Kelly Cervantes:	00:00	I'm Kelly Cervantes, and this a <i>Seizing Life</i> , a weekly podcast produced by Citizens United for Research in Epilepsy, CURE.
Kelly Cervantes:	00:18	In today's episode, we will be talking about post-traumatic epilepsy with a special focus on its impact on veterans. CURE has a rich history supporting research for post-traumatic epilepsy, PTE, including research on the role of inflammation and potential indicators of risk for epilepsy following head injury. Post-traumatic epilepsy can develop years after a traumatic brain injury and is a major concern for those in the military. Over 40% of combat troops who suffer severe traumatic brain injury are at risk of developing PTE, which can deeply impact their recovery process and create lifelong challenges. In fact, CURE is the recipient of a sizable grant from the Department of Defense to support further research on PTE.
Kelly Cervantes:	01:04	To help you understand more about the role PTE plays in traumatic brain injuries, I'm excited to have Dr. Jordan Grafman on the show today. Dr. Grafman is a professor at Northwestern University in the Department of Physical Medicine and Rehabilitation and the Department of Psychiatry at the Feinberg School of Medicine. He is also the director and brain injury research chief for the Shirley Ryan Ability Lab. He brings his wealth of experience to help us better understand how traumatic brain injury can lead to post-traumatic epilepsy. Dr. Grafman, thank you so much for joining us today.
Jordan Grafman:	01:40	Thank you for inviting me. I appreciate it.
Kelly Cervantes:	01:42	Of course. I want to start by getting to know you a little bit. What drew you to post-traumatic epilepsy research and the work that you've done for veterans? Do you have a vested interest in neurological conditions?
Jordan Grafman:	01:58	When I started, I was going into the Air Force as an officer and researcher. I was assigned, at the time, to Walter Reed Army Medical Center because the Vietnam head-injury study was just starting. A neurologist at the NIH at the time, Bill Caveness, had knowledge that post-traumatic epilepsy caused by penetrating brain injuries results in a significant proportion of those people who suffered the penetrating brain injuries having epilepsy, and he was interested in the mechanisms of epilepsy. He persuaded neurosurgeons in Vietnam in MASH units to send back materials indicating usually who survived so that they could be followed

up with later to determine how many of them developed epilepsy.

Jordan Grafman:	02:51	In a way, I lucked into that program at that time. It was very fortunate because, within the study of brain function, studying people who have had brain injuries after combat has led to a whole wealth of new information about how the brain works. I was very fortunate to be on this study team, led by neurologist, Dr. Andre Salazar. I was the head of neuropsychology on the team, a cognitive neuroscientist, and we studied these vets for about 15 years after their original injury in Vietnam.
Kelly Cervantes:	03:29	Oh wow. It's encouraging for me to hear that there was sort of a vested interest in this and that, for decades now, post-traumatic epilepsy has been studied. I feel like there is sometimes there can be such a lag in epilepsy research. So, it's actually personally, I find it interesting that this research has been going on. Although, on the other side, there's still so much more needs to be learned.
Jordan Grafman:	03:58	It's true. It's true. As I mentioned, one of the features of having a penetrating brain injury, which is usually due to a low-velocity shell fragment penetrating the skull and the dura and entering the brain, is that it usually only occurs during combat. So, if there's no combat, we're happy we're at peace, but you're not going to get the cohorts, the population that you want to study until there's another conflict, unfortunately. When it does happen, you have so many of the veterans who were in combat who had brain injuries having epilepsy that it allows you to study it in a lot more detail.
Jordan Grafman:	04:38	As opposed to closed head injuries, which is sort of like a concussion in sports, for example, or is typical in car accidents. You can still have seizures, but the percentage of people who have seizures after a closed head injury is much lower, particularly with mild and moderate injuries. It gets a little bit higher with severe closed head injuries because, often in those injuries, there's bleeding in the brain or there can even be a skull fracture with maybe some skull fragments going into the brain. All that increases the likelihood of having epilepsy after even a closed traumatic brain injury, but you get double the numbers with penetrating.

