about these diseases.

00:20:43 So education's super important. And then on the research side of things with the brain bank we're tasked to be the stewards of this precious material. And we take that responsibility you know, very seriously in that we are given this very precious gift of what I think is the most amazing organ that we have. And we need to maintain it so that it could be usable, potentially by the family if they needed to do genetic studies in the future. And so we freeze material down, and we can make DNA and do genetic studies if the family wishes that in the future, but then we de-identify the material and we either freeze it or we prepare it so that we can make slides to provide to people who want to research a specific question that can only be answered really with material from somebody who has passed away.

00:21:52 We're a little bit different in, in the brain bank and, and in especially neurodegenerative and neuropsychiatric brain tissue very different than cancer. So in cancer, people are having surgery and the tissue comes out during surgery and it's also banked. So we have biobanks and I run the biobank for the cancer center of all different kinds of cancers. And we retain those as well. We make our diagnosis, and then we retain tissue if the family's allowed us to the family or the person in that case, if they're living, has to consent to allow some of the tissue to be bio banked. And sometimes it's bio banked together with blood. And so combining the clinical diagnosis, blood and tissue can all be can all be very helpful. But for neurodegenerative diseases, we don't biopsy those tissues while people are living.

00:22:48 There are ways of making a diagnosis and getting important information about neurologic disease through imaging studies, MRI, CT PET scanning or from the fluids that bathe the brain called CSF, cerebral spinal fluid or from blood that can help tell us about and make a diagnosis. And, and that can be very important to have in conjunction with autopsy material, but the autopsy and the, sometimes the end stage of disease where somebody has lived with a diagnosis for a long time. But there are instances too, where people die at the beginning or at the middle of their disease, where we can learn an amazing amount about a particular disease by studying it under the microscope and, and molecularly that we wouldn't be able to in, in any other way. And so we have these tissues, they're well curated. So we kind of see ourselves also, you know, as brain bankers, bankers, but also sometimes as custodians in a museum librarians in, in, you know, the library where we have these materials, and then

somebody can ask a very specific question, we can go to our bank and we can provide them then with data de-identified data and tissue for their study.

00:24:21 So that's kind of a long, a long answer to a, to a question, but I think people, I haven't ever really thought about what brain banks are that in a nutshell is, is what I think brain banks serve for the public.

Susan Manfull: 00:24:35 Well, in the years that I've known you and certainly including this conversation, I've I've come to find your work so interesting and and valuable. You sort of alluded to this in, in just a few moments ago, but I wonder if you could just maybe sum up why it's so important to have this tissue, the post postmortem tissue, to, to study or, or let me reword that. How, what can we find from postmortem tissue that we can't find from the tissue in a living person? Maybe I should, I'm gonna, I'm gonna cut that. Okay. I, I'm wondering if you can elaborate on on the real value, why are we studying postmortem tissue? What can you learn from that that you can't learn in other ways?

Dr. Brent Harri...: 00:25:38 Sure. That's a, that's a great question. So from every individual, we can learn something, whether they're living or, or they're dead. And by looking at the brain and the spinal cord sometimes and other organs we are able to delve into the tissue in a more precise way than if we're doing imaging studies or looking at bio fluids. And as I said before, we don't really biopsy the brain for many things other than cancer. So understanding neuroinflammation in the brain understanding neurodegeneration is, is, is really left to when somebody dies and has one of these conditions or diseases. And in situations we can spend lots and lots of time. And, and the brain is a, a, a a, quite a large complex structure as, as we all know. But being able to look at different areas that would not be accessible during life allows us to look at the relationship of the cells in the tissue with each other.

00:27:09 And they could be immune cells that are coming in from the periphery to the brain that would not necessarily be picked up on imaging studies. They could be infectious disease that could be queried by studying with stains or with PCR of the tissue to look at the nucleic acids of an organism that would not be necessarily visualized on imaging studies. And then we can look at the molecules, the receptors that that brains have on the cells have and the relationships of the, the major cell types, the neurons, the glia, the blood vessels in a, in a very different, often two dimensional way, but in terms of a molecular analysis in a much more in-depth way than you can with you know, with, with imaging studies or biofluids. There is certainly value, though, because when we're looking at a brain, it's at one stage of disease, it's a one time point.

00:28:28 By having those other studies beforehand, biomarkers of imaging or biomarkers of biofluids, you can do longitudinal studies. And I'm, I'm involved in a lot of those for various different diseases as well, specifically with a LS, where we have a, a large multi-institutional study to try to enroll every patient with a LS, it's an audacious study that just started a year or two ago. But the idea is to study them and, and work with them so that they get access to large multicenter clinical groups and that they can participate in, in research to understand their disease. This is a big undertaking for a lot of areas of medicine. Right now, we're in the data era. We're in the information data era, and, and having large numbers of, of data points is, is essential to trying to understand our very complex species.

