Transcript of Cyberseminar

Traumatic Brain Injury

Effects of low-level blast exposure on the nervous system

Presenter: Gregory Elder

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Dr. Ralph DePalma: … program at the Bronx VA and he has worked closely with the Department of Defense Investigator Dr. Steven Ahlers to explore the biologic basis of blast induced TBI in a rat model of mild TBI, in particular exploring the relationship of blast exposure to the induction of Post-Traumatic Stress Disorder related traits. And today he will provide an update on what is now known about the effects of low-level blast exposure on the nervous system and the relationship between blast exposure and PTSD. Greg, a pleasure.

Dr. Gregory Elder: Thank you very much.

Unidentified Female: Dr. Elder, are you ready to share your screen?

Dr. Gregory Elder: Yes, I am.

Unidentified Female: All right. Great. We are up and running.

Dr. Gregory Elder: Okay. Well thank you. Thank you very much, Dr. DePalma. As Dr. DePalma mentioned, what I am going to talk about today are going to be the effects of low-level blast on the nervous system. I will just say at the beginning that my only disclosure is that I do receive research support from the Department of Veterans Affairs, the RR&D, Development Service. I have three poll questions in my presentation today and so I thought I would just start with the first question just to kind of get a sense of who is in the audience today. So Poll Question #1 is what is your primary role in the VA? I have given you choices like student, trainee, or fellow, clinician, researcher, manager or policy-maker or other.

Unidentified Female: Thank you, Dr. Elder. It looks like we have a very responsive group and answers are streaming in. We have already had 80 percent of our audience vote so we will give people a little bit more time. And for those of you that are new to this, simply click the circle next to the answer that best represents your primary role. We do understand that many of you wear many hats in the VA, but we are trying to get an idea of what your main portion of your time is spent on. All right. Now it looks like the answers have stopped streaming in so I am going to go ahead and share those results. It looks like we have six percent of student trainee or fellow. We have 62 percent of our audience respondents are clinicians; 14 percent identify as researchers; 5 percent manager or policy maker and 13 percent are replying other. So thank you to those respondents.

Dr. Gregory Elder: Okay. Thank you. So we have mostly clinicians in the audience, which is probably where I would put myself in addition. I am trying to get my slides – okay, there we go. So the whole subject of blast effects on the nervous system of course has gained a lot of prominence really because of the wars in Iraq and Afghanistan, where TBI has indeed been common with estimates that probably 20 to 30 percent of returning veterans have suffered a TBI. Now initially most of the attention was focused more on the moderate to severe TBI. That is those that would be recognized in theatre like the story of Sergeant David Emme that was told in the New England Journal of Medicine back in 2005, where he said the next time I come to I am at Walter Reed like ten days later. And in fact, the war in Iraq has led to the highest number of military related severe TBI since the Vietnam era. However, what became clear fairly quickly was that, in fact, most of the TBIs, were mild and many of these were not even being recognized prior to discharge. Now as you can imagine of course in a war zone, there are many reasons that TBIs can happen. But in Iraq and Afghanistan, because of the very prominent use of Improvised Explosive Devices, TBIs secondary to IEDs, secondary to blast, have been by far the most common cause. And I put this slide in just to kind of remind me to say that I think sometimes when we hear the term IED, Improvised Explosive Device, we think of something that is kind of contained. That is kind of maybe if you are close to it, it can impact you, but of course that is not true at all. The devices that are being built today are, in fact, enormously powerful. They can flip armored vehicles over. They can cause huge amounts of destruction. And you can find a lot of videos of explosions on the internet. I put a web link to one here if you are interested. And this is something that is on YouTube that the BBC put together. It shows a nice picture of the shockwave in slow motion and if you are interested, this is well worth looking at.