Kelly Cervantes:	05:22	That makes so much sense then why the statistics are what they are in these veterans with the higher percentage of post- traumatic epilepsy because that part of our population is at such a higher risk of having those penetrating brain injuries. Talking about the difference between the penetrating and the closed head injuries, are there any other trends that you have found with veterans versus the regular population with traumatic brain injuries that sort of sets the veterans apart for being at risk for PTE?
Jordan Grafman:	06:04	Anybody who has had a traumatic brain injury is at higher risk of having a spontaneous seizure than someone without any prior traumatic brain injuries. So, you're at an increased risk just having a traumatic brain injury. But the odds are quite small if it's a mild or moderate closed traumatic brain injury. As we talked about, the odds go way up if you have a penetrating brain injury or if you have a severe closed traumatic brain injury because, in that case, you have bleeding in the brain, for example. It just raises the risk.
Kelly Cervantes:	06:41	What have you learned from studying the Vietnam veterans that we're able to use now for our veterans of Iraq and Afghanistan and Syria?
Jordan Grafman:	06:56	Let me take even a step back before that, before sorting the medical applications, things that are learned. On the basis of our Vietnam head injury study, both the military and the Veterans Administration opened specialized brain injury units. They didn't exist before we did our study, and Dr. Salazar, the neurologist on our study, along with civilians, petitioned to Congress to give the money so that these centers could be opened. This gives people who have a traumatic brain injury, at least while they're in the military, places to go where they'll see experts on post-traumatic epilepsy and traumatic brain injury rather than being shuttled around to any person in the medical healthcare system in either the military or the VA.
Jordan Grafman:	07:50	So that was the first step. What we also learned, for example we've learned many things, I'll give you one example. Often, when somebody had a penetrating traumatic brain injury in Vietnam, they were put on [inaudible 00:08:03] to try to prevent seizures from occurring. Unfortunately, it had no effect. So, using anti-convulsant medication early on may be somewhat helpful, say in the first week, but, after that, it doesn't much
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help in preventing the onset. Now they obviously are helpful in
controlling the frequency or the severity of epilepsy, but not the
occurrence. So, we were able to substantiate that as well.

- Kelly Cervantes:08:34Has there been an increase or a decrease in the percentage of
post-traumatic epilepsy, or is it a constant from 50 years ago to
now?
- Jordan Grafman: 08:47 There's been no change.
- Kelly Cervantes: 08:49 None whatsoever.
- Jordan Grafman: 08:50 No. It's the same percentage.
- Kelly Cervantes: 08:52 That's horribly frustrating, I'm sure...
- Jordan Grafman: 08:55 It's frustrating.
- Jordan Grafman: 08:55 ... as a researcher and a scientist.
- Kelly Cervantes:08:58It's frustrating, but it also points out the importance of dealing
with the issue since it's common, and there's been no change in
its presentation across conflicts.
- Jordan Grafman:09:07But the research studies are being done to try and find those
preventative treatments that can try and stop those.
- Jordan Grafman: 09:18 Absolutely. I mean there's ... across a range of kinds of studies. For example, the first thing we noticed, and other people have substantiated this, was that having a family history of epilepsy doesn't make you more or less likely to have it after a traumatic brain injury. So that's not really ... that doesn't seem to be a big factor. The amount of damage in the brain contributes up until the very largest sorts of amounts of damage. And in that case, sometimes people don't have epilepsy at all. It's a funny looking curve if you're trying to better understand the severity of the penetrating injury.
- Jordan Grafman: 09:59 Because in penetrating brain injuries, we have the advantage of being able to estimate the total brain volume loss. In closed traumatic brain injuries, especially the mild to moderate traumatic brain injuries where less is known about why just a small proportion of people have epilepsy after the mild to

moderate traumatic brain injury, it's hard to estimate the amount of brain damage in those cases.