00:29:38 So we, we are a very diverse group of people, and everybody's biology and everybody's disease and condition and how they go through life and what medications they're on and what they eat, we're all different. So we are not lab animals. We are individuals. And so understanding the complexities of disease and how it affects one person versus another really relies on on studying many, many people. So people who volunteer for clinical trials and people who volunteer to donate tissues are really helping out humankind, I think, in a very, very special way that that, that allows scientists and clinicians to get better and better at providing new ideas of mechanisms of disease and potential targets for, for therapy. So I think that's maybe the beginning of, of the, of the answering the question, but I might need you to, to remind me the question again. I got a little off target.

Susan Manfull: 00:30:50 No, actually, I think you're pretty much right on, right on target. I'll just ask a couple of other follow up questions. So we're gonna be talking about pandas and pans in other neuro immune disorders. And I, I think that I, I'm wondering if you can discuss this sort of macro question, our issue a little bit. We know from the clinical symptoms of those with pandas and pans or we have an idea that they are that those symptoms are merging from activity that's going on in the basal ganglia. And how do we know that? Well, we know that because say Parkinson's disease has, with, with some similar symptoms, and you can probably elaborate on this have the research has been done on that, and we know that a lot of the, the issues surface in the base basal ganglia, and you can provide some better examples, I'm sure.

00:31:59 But we don't know for sure. So with studying postmortem brain tissue, you can confirm or, or not confirm that it is largely the problems are taking place in the basal ganglia that in a very macro sense. And then you can hone in on what's going on in a much more macro sense, because we don't know why those, those, the symptoms that we call pandas or pans, we don't know exactly the underlying mechanisms that produce those

symptoms. So I, I eventually, I hope that by studying brain tissue, we can get to the second part, but we could definitely, and I think you have gotten to the first part of where is the action in the brain that's leading to these symptoms. Am I correct?

Dr. Brent Harri...: 00:32:59 Yeah, that's absolutely correct. So neurologists are always trying to pinpoint where in the brain and multiple places in the brain certain neurologic diseases occur. Same with psychiatry and neurosurgery. Understanding the normal function of the brain you know, has, has gone on now for hundreds of years. And, and more specifically in the last 50 years to get a better feel for what areas of the brain control, what aspects of our our complex life. And then trying to understand if it's, if it's one area that is affected. And, and I got very interested in neurodegenerative diseases, and there are some overlaps in neurodegeneration of mechanisms, but then it always would, you know, struck me as being fascinating by why in this one neurodegenerative disease like Parkinson's disease, do we lose dopaminergic neurons in the substantial nigra?

00:34:08 And why is it in Alzheimer's disease that we get plaques and tangles pre predo predominantly in the limbic system, in the hippocampus and in the frontal lobe, but other areas are, are kind of spared and in a LS, you know, why is it that these motor neurons that control our skeletal muscle movement in the brain and the spinal cord to generate but other areas we, you know, think are not as affected, though, if you do very careful testing of all of these neurodegenerative diseases, you do find areas that maybe aren't as affected as the primary area, but also have changes. So that always struck me as, as being, you know, very interesting and having, you know, the ability to not just look under the microscope cells, but to understand the neurotransmitters and the receptors that are all different in all different areas.

00:35:11 And the communication that happens between neurons and glial cells is different in different areas, allows you to start thinking about targets for intervening, whether or not you're intervening by surgery to take something out. You might be intervening with electrodes and deep brain stimulation of somebody with Parkinson's disease to activate a very specific area of the brain for function, or you might be using drugs that that interact with specific receptors in specific areas of the brain to, to treat a neuropsychiatric disease. So those are all areas where we learn, you know, collectively as, as neuroscientists what the function, normal function is. And then we study as neuroscientists who study disease, what happens in those areas is, is it a loss of a cell type? Is it a, an upregulation or a downregulation of a specific receptor or a second messenger system within cells?