So in this presentation, I am really going to talk about four questions. What are the effects of low-level blast, and by low-level blast I am going to be referring to either mild TBI or subclinical blast. I am going to talk about why is there a relationship between blast-related mild TBI and Post-Traumatic Stress Disorder. I am going to talk a little bit about is there a relationship between low-level blast exposure and chronic neurodegenerative diseases. And then I also want to touch on the subject of is blast pathophysiologically different from non-blast TBI? That is, is it different from the kind of injuries that would be typically suffered in a civilian closed head injury like a motor vehicle accident or a sports injury. And so in terms of the effects of low-level blast, why does it matter? Well, as we just said, most of the TBI that has been coming back from Iraq and Afghanistan has been blast related. More than 75 percent of it is mild TBI. There is the clear impression that because of the improved personal protective equipment, better care in the field, that this has mitigated the severity of other injuries, particularly the effects of blast on the lung so that there are more soldiers who are living to experience the effects of their TBIs. Subclinical blast exposure has certainly been common in operational settings such as Iraq, where at the height of this thing, you talked to folks who come back. It was like every day that they were going out, they were being exposed to some kind of a blast. And why is there a controversy still in this field? Well, there is a controversy still because it is so hard to separate mild TBI from Post-Traumatic Stress Disorder. And in practice, if they have blast related mild TBI, then they also have PTSD. And, in fact, that has been one of the striking features of the mild TBI cases that are being seen in the current veterans is this high prevalence of PTSD in association with mild TBI. If you look at population-based studies, it is probably30 to 40 percent of those who have mild TBI have PTSD. But in clinic based populations, certainly like we would see here at the Bronx VA, it is over 90 percent. In fact, it feels like it is basically everybody. If they have had a mild TBI and they are symptomatic enough to be seeing you, then they also have PTSD.

And the problem in distinguishing the two disorders comes down from the fact that they have a lot of overlapping symptoms, and if you have symptoms that are more along the hypervigilance, the increased arousal, the flashbacks, the sort of avoidance phenomenon, you are more likely to be labeled as having PTSD. As opposed to if you have the more kind of what we think of as organic symptoms – headaches, cognitive disturbance, dizziness, balance. You are probably more likely to be labeled with having a Postconcussion Syndrome. But there is a whole bunch of symptoms in the middle where the two disorders clearly overlap. And the moderate to severe TBIs are recognizable usually by their more severe cognitive defects. But the neuropsychology of mild TBI and PTSD look very much the same. They are hard to distinguish. And the whole distinction has become more complicated by the newer definitions of mild TBI, in that a TBI, of course, requires an event. It requires some sort of head trauma. You have to have been hit in the head by something. And historically, a concussion was regarded as you had to have loss of consciousness in order to have a concussion. And certainly that was the definition 30 years ago. However, that definition has been redefined largely because of the work coming out of the sports medicine literature, which is suggesting that you do not have to really lose consciousness in order for something bad to happen to your brain. And so it has been redefined. We now call mild TBI any disturbance of neurological function. It can be as little as being stunned, dazed, confused or seeing stars. So we have, in effect, lowered the threshold for labeling an event as being a TBI to pretty much the minimum threshold that you can.

So this has led to the question of are we over diagnosing TBI? This question was really first raised in a paper that was published by Charles Hoge and collaborators back in the New England Journal of Medicine in 2008. And basically what this was is they surveyed over 2,500 troops who had returned from a yearlong deployment to Iraq. And it was questionnaire based, but they used accepted criteria to decide on how many had suffered TBIs, how many had PTSD, depression, other physical symptoms. And they found that about 15 percent of them had suffered a TBI and it was nearly all mild TBIs. And the TBI, of course, had a lot of symptoms that distinguished them from the non-TBI – complaints of memory, concentration, attention, other physical symptoms. About 30 to 40 percent of them also had PTSD. So then what they did was they did a multi-various logistic regression, which is basically a statistical analysis that allows you to sort of sort out what seems to go with what. And they found whey they did that, that when PTSD and depression were included in the analysis, the associations between loss of consciousness that is TBI and these other multiple physical symptoms disappeared except for two: headache and heart pounding. In other words, if you take the PTSD and depression out of the equation, the only symptom that seemed attributable to TBI were headache and a pounding heart, only one of which we would normally consider as being part of a classic Postconcussive Syndrome. And there have now been multiple subsequent studies that have found essentially the same thing. There are a bunch of these studies now, all basically coming to the conclusion that if you have really only TBI with loss of consciousness as associated with significant symptoms. And of course most of the mild TBIs that we are currently seeing do not have loss of consciousness, or that the postconcussive symptoms that are being seen, again, if you factor in depression and PTSD, seem to be largely non-specific. There was an Institute of Medicine report that was published earlier this year that reached the conclusion that in terms of long-term adverse health outcomes in humans, there is sufficient evidence of a causal relationship to blast only for penetrating eye injuries and some long-term effects in the genitourinary organ. But for postconcussion symptoms and persistent headaches following blast related mild TBI, they concluded that there was really only sufficient evidence for an association.