Kelly Cervantes:	10:28	Sure.
Jordan Grafman:	10:29	It's a little bit easier if it's a severe closed traumatic brain injury. That's another kind of predictor. It's more predictive if you have a penetrating brain injury. Genetic predisposition, well, there are some genes that may play a role in the case of post- traumatic epilepsy, and those are genes that are often concerned with the plasticity of the brain. They may be concerned with certain chemicals that are in the brain. For example, there are chemicals like glutamate, which are very excitatory in the brain.
Jordan Grafman:	11:05	They help our brain be very active, and, if you have the wrong variant of that gene, it makes you slightly more likely to have epilepsy. It makes sense, in a way, because, if they're already excitatory, and you have the wrong polymorphism for it, perhaps there's an over-abundance of it making it more likely you might have a seizure. Then, of course, there are other sorts of issues that involve how the networks of the brain function. Part of the way we function, we have inhibition, and inhibition controls the activity of brain regions, and, if you have damage to neurons that are interested in inhibiting abnormal functions, then it makes it more likely that you might have excitatory activity in an area of the brain.
Jordan Grafman:	11:57	There's lots of work going on now in immunology and neuroimmune functions because there's some evidence, and this is particularly true for closed traumatic brain injuries, that you can have abnormal microglia, these little cells that damage and that eat up neurons. They're trying to get rid of the trash in the nervous system. They're overabundant after a traumatic brain injury, at least in some people, but not in all people. There's a thought that, if to help control that activity through various means, you might be able, if not to eliminate epilepsy or seizures, you might be able to better control the frequency and severity of them.
Brandon:	12:40	Hi, this is Brandon from Citizens United for Research in Epilepsy, or CURE. If you want to know more about advances in our understanding of post-traumatic epilepsy as well as the exciting

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new therapies being developed, check out our free webinar at <u>CUREepilepsy.org/PTE</u>.

Kelly Cervantes:	12:55	For this population that is experiencing PTE due to the TBI, are those seizures then more generalized? Are they more localized? Then can you also speak to whether this kind of epilepsy is more intractable or is it more often treatable?
Jordan Grafman:	13:18	Usually, especially with penetrating traumatic brain injury or severe closed traumatic brain injury, the first seizure is usually a generalized seizure. There's been some discussion about that because people often don't witness the first seizure. It might be a partial to generalized seizure. That often occurs, and there's a focal onset. Later though, if it's a late seizure, then they're usually partial complex seizures and not generalized seizures. I might add that although most people who have a traumatic brain injury who wind up having seizures may have their first seizure, say within five years of the event. In our valuations, because we followed our vets up until their sixties, about 18% had their first seizure after 15 years.
Kelly Cervantes:	14:16	Oh my gosh. But a majority
Jordan Grafman:	14:17	If the risk doesn't go away
Kelly Cervantes:	14:20	But you said the majority of them have it within the first five years.
Jordan Grafman:	14:22	Even within the first year.
Kelly Cervantes:	14:24	Okay, so within the first year, five years. But the risk is always there, even 15 years later?
Jordan Grafman:	14:31	It is always there, and when they're in their 60's, which is now 45, 50 years after their original traumatic brain injury, about two-thirds are still on anti-convulsant medication.
Kelly Cervantes:	14:44	Interesting. So then, going back, is this a more treatable form of epilepsy or is it as intractable as every other form? Is there a greater success rate in treatment?
Jordan Grafman:	14:59	If you're asking whether medication helps control their seizures where they're either not present, you don't see them anymore,