	00:36:26	That is the, the detriment. And, and, and I think pathologists are focusing primarily on where's the damage to the brain, and is it a regional area of the brain, or is it a is it a a receptor or a genetic change to to that cell? Is it a neuroinflammatory change? And so you, you brought up the, the disease and and condition pans pandas where, you know, the basal ganglia, as you said, we think is affected. And we know that because of the clinical signs and symptoms that patients with with this disease have. But we also know it because people with the, the, the disease and and condition get image studies, and there are, are research studies to show that there are changes in the basal ganglia that the neuroradiologist can read as a, a difference in that area.
	00:37:31	So to then be able to take that information from what the clinicians know, the signs and symptoms to what the neuroradiologist can tell you from the imaging studies to then what we find actually in the brain at autopsy is sort of the full circle of, of trying to understand and confirming our thought processes. Now, the reality is, what I see under the microscope is the tip of the ice iceberg and so many, many diseases it's less, it's a localized cancer or a localized infection in a certain area of the brain involve multiple areas of the brain. The circuitry of the brain is, is being discovered now, and, and the understanding of, of pathways of communication in the brain and detriments to that very complex circuitry are being understand understood in certain diseases. But I, we still have a long way to go, I think.
	00:38:32	And so in conditions like pans and pan does I think it, it, it's a, it's a newly discovered disease entity. Certainly I'm sure it's been around for a long time, and it was just not recognized. I certainly didn't learn about it in medical school when I was in the eighties and nineties and didn't learn about it much, even in my residency because nobody had ever looked at a brain with, from somebody with pans and pandas. So it wasn't in the, the neuropathology literature. So the understanding of, you know, either new diseases or new entities can benefit tremendously from understanding the tissue at the tissue level and the cell level and the molecular level. And we can't do that if we don't have material to look at.
Susan Manfull:	00:39:37	Wow. Well, that's kind of a good segue to talk a little bit about the pond Brain Bank Pond is the acronym for Pandas pans and other neuro immune disorders pond. And you established that in January of 2022, if I recall correctly, and
Dr. Brent Harri...:	00:40:02	Right before Covid,
Susan Manfull:	00:40:04	I
Dr. Brent Harri...:	00:40:04	Think.

Susan Manfull:	00:40:04	No, it was actually right after Covid.
Dr. Brent Harri...:	00:40:07	It was it, right? That was it after Covid?
Susan Manfull:	00:40:08	I think so.
Dr. Brent Harri...:	00:40:10	Oh, you're right, you're right.
Susan Manfull:	00:40:11	Yeah, because I, I remember we just a bit of a background here. Our, when our daughter died, we were asked if we would consider donating her brain to one of the, the brain banks at the National Institute of Mental Health, NIMH, which we did. And then for a variety of reasons, we decided that it would be a better idea to move her, her brain. And I knew Dr. Jim Giordano, who is a neuro ethicist at, at Georgetown University actually is the chief of Neuroethics, the Neuroethics studies program, and a professor in neurology and I think biochemistry. And he wears a number of other hats. Anyway, I was acquainted with him through my daughter Alex Manfield, and he suggested that I speak with you to see if you might be interested in inclined to accept her brain. And so we did that before January, 2022.
	00:41:27	I think it was just before Covid, maybe. Yeah. Because they actually didn't move her brain until pretty much after Covid, if I recall correctly. And I know that I am very grateful that you said yes, and there's a whole community of people who are very grateful that you said yes, you would be interested in, in learning more about pandas and PEs, because I, I don't know that you've, you've emphasized what a strong interest you had in the role of neuroinflammation in some of these disorders that you were interested in. Like well, we'll leave it at that. So you established this with the help of the Alex Manfield Fund. I'll, I'll quickly add, and since that time, you've, there have been, sadly, more brains that have been added to the repository. And you, how many do you have now? 12.
Dr. Brent Harri...:	00:42:38	We have nine, nine brains in the, in the bank right now. And so we've been in existence for two or three years, and nine, nine folks have made the decision, and families have made the decision that they they learned about the, the pond brain bank, and there are not too many others like it around the world that this would be a good repository to, to be able to, to kind of take the tragedies that have occurred and, and make something good and, and try to, to learn from, from them.
Susan Manfull:	00:43:15	So there has been one studies that has been published based on one of the brains, which happens to be Alex, I, as the mother will, will say here. And that was, that was published two years ago.