So this has sort of raised the question of well, could it be that most of what we are looking at here is really PTSD? That these are patients that are now being called mild TBI but really their predominant symptoms are being driven by the PTSD and maybe we are relabeling them to an extent as mild TBI because that is kind of the fashion of the time. And so now I thought I would put in my second poll question here to maybe kind of get a sense of what this audience might think about this. Poll Question 2 I am just going to ask what is your primary specialty or primary area of interest in the VA. And our choices here will be either Primary Care, Neurology/Neurosurgery, Rehabilitation Medicine, Mental Health or other.

Unidentified Female: Thank you. It looks like our respondents are slowly getting their answers in. We have had about three-fourths of our audience reply so far so we will give everybody a little bit more time to get their answers in. Once again, we have a nice responsive group today, so we appreciate you giving your input. All right. It looks like the answers have stopped streaming in. We have had about 85 percent of our audience vote. So I am going to go ahead and close this poll and share the results. We have four percent replying Primary Care, another four percent Neurology or Neurosurgery, 30 percent rehabilitation medicine, 37 percent mental health and 24 percent say other. So thank you again.

Dr. Gregory Elder: Okay. So it seems like the predominant is really a mix of rehab medicine, which of course is where the TBI programs would be housed, and mental health, where the PTSD would be. Okay. And I am trying to get my slides going here again.

Unidentified Female: Let us see. Maybe I need to – we should have them up but I can. There we go.

Dr. Gregory Elder: Okay. So now there are other studies that have suggested that this link may be more than coincidental. For example, there was this study that was done in burn patients at an Army center several years ago, in which they looked at patients who had suffered burn injuries either because of primary blast injury. And they separated those who had TBI from those who did not have. And it seemed like there was really more PTSD in the burn patients who were associated with mild TBI and primary blast. Or there was a study that was done of survivors of the Oklahoma City bombing, in which they looked at head injury as a predictor of PTSD. And what they found was that there was a significant association between PTSD and head brain injuries, while PTSD was not so highly correlated with other injuries. And there have also been other studies. For example, in Vietnam veterans suggesting that TBI is associated with more severe PTSD. There have been studies in OIF/OEF veterans suggesting that PTSD is more prevalent in veterans reporting a mild TBI as compared to veterans who suffered no injury. And the relationship between TBI and PTSD is actually kind of interesting in that they are really kind of different ends of a spectrum, if you think about it, with TBI being kind of the classic organic brain disease and PTSD a psychologically based reaction to a stressor that was not associated with a physical injury. In other words, to have a TBI, you have to have been hit in the head by something, whereas with PTSD we are talking really about a psychological stressor. That is you are standing in mid-town Manhattan and you see the planes hit the World Trade Center and you are not physically impacted by any of this but you are so psychologically traumatized that you develop PTSD. And it has actually also even been suggested that the post traumatic amnesia associated with TBI may even protect against PTSD. And the idea here being that well, if you cannot remember the event, how can you have been psychologically traumatized by it? Now it is clear that people who have mild or severe TBIs can sometimes develop PTSD, but there does seem to be some sense that they seem to be relatively protected.