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		or there are few, yes. I think it's important to add that we've had the advantage of following them their whole lives. I've known them since I was a kid almost. What we see is that they manage to have fruitful and productive lives from the outside, they don't look any different than perhaps somebody looking at you or me.
Kelly Cervantes:	15:28	Are there certain medications, are there certain treatments that doctors have found work better for a PTE than might work for generalized epilepsy? Are there any "go-to" treatments that the doctors might use, or is it a crapshoot just like everything else?
Jordan Grafman:	15:47	I think what you said is correct. It's a crap shoot. They start on one medication, and, if that doesn't work, they try another one. The goal is, of course, to reduce the frequency and severity of seizures. That was true for our vets, much as it is true for children or adults having their first seizure. You just want to prevent it, and you keep trying. There are common meds that are available, and those are the ones that are used.
Kelly Cervantes:	16:13	Is there exciting research on the horizon that's saying, "You know what, let's go down this path. Let's focus on this because maybe we can prevent epilepsy from occurring if we know in these higher at-risk populations."
Jordan Grafman:	16:27	The more you learn about the molecular mechanisms of epilepsy, the more you can develop, hopefully, treatments that target that. But we don't do whole genome genetic testing yet in every soul. We're not doing that, and there's lots of ethical issues involved with doing that. We can't really do that when somebody enters the military. Although we can draw blood, we can find out about their genetic predisposition before they go into combat, but the military's not going to use that to eliminate people from going into combat.
Kelly Cervantes:	16:57	Of course.
Jordan Grafman:	16:58	But if you understand better the molecular mechanisms, and there's a lot of research to try to do that, then maybe you can develop better drugs or better treatments to target those mechanisms that are more likely to go awry with a traumatic brain injury. So that's one approach. Another approach, as we talked about before, is trying to better understand the brain's immune system. There may be some differences in the brain's
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		immune system from the body's immune system and people didn't pay as much attention to that until the last 10 or 20 years.
Jordan Grafman:	17:33	Often now focusing attention on disorders other than epilepsy, as a byproduct, we are going to learn a lot more about neuroimmune functions and abnormal neuroimmune functions after the traumatic brain injury occurs. If we can control those a little bit better, that may also reduce the likelihood of somebody having epilepsy. So that's hopeful.
Kelly Cervantes:	17:56	That's fascinating.
Jordan Grafman:	17:57	That's hopeful. Then, of course, with genes, there may be some genes that are not so much going to help predict who has epilepsy but might tell you something about the brain's response to epilepsy. Now if you can and this is a little bit into the future, but, if you can manipulate those genes in some way using techniques like CRISPR, the new genetic techniques that allow you to edit the gene, then maybe that might be another way to help improve people's likelihood of not having epilepsy after brain damage.
Kelly Cervantes:	18:32	Have you seen any differences in PTE based on the branch of the military that the person is serving in or in where they are in combat? Are there certain branches, I guess, that are more likely to see higher rates of PTE?
Jordan Grafman:	18:52	Sure. If you're a ground force, you're obviously more likely to see it than if you're in the Air Force or on a ship. It can still happen for various reasons. If you're a ground force, then there are lots of ways that could occur. You could be in a vehicle, there could be a roadside bomb, you could be thrown in a vehicle and hit your head against one of the surfaces of the cabin you're in, for example. That no doubt happens a lot in those circumstances where you have these roadside bombs. On the other hand, if you're in the bush, if you're in a mountain area and somebody fires a mortar and the mortar explodes upon hitting the ground, then you're more likely to have potentially a penetrating brain injury from the fragments, which are at low velocity and won't kill you. Bullets tend to kill. So those kinds of shell fragments are what's going to injure people.