Dr. Brent Harri...:	00:43:34	Yeah, something
Susan Manfull:	00:43:35	Like
Dr. Brent Harri...:	00:43:35	That, year and half, two years ago.
Susan Manfull:	00:43:36	Yeah. So in, in that study, this brain was, was examined very closely, and the clinical information was also made available so that that enriched, I think the the, the pathological part, no, not the path, what do we call it? The brain to the, the see, this is what happens to me. I kind of lose my words with this kind of stuff, let's just say.
Dr. Brent Harri...:	00:44:12	Yeah. I mean, we call, we go ahead.
Susan Manfull:	00:44:14	Let's just say that you, you had access to the clinical information, which I think enriched the neuropathological information, and I'm wondering if we can, can talk a little bit about that. And a good starting point might be what it was that you examined so that people understand that.
Dr. Brent Harri...:	00:44:41	Yeah. So this was several years ago, not that many. And I, I met with you and your husband, and we talked a little bit about how our brain bank and, and my personal interests in, in neuroinflammation might be beneficial to to starting a, a, a, a bank that, as I said earlier we really had no idea about the neuropathological findings in this disease and in this condition. And thankfully, not too many people die from this disease. It is, it is. I, you know, I I think you've had others, others on, on your podcast that have talked more eloquently than I can about the epidemiology of, of pans and pandas and, and the prevalence worldwide. But in, in the situations where somebody does die having the tissue available for close examination and then for research distribution is, is I think, essential to, to understanding more about, about the particular disease.
	00:45:57	So I I decided together with my institution that we would like to begin a, a a bank that dedicated collection specifically for pans and pandas, but recognize that other neuro immune diseases, and there are quite a few of them don't often make it into brain banks either. And that there are researchers who re who, who very much need to have these tissues because we don't get biopsies, as I said before, to be able to form ideas and hypotheses about the disease, and then take that information, even if it's from one case study back to the laboratory to ask questions in animal models. And, and working with patients to have clinical trials for understanding these, these complex and turns out in some cases very preventable diseases. So I agreed to to start the bank and, and to serve as a custodian for tissues and, and let the community know and, and let a variety of other folks that might

come across deaths in this condition know about this so that we could learn more about whether there are similarities or differences in pans and pandas because that's as important in, in disease understanding.

00:47:44 As, because you might have different treatments for different diseases, they might be very different kinds of diseases. And then to retain the tissues and, and have a robust way that scientists who wanted to get access to the clinical and pathological data, we call it clinical, clinical pathologic correlation or clinical pathologic information again, in, in a de-identified manner they would have access to that and they could query that information and ask their scientific question. And, and so we did begin it in 2022. And over the last two or three years we've had both adults children young adults and a couple of older adults who may have had this condition for a long period of time and their families wanting to make the donation to, to the bank.

Susan Manfull: 00:48:52 So can we talk a little bit about, about what you found and going through the paper, and I will provide the, the reference for this on the podcast what do we call it? And, and the podcast website, <laugh>, I'll provide the reference for this. You found mild gliosis and and Alzheimer's type two astrocytes. Can you talk a little bit, well, first of all, can you talk a little bit about what gliosis is?

Dr. Brent Harri...: 00:49:28 Yeah. The, the two major kinds of cells that we have in the brain are really not just two cell types but the, the large umbrella category are called neurons and glia. And most people, I think, have heard of neurons before. They're kind of the active chemical electrical cells that communicate with each other and form synapses and allow us to do all of the things that we're, we're doing throughout the day. Glial cells GL is Latin for glue. And so the early microscopists actually who studied these cells under the microscope found them and said, well, these aren't neurons. They look different, they're different sizes and shapes, and they're kind of surrounding neurons. They're, they're similar. And so they thought maybe they're the glue that sort of holds the, the brain together. And so they called them glial cells.

00:50:28 We now know that just like there are multiple different kinds of neurons that have different neurotransmitters and have lots of different functions, there are lots of different kinds of glial cells or a few different kinds of glial cells, and they probably are different in different regions, and they are in close proximity to neurons. We say that, you know, a, a region of cells in the tissue is a neighborhood. And, and that neighborhood has neurons, glial cells blood vessel cells and it's bathed in CSF. And those cells are all communicating with each other to be able to, to do the

important things in the neighborhood. And if there is a problem a disease that happens, it probably affects all of the cells to some degree in this complex neighborhood. It's not usually just one cell type that gets injured or changes.

00:51:28 When there's an injury, there's going to be a reactive change to that injury. And one of the functions one of the types of glial cells is called an astrocyte. And astrocytes have many different functions. They make growth factors. They buffer potassium they are at synapses and, and often situated around nodes of ro. And they recycle neurotransmitters. But one of their functions in injury, whether it's trauma, neurodegeneration, infection, stroke is that they become reactive. It's a, in quotations reactive, and they change their shape, they change the molecules and the, the things that are inside them. And they have the ability to put out long processes to, to be able to interact with the area of injury. Sometimes they wall off areas of injury. And so gliosis is a generalized term that we use when there is a a traumatic or pathologic process happening in a certain area of the brain that has gotten the astrocytes revved up to do something.

Susan Manfull: 00:52:57 Okay. So there was evidence of this mild gliosis found in, in this brain. Can you talk to us about, I guess maybe the, well, just just to review, can you talk to us, so the glial cells are you said there are several, there's astroids, there's microglia, right?