Now the other way you could look about this, though, is you can think well, maybe a neural insult may alter reactions to a psychological stressor and perhaps increase the likelihood that PTSD is going to develop. So you could think well, could it be the blast or other injuries damaged brain structures that are involved in the development of PTSD. So what brain structures are involved in PTSD? And one of the nice things about PTSD is there actually are reasonable models of PTSD based on human functional imaging studies suggesting that there is heightened amygdala activity associated with decreased hippocampal and orbital frontal activity. And it is thought that this inadequate frontal inhibition of the amygdala, which is involved in fear responses then leads to these exaggerated amygdala responses say in response to psychological threats. Now, of course, in service personnel in a war zone inevitably they have exposures to all the PTSD stressors that you could ever ask for independent of TBI events, making it hard to kind of sort the two out. So this is where some of us have begun to explore some of these questions in animal models, which I think have begun to give us at least some sense of what some of the answers may be. And just to tell you a little bit about how this research is done, this is just a shock tube at the Naval Medical Research Center in Silver Spring, Maryland. It is basically just a big long tube. You can put a mouse or a rat in one end of the tube. There is a pressure generator at the other end. There are these Mylar filters which break at predesigned pressures, which is how you control the blast. And that way you can deliver a controlled blast to an experimental animal. And what Steve Ahlers, who has been collaborating with us on these studies at the Naval Medical Research Center did, was he took rats and he exposed them to progressively higher blast over pressures. With the idea of trying to see if he could find a dose response or let us say a cut-off point, something that you could say which models a mild TBI. And what he found was that somewhere between pressures around 10.9 psi and 17.4 psi seemed to be the dividing line between where you saw mild transient disturbances without a lot of pathology. That is conditions that we could say are low level blast versus higher levels where you have really overt pathology, brain hemorrhages, pulmonary, really polytrauma.

And you might wonder well, how does this correspond to what would be a relevant exposure in humans or what is a relevant exposure in humans? That is kind of hard to say because it depends on the blast wave peak overpressure, how far you are from the detonation, environmental factors. For example, explosions that occur within structures or adjacent to walls can get amplified and can actually cause more damage than if they occur out in open spaces. So it is hard to exactly tell, but the best controlled data that I am aware of has actually come from studies that have been done in the Department of Defense on these guys who are known as breachers. And breachers are these guys whose job is to go in and blow things up. So there is something in the way that needs to be moved and they go in and they blow it up. And during the course of their training, they are exposed to sequentially higher blast exposures so that they kind of get a sense of the feeling of what it is like. And they begin to know when to back off. But the idea is not to produce concussion. And there have been studies done in these guys of putting pressure sensors in their helmets and measuring the kind of pressures that they are exposed to. And about 12.9 psi is the maximum breacher exposure that they would see. So that is sort of in the same range as to where we are seeing the line that we have drawn within the experimental animals. Now as we said, of course, coincident exposures are hard to control for in clinical studies but in animals we have control over the conditions, the studies are done under anesthesia so there is no psychological stressor. So we just kind of ask the question would blast exposure in an animal induce PTSD related traits. And the kind of traits that we would be looking for? Well, the core features of PTSD are of course the re-experiencing phenomenon that includes the flashbacks, the nightmares, the avoidance phenomenon, the hyperarousal, the associated features of the anxiety, the mood and other changes. We cannot really assess re-experiencing phenomenon in rats. But these other areas we actually can assess to a reasonable degree. So what we found, let us just take for example acoustic startle or hyperarousal, which again is a core feature of PTSD. And PTSD is not just a subjective jumpiness, but there are actually physiological studies in humans showing that acoustic startle increased in PTSD patients. And so the way you can test this is the rat just goes in a tube. There is a motion sensor in the bottom of the tube and it sits there quietly. And then it is exposed to an acoustic startle of 120 decibels. Now I will just ask you to look at what is in the red box. So after the acoustic startle, you see that the controls jump, but what you see is that the blast exposed jump more. So they have increased acoustic startle.

PTSD we conceptualize as being a prolonged and exaggerated response to a threat. So you can ask are these rats that have been exposed to blast more responsive to a PTSD related stressor. And there are a number of different systems that are used to test this, but we used one which uses exposure to a predator scent, cat urine. And the way you do this kind of study is basically you just have this open field box, which I show up in the right, and you measure the activity of the animal in the box for ten minutes. Then you move it to another box in which you have bedding that has been well-soaked with cat urine. Then you measure the activity of the animal for ten minutes. Then you move it to a clean open field cage and you record its activity for another 40 minutes. And then we brought them back three days later and we repeated the whole thing again in the open field. And what we found was if you look at during the ten minute pre-exposure time, there is no difference in the amount of time that the animals are spending in the center of the chamber. That is the time that they are in the center as opposed to being around the edges. But what you notice during the ten minute exposure is the two begin to separate. The blast exposed start spending less time in the center and more time at the edge. So they are kind of hugging the wall. And this is a phenomenon that continues into the post-exposure period. And this phenomenon of the animal tending to hug the wall in rats and mice is taken as a manifestation of anxiety. And so we brought these animals back in three days later and we repeated the exposure. Or let us say we repeated the test in the open field. So this time there is no cat urine. They are just sitting in the open field. And I just ask you to look at what is in the red boxes and I think you can see again, even three days later, the ones that were blast exposed are spending less time in the center over the whole 30 minutes. And the effect, if anything, is even a little more prominent at three days than it was in the initial. So even though it is three days later, these animals are still spooked.