Kelly Cervantes:	19:51	Looking at the comorbidities of PTE, do you see any correlations between PTSD and PTE?
Jordan Grafman:	20:01	Epilepsy itself doesn't, in the case of traumatic brain injury, contribute any more to somebody having post-traumatic stress disorder. The reason that people do or don't experience PTSD after a traumatic brain injury is usually due to the combination of the exposure they had, the experience they had, and where the brain injury occurred because there are some brain injuries if they damaged certain tissue, they lessen the likelihood actually of having PTSD. It's a paradoxical effect.
Kelly Cervantes:	20:32	That's fascinating. Do these vets experience the same stigma around their epilepsy, I'm assuming, as anyone in the general public will? Has that stigma been decreased over the years as we see the same with PTSD? I feel like some of that stigma has been decreasing. Do you see that with PTE as well?
Jordan Grafman:	20:59	I think they face the same issues as anybody in civilian life would have if they had epilepsy. They have to be careful about driving. You can drive if your epilepsy's controlled after a few months, and there's been no further episodes, depending on the state. There are different state laws. But they must deal with that right away. They have to in many cases, if you've had a combat-related traumatic brain injury, you're retired. So, the VA always has to make some decision about disability benefits. That potentially can be an issue as combat veterans navigate the VA system. Not all of them are happy doing that, I might add. One of the advantages of us following people over their lifetime is we can provide them with letters, support, whatever they need. We've bonded with the vets that we, in particular, have been seeing, which is why they came back in hundreds, in large numbers, to be with us again because they felt we understood them, we cared about them, and we also cared about their spouses and families.
Jordan Grafman:	22:08	I might add that we've done some recent studies about the burden of When we ask caregivers Caregivers here, because the patients are all males, are wives usually, sometimes friends, sometimes brothers, but usually wives. They feel that their burden they report a greater burden in caring for that combat vet who had traumatic brain injury than caregivers or wives of vets who served in combat but never had a brain injury.
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Kelly Cervantes:	22:37	Why do you think that is?
Jordan Grafman:	22:39	They have to navigate healthcare systems partly. That creates a little bit of a burden. They have to help that person. Usually, if there's more of the brain that's damaged, there are more functional challenges because of not being able to express yourself quite as well or not being able to reason quite as well and maybe some changes in mood state. All that contributes to a challenge in navigating healthcare systems and life in general. So, the spouse, the caregiver, take on a bigger role perhaps than they ordinarily would, even in the case of somebody who went through combat and served in Vietnam. There's an added effect and, particularly with epilepsy, because it reflects comorbidities, as you were saying before, other kinds of problems. Then it makes it more of a challenge, but they do it. They hang in there.
Kelly Cervantes:	23:33	We hear about the VA in the news all the time that sometimes our vets are not receiving or don't have access to the greatest care. It's not managed as well as it could be. Do they have access to amazing epileptologists? Are they able to get their hands on the same antiepileptic drugs that the general population has access to? Are there additional hurdles that they have to go through? Are they being taken care of as they should be?
Jordan Grafman:	24:05	No, I am not in the Veterans Administration, so I can only tell you what I hear from the vets we followed. In general, they have to advocate for themselves a little bit harder. Sometimes, they may live in a rural community, in North Dakota for example, and they have to travel long distances to get to care. Often, when they get that care, they're not specialized. Now, there are great VA hospitals with epileptologists who are specialized or have a lot of knowledge about traumatic brain injury, and, generally, people will get very good care if they can get into see them within a reasonable amount of time. That's always a challenge. There are long waiting lists often at those VA's. So, it's hard. They all have access to normal medications that are typically used to treat epilepsy, but, depending on where they live, depending on how long they have to wait, they can often feel like they're getting the shaft, shall we say.
Jordan Grafman:	25:04	In order for them to be motivated, they have to really be advocates and assertive. I don't think you have to be aggressive, but you certainly have to be somewhat assertive. I'm always
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		willing to help with those assertive moves by writing letters, or if I know somebody, contacting somebody at the VA or other healthcare systems they're involved with. We don't get many of those, but we do get them occasionally. We get phone calls from our vets saying, "Can you help out?" And we immediately do that.
Kelly Cervantes:	25:33	Well, they are lucky to have you as are we lucky to have you on our show today. I just want to say thank you so much for coming out and for chatting with me and opening my eyes to this whole other world of post-traumatic epilepsy.
Jordan Grafman:	25:51	I'm glad to hear of CURE's partnership with the Department of Defense and trying to work towards a better understanding of post-traumatic epilepsy. Every little bit helps.
Kelly Cervantes:	26:00	Doesn't it though?
Jordan Grafman:	26:01	Yeah.
Kelly Cervantes:	26:01	Thank you so much. Thank you.
Kelly Cervantes:	26:06	Thank you again, Dr. Grafman for helping us understand how post-traumatic epilepsy can affect those with traumatic brain injuries. If you want to support veterans with post-traumatic epilepsy, go to <u>CUREepilepsy.org/Veterans</u> . Your support is greatly appreciated. Also, make sure to visit @seizinglifepodcast on Facebook and Instagram and @seizinglifepod on Twitter. Finally, you can sign up for information about upcoming podcasts or listen to past episodes by visiting seizinglife.org. Thanks so much.
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