Dr. Brent Harri...: 00:53:18 Microglia is another type of, of they're sort of the resident immune cells within the brain. They actually into the brain from our, our bone marrow immune cells during development, and then they stay put, and they have a lot of similarities to lymphocytes and macrophages in the in the rest of the body. And then the other cell type other glial, major glial cell type is the oligodendrocyte. And they are important also in communicating with neurons and making the myelin that enwraps the axons within, within neurons, but they also have metabolic regulatory functions as well.

Susan Manfull: 00:54:03 So with all of them, they have well, you said reg regulatory functions, but there are positive things that the glia cells are doing, right?

Dr. Brent Harri...: 00:54:16 Absolutely. Okay. Absolutely. They, they do help to maintain a healthy neighborhood.

Susan Manfull: 00:54:21 Okay. So gliosis refers to a situation in, in the brain in which the, the it's no longer considered healthy. Is that correct?

Dr. Brent Harri...: 00:54:34 There's a problem that's happening, yeah. And then the ggl cells are reacting to that problem to try to help it. And sometimes they are, they're helpful and, and sometimes they have a hindrance to

further support. But they are, they are reactive, like your immune system is reactive to an infection and too much of, of an immune response can, can cause damage to tissue and too much swelling. Same in the brain. Too much gliosis probably is not healthy for the tissue and can prevent repair in some instances.

Susan Manfull: 00:55:17 So in this case, you found the gliosis in in the basal ganglia, certainly. In the cardiac nucleus in particular, if I recall from the, the autopsy and from your, your paper and, and the thalamus as well. Were there other areas that you found here, the temporal lobes, the hippocampus and the basal ganglia show mild gliosis. And did you expect that? Did you expect a find?

Dr. Brent Harri...: 00:55:54 Well, I didn't know what to expect. This was the first brain that had been looked at in this condition. And, and so we sampled widely because we didn't know what, you know, what to look for. We had a, we had a good sense that from other papers and things, that this was a, a neuroinflammatory disease and probably mostly related to antibodies that we're able to get into the brain that were cross reacting from infectious disease and then getting into the brain and, and causing you know damage, either, either direct damage or indirect damage by interacting with neurotransmitters or receptors. But we had really no idea what, what to look for. And so we did our standard examination of, of sampling many different areas of the brain, and then seeing what what we saw on the initial slides and then doing staining to further clarify what we what we suspected or, or I would say, you know, what we could identify with the stains that we used.

00:57:13 And so in this case, those areas that you mentioned seemed to have the most degree of in, of gliosis specifically the caudate and the putamen and the thalamus. And these are areas that are important in lots of, of different functions that we have movement, but also they are, are attached to the limbic system. They are important in regulating hormone levels specifically in the thalamus and, and and then in the hippocampus memory and the temporal lobe various different aspects of of I think memory is the, the most important one. So in those areas, we, we found gliosis and we also found mild lymphocytic inflammation. And that was, you know, that both of those things were not completely surprising to us. But then required further stains to kind of try to classify and, and to try to understand a little bit better.

00:58:32 The inflammation that we saw was lymphocytic inflammation, often around blood vessels. And when you look under the microscope using our standard stains that we use for all areas of pathology called hemat, toin, and eoin, or h and e stain, you can recognize the lymphocyte and, and from a glial cell or from a, a neuron, but you don't know really much about that lymphocytes.

And, and the immune system is almost as complex as the nervous system in that we have lots and lots of different types of lymphocytes that have many different functions. And the B cells make our antibodies and they interact together with the T cells and macrophages that either can come into the, the brain from the periphery or, or microglia can turn into macrophages. So we wanted to first characterize those lymphocytes, those few lymphocytes that we saw around blood vessels in those areas and that we found that they were both B cells and T cells, but pre predominantly T cells.

00:59:39 And that was interesting to learn about. I'm not an immunologist. And so I would say, you know, we still have more research to do on the immune cells that have come in from the periphery in, you know, in, in the, in these cases, not just in, in the first case, but in, in others as well. But understanding, you know, the, the uniqueness of, of the T cell response and, and the B cells, I think was one of the things we, we talked about in the paper. And we, we looked for a different marker called CD 25, which is a marker that's important in regulating those T cells and getting them to do what they're supposed to do. It's often studied in lymphoma and hematologic malignancies. It's upregulated, but it may be important in neuroinflammatory diseases as well in trying to understand.