And there are other studies that we have also done. We have also shown that these animals exhibit anxiety in another type of maze testing. We have also looked at them in fear conditioning tests that specifically measures amygdala activity and we see differences in both of these in the blast exposed animals. And, in fact, it is not just us. There is another group at the University of Tennessee that has actually found really quite similar findings. That you can induce these PTSD related traits in these animals just because of blast exposure. And again, these are effects that we are seeing in anesthetized animals, suggesting that no psychological stressor is necessary. So what this would suggest, then, is that blast injury itself may induce PTSD related traits without a PTSD stressor. Or perhaps heighten the reactivity to PTSD stressors that are subsequently experienced. So you can turn this around and say well then, maybe it is not all PTSD. Rather maybe blast can induce a state that looks like PTSD. So maybe the problem is not that all the patients in the TBI clinic really have PTSD. Maybe there are a lot of patients in the PTSD clinic who really have blast. And before I leave this portion of the human studies, I will just say that a very active area of interest in recent years has been to apply modern imaging techniques to humans who suffer blast injury. And there are now over 15 papers that have come out on this in one form or another. They have used diffusion tensor imaging, functional MRI, PET. Most have image mild TBI, mostly have been done in patients who were anywhere from months to years after the injury. And the results are a little inconsistent between different studies. But the one consistent finding that seems to have been in the DTI studies is that they always find evidence of diffuse axonal injury that is manifested by lowered fractional anisotropy, suggesting that there is some sort of diffuse axonal pattern of injury that we see with chronic blast.

And so you can ask then if we compare DTI in blast to PTSD, do they look different? And unfortunately, the studies giving us the exact comparisons that we really like to have do not exactly exist. But what can be said from the DTI literature in PTSD is that it looks like the adult onset PTSD is associated with clusters of both increased and decreased fractional anisotropy in various structures, but it is not the consistently reduced pattern that is seen in blast related TBI. And within the studies of the blast related TBI, what they found is that the findings really do not seem to differ between veterans with versus those without PTSD, suggesting that the abnormalities themselves in the blast subjects probably cannot be explained just by comorbid PTSD.

So this brings me then to my third poll question, which is going to be just does it matter whether we call it PTSD or TBI? And I ask this because some people do say well, we are going to treat their symptoms one way or another so does it really matter what we call it? And our choices here are yes, no or maybe.

Unidentified Female: Thank you very much. It looks like our audience is a little slower to respond on this one, but we will give people as much time as they need. So far, we have had about two/thirds of our audience reply so we will give everybody a little bit more time. Thank you. All right. Things have picked up quite a bit. It looks like we have about 85 percent of our audience have responded. And the answers have stopped streaming in so I am going to go ahead and close the poll and share the results. It looks like we have a resounding 73 percent say yes, it does matter whether we call it PTSD or TBI, eight percent say no and 19 percent say maybe. So thank you to our respondents.

Dr. Gregory Elder: And I agree with that. I think that it does. I think it affects how we conceptualize the disorder. It affects how we begin to think about treatment and if we think about it, the treatment of PTSD and TBI are conceptualized very differently. We think of TBI as being the classic sort of organic disease, whereas, again, PTSD treatment goes in a different direction.