01:00:37 And so we wanted to, to use that marker. But there are still other markers and other areas of investigation that people who know more about immunology have started to look at with some of these tissues have requested the tissues and are looking at specific receptors and, and immune cells and trying to understand things about this disease as well. I mentioned too that we think that this is a disease that is often caused by abnormal or too many antibodies that are produced against some of the, the bugs that people have infections to, that somehow get into the brain, or that the cells that, that make the, the antibodies, the B cells, the plasma cells get into the brain and, and start making antibodies that really aren't supposed to be in the brain, and that there's some cross reactivity between these antibodies and molecules in either neurons or glial cells that then causes a derangement. Unfortunately, neuropathology can't really see the antibodies, and we don't have a great technique to be able to isolate the these specific abnormal antibodies in tissues. Either frozen tissues at autopsy or tissues that have been, have been fixed. So that's why looking at the, the antibodies, the potential antibodies while people are living by either CSF or blood is an important diagnostic thing that that can help to make, make the diagnosis. But unfortunately we can't, we don't have a great technique to be able to look at specific antibodies. Neuro, pathologically,

Susan Manfull: 01:02:29 You can look at the proteins though, correct?

Dr. Brent Harri...: 01:02:32 You can measure in general proteins. Yes. You just can't ask the question though. Are there specific antibodies against, for example, streptococcus bacteria? Because the unique aspect of that protein we don't have a, a mechanistic way or another antibody that recognizes that specific antibody. So we can say that there are there are antibodies in the brain tissue, but not specific antibodies, if that kind of makes sense.

William Manfull: 01:03:19 Mm-Hmm <affirmative>.

Dr. Brent Harri...: 01:03:19 So the, the diagnostic way of doing it is actual, or one of the diagnostic ways of looking at autoimmune diseases in the, and I'm not sure if this is done still, is to take CSF from somebody who has a putative neuro immune antibody related autoimmune disease, and take that antibody and then look at animal tissues, put that antibody on the animal tissues and see if it, it lights up specific areas. But we can't really, if we don't have the serum from somebody, we don't know whether or not those antibodies have sat down on top of the other proteins in the brain specifically to to cause an interaction. And if there's somebody in the audience who's listening to this and knows a method of doing that, please, please get in contact with me because I haven't been able to, to find a technique that does that postmortem.

Susan Manfull: 01:04:20 So there is some very interesting research that will be brought to light pretty soon in which the researcher was, was through proteomics trying to identify a protein or proteins that might be able to be used as a quote unquote biomarker. And so it looks promising, and that made me wonder whether we could go back and look for that protein or those proteins in the brain tissue. Is that possible?

Dr. Brent Harri...: 01:04:55 That is possible. Okay. And when they're, and that's exactly what, you know, the purpose of, of having the tissues available as new discoveries are made if you have a target and you've learned a biomarker against that target, you can go back and see if that target is within the tissues, either at the protein level or if it's a pro an RNA at the RNA level to see if it's expressed in a particular cell type that is a possibility. Yes.

Susan Manfull: 01:05:30 Okay. Okay. So the gliosis, just from a really lay person's kind of standpoint and I, people other neuropathologists, and I believe you have to told me that you just simply wouldn't expect to find that much gliosis in a 26-year-old, recognizing you're probably not looking for gliosis in the average 26-year-old, but still, is it safe to say that we wouldn't expect to find that much in, in a healthy 26-year-old?

Dr. Brent Harri...: 01:06:05 That's correct. Yeah. We, we, we, you know, if we don't have another reason for the gliosis, we, we just wouldn't expect to see it if the person didn't have a tumor or a specific infection to an area or a stroke. And, and younger people can have all of those things, but we didn't see any of those findings you know, in that particular examination.

Susan Manfull: 01:06:28 So anything else you'd like to recog mention that you found in in this research?

Dr. Brent Harri...: 01:06:37 Well, we, we found similar findings in at least one and maybe two other cases of, of, of the brain bank. And I think that's important when you have, you know, newly described cases. And so we will probably have another publication that we will write up on, on some of these findings. We, we don't have frozen material in all of the nine cases. Sometimes we only have formal and fixed paraffin embedded, then we can make slides from them. But we can still we can still examine for different markers of immune cells and for gliosis. And we have been able to find that in a couple of other cases.

Susan Manfull: 01:07:25 So how, how quickly does gliosis occur? Is that something that can be answered?

Dr. Brent Harri...: 01:07:31 Yeah, we, we usually think that the, the astrocytes react within about a week of some of some problem. And that comes from hypoxia, ischemia kind of research, stroke kind of research. And also trauma certainly things are happening immediately. But from what we can see under the microscope and the production of some of the proteins that the glial cells make we often don't see the, the major changes for at least a few days under the microscope and, and a little bit longer. Now, if you measure changes to glial cells in experimental models they happen quicker than that. Hmm.

Susan Manfull: 01:08:21 But

Dr. Brent Harri...: 01:08:21 From what the neuropathologists can see for gliosis, I would say it's usually, you know, five days to seven days is the, some of the earliest changes that I, I see.

Susan Manfull: 01:08:31 And can it be reversed?

Dr. Brent Harri...: 01:08:34 Yeah, I think it is a reversible reversible finding in neurologic disease that the astrocytes have this phenotype. And they, you know, astrocytes usually have a regionality and don't make a lot of a particular protein called GFAP, and that's our marker for gliosis. So we stain for GFAP to tell us that there are glio cells. And I think that most people, most neuroscientists believe that it

you don't become a glio cell and then you die. You probably have, you know, a decrease in the amount of GFAP if the, if the problem goes away. And you don't have long, long-term changes in all of the glial cells. Now, depending on what the insult is, you can have long-term permanent changes in glial cells and, and they can be glio for forever.

01:09:43 But that's usually in more severe things like stroke or around brain tumors. I think the typical, you know, infections that we get throughout our life the small bumps maybe have a limited gliosis that probably goes away. So I don't see at the end of life when I, and I look at many, many, many, many brains I don't see gliosis in people who are in their seventies and eighties unless they've got other things going on. So it's not it's not a, a permanent condition in my mind.

Susan Manfull: 01:10:27 Okay. Well, I, I think that this, this paper, it's the first study that's, or first results that have been published of a, an individual with pandas or pans, a first clinical pathological study that's been published so that we can see what's going on in the brain and also correlate that as much as possible with the, with the clinical history of that individual, this case being Alex. So it's one case study. And so there are limitations in drawing conclusions from, from case studies of course, but you've just indicated that there are a couple of other you found similar information in a couple of other brains or brain tissue, correct? That's correct.

Dr. Brent Harri...: 01:11:34 Yeah.

Susan Manfull: 01:11:34 So, increases our confidence in the presence of, of gliosis and, and some of the other things that you observed. What, what research, do you have any any research that, that you would like to see done or that's in your pipeline in this area?

Dr. Brent Harri...: 01:11:58 Yeah. Yeah. So, you know, as I said, my, my major area of research is, is really in neurodegenerative diseases and, and a LS I, but I, but I you know, I think most neuropathologists like to study multiple different things, and, and when there is this interest of something novel that really hasn't been looked at before you know, I'm a team scientist and I love collaborating with people who have great questions and, and that I can help them out with giving them tissue if they have a good scientific question. And we actually have you know, a, a really nice board of biospecimen use we call the biospecimen use committee, that we have people who want to, you know, ask a question. And we then provide the person, the person's question and they write a small description of their research project and we send it to the biospecimen use committee, and they, they make a decision because I would say at this point in time, we still, depending on

what they are asking, we still don't have lots and lots of cases to be able to give material out.

01:13:15 And so we we're guardians of this material, but we want to get it, every banker doesn't want to have tissues and slides staying in their bank. They want to get it out to, to researchers. So I offer, you know, to be a a collaborating scientist on just about all of the, you know, the, the projects that, you know, are requesting tissues just because I can help, you know, especially as a neuropathologist with understanding imaging and ways of staining tissues that can be very helpful. So I think we, we need to further clarify the immune response the lymphocytic response. I think that there are ways now of in, in biology called spatial profiling where you can take a piece of tissue, you can first look at it to see, know the region, and know, you know, the types of cells that are in that tissue.

01:14:13 But then there are very sophisticated ways of, of saying at a single cell or a small group of cells, you know, what are those cells making in terms of proteins or RNA that might be different in somebody, you know, two or three or four people with this condition in a specific area compared to two or three or four people that don't have this condition. Are there proteins that are upregulated, proteins that are down regulated? And so I think those kinds of questions really still need to be done. And, and we have the capabilities of, of doing them now. Those in my mind are, are really important. And then I think the, you know, the queries of people that are trying to understand very specific protein markers that you mentioned earlier that they found as a biomarker maybe from biofluids and then going back to our tissues and asking the question, you know, what areas of the brain actually express these specific proteins that might give us some insights as well into what areas of the brains are being affected in this particular disease.

Susan Manfull: 01:15:32 Wow. I, I think it's important to, to get the word out there as much as we can about the presence of, of the, the brain Bank. Of course we hope that in, in my heart, is that there will be no more additions to the pond brain bank. But if, if there is a if there is a death that occurs, I, I would like everyone to know about the existence of this so that we can learn more and be able to effectively treat people with these disorders. That's, that's our goal in the, with the, at the Alex Mantle Fund. So, in my, my final question, I guess, unless you would like to add something else that I haven't thought of asking or a question I skipped,

Dr. Brent Harri...: 01:16:37 I think we've covered quite a, quite a bit.

Susan Manfull: 01:16:39 Okay. So I'm, I'm wondering, you talk a little bit about this in the paper. What where do we let see here so what did

neuropathological reports like this, tell us about the need to change the nomenclature to refresh the listener's mind. Pandas, the P in PANDAS stands for pediatric autoimmune Neuropsychiatric disorder associated with strep, the P in pans, which is the broader category that encompasses pandos. The p there also stands for pediatric. You just did a your research was conducted on a 26-year-old, and you mentioned that there are people who are older than who have had their brains donated to the, to the Pond Brain Bank. What does that tell us about changing that nomenclature?

Dr. Brent Harri...: 01:17:45 Yeah, I think, you know, I think that while it is very, very crucial that pediatricians know about this disease, because the, the predominant number of people are pediatricians, young adults and older adults certainly get neuro immune disorders. And, and there are others that have similarities like Guillain-Barre disease that you know, affect anybody at any age potentially. But, you know, diseases get named for a variety of different ways. We're finally getting away from actually, you know, in many cases, although not all, getting away from the researcher who first, first studied them and, and the disease being called that. I think in medicine, we're trying to have scientific names for diseases. And oftentimes the first group of people that are recognized with the disease get that noer of, of, of, of the disease. And, and it needs to be changed.

01:19:01 Young adults often aren't getting as, as much care as kids. You know, they're not seeing pediatricians. They are usually young and healthy. And, and I think the, the recognition that young adults especially can get this situation, they get infections just like the rest of us is incredibly important. And that primary physicians, as well as psychiatrists, as well as rheumatologists, as well as pediatricians recognize that this is a disease not just of, of in the pediatric population. And, and I think the only way to, to make people aware of it is to study it more and to get more NIH research to study the epidemiology of the disease to study the pathology of the disease and to do more clinical trials for people with the disease, because we learn in each of those clinical trials of what works and what doesn't work to help people down the road with it.

01:20:20 So I, I do agree that we probably do need better, better nomenclature and, and better, better names for this for the scientific and, and clinical community, mostly for the clinical community, so that they are, they keep their radar open and their, you know, their thoughts open about when somebody comes in with different conditions to ask them the right questions and, and to to, to do the right testing. And sometimes it's really wide, and, and other times it's not. And not just one test. Maybe if you get lucky and that test comes through, then you've got your

diagnosis. But in general primary care physicians are among the smartest and, and to me, the most respected physicians we've got and it's not just physicians, it's, it's PAs, it's nurse practitioners and all, all clinical care folks that are working with people with large numbers of people.

01:21:20 You know, I definitely, if you're learning about this it, it's, it's very important. I have a a friend of my son who's a a child psychologist, and I asked her if she had learned about it, and she said, yeah, I, you know, I just had a, a, a course that mentioned it, and I said, I was studying, and we started a brain bank. And she she said, yeah, I, I actually think I might have had a patient with this. And I talked with the family about it. And so it, it is getting more recognition, but it is in, in incumbent upon the people who are studying it in medical schools to make sure, and, and nursing schools that they are teaching about this. And I've incorporated now in in one or two of my lectures with the medical students about these conditions and, and we talk about it amongst other neuro immune conditions.

Susan Manfull: 01:22:19 That's great. And I know with the fellowship funds that the Alex Manfield fund has provided to Georgetown in the neurology department, that I think that it's going to be included in many more curricula as well. So, Brent, thank you for everything that you do, and thank you for, thank you for everything you do and including this this podcast interview. We are, we are all very grateful. I think you're really a, a key member of the team helping to move understanding of this forward so that we can identify the best treatments and and how to diagnose this more effectively. Thank you very much.

Dr. Brent Harri...: 01:23:16 Thank you. And thank you to the Alex Manfield Foundation and, and your family for entrusting us and, and for allowing us to, to help get these important findings and, and tissues out to the wider scientific community.

Susan Manfull: 01:23:34 Thank you for those words. Thank you. Okay. That's, that's a wrap, <inaudible>.

William Manfull: 01:23:43 This concludes episode 10 of untangling pandas and pans. Thank you for listening. For more information about pandas and pans in the Alex Manfield Fund, please visit the alex manful fund.org. The content in this podcast is not a substitute for professional medical advice, diagnosis, or treatment. Always seek the advice of your physician or other qualified healthcare provider with any questions you may have regarding a medical condition.