Okay, so to move on to the next two questions. The one being is there a relationship between low-level blast exposure and chronic neurodegenerative diseases. And the second is blast pathophysiologically different from non-blast TBI? And here, by non-blast TBI, I mean the type of injuries that you would see in civilian head injuries. That is motor vehicle accidents, sports injuries, these types of injuries. And maybe to just take sort of the last question a little bit first. Remember that what happens in a blast is a solid or liquid explosive that is basically converted instantaneously into a gas. That creates a blast over pressure wave that propagates through air at supersonic speeds, which is then followed by a blast wind that can propel shrapnel and other things within the explosive device itself. But it is basically a blast wave that is being progressed through air. So the question would be is that different from the kind of injury that you would get, again, in a motor vehicle accident or a sports injury where – and the mechanisms enclosed impact injury. I mean, we feel like we know a lot about those in terms of you have bleeding, you have contusions, you have coup/contracoup injuries where the front of the brain is thrown up against the frontal and the temporal bones, the back of the brain is thrown up against the occipital bone. And associated with this, you can get stretching or tearing of axons that produces this diffuse axonal injury. And that all activates a variety of secondary cascades and similar mechanisms are probably involved in the moderate to severe blast related TBI. But what about the effects of just that primary blast wave itself?

And the other interest in this question and really which generally exists in the TBI field, is the question of are there chronic effects of blast? And the interest in this area has come from, there is a fair amount of evidence that suggests that a single severe TBI earlier in life predisposes to Alzheimer ’s disease later in life. And whereas repetitive mild TBIs have been associated with this entity called chronic traumatic encephalopathy, which has been historically best defined in boxers where it was called dementia pugilistica, but more recently it has been seen in NFL football players and in others. And CTE is a disorder that has a different pathological basis from Alzheimer ’s disease. Alzheimer ’s disease is a combination of the plaques and tau pathology, whereas in CTE it is the tau pathology. And the question of course comes up, we have all of these repetitive mild TBIs that have been going on in veterans coming back from Iraq and Afghanistan. Is it possible that these are going to have effects long-term? And, in fact, there are already six cases of CTE that have been reported in OIF/OEF veterans. These were all in cases that suffered repetitive TBIs. They were all except probably for one case really mixtures of both blast and non-blast TBIs so it is hard to sort of exactly sort out the role of the blast, but that does not mean that it is not playing a role. And this just shows you a picture of what the CTE pathology looks like. Down in this panel D, this is the kind of tau pathology that you see within neurons that are affected by CTE. And so this has gotten people to thinking about well what could be the causal connection between TBI and, for example, Alzheimer ’s disease? And in Alzheimer ’s disease, the central hypothesis has been that maybe it is related to elevated A beta. And remember that A beta is this protein that is deposited in the plaques that you see in Alzheimer’s Disease and which is thought to be the toxic entity that drives the progression of the disease. And in fact, A beta is elevated after traumatic brain injury in humans. In fact, you can see plaques like these that are shown down in the panel on the lower right that can appear literally within hours of a severe TBI in human. And in experimental animals, A beta is increased after non-blast TBI very consistently. If you take mice that are unable to generate A beta, they showed less cortical volume loss and fewer impairments in spatial memory tasks when they are subjected to a TBI. And furthermore, if you take wild type mice and you treat them with a gamma-secretase inhibitor which blocks the production of A beta, then what you see is that in fact the tissue damage and the behavior after they have had a TBI actually becomes quite less. So there seems to be a significant role as a protective effect in these disorders.

So this led us to wonder what happens to A beta following blast injury. So we looked at this in a number of the rats that we had been studying and I will just call your attention to the data here in the red box. And what we found, somewhat to our surprise, was that rather than being increased following after blast, A beta in the rats was actually decreased. So it was actually going in the opposite direction. And we thought well, that was kind of strange so let us look at it in another model. And we were able to get a hold of some tissue from some mice that had been exposed to blast. We did the same study. Again, look at the data that is in the red boxes because again in the mice, both the 40 and 42 forms of the A beta were decreased. So there seems to be something that is just a little bit different about blast. And in terms of the blast related tauopathy, there there may be more of an association. There are now multiple studies which have shown that if you expose mice or rats to blast exposure, they do seem to have abnormal forms of these proteins, these abnormal forms of tau that accumulate within cells. For example, if you just look at the red box. This is from the Goldstein study, which shows if you look at these neurons that have tau positive inclusions and just compare it to this human neuron over here on the left. And just to continue this theme then of how blast and non-blast may be effecting, this is an interesting study that came out back about a year ago. In which what they did was they took mice, and they subjected them to a physical TBI injury, that is something that would approximate more like a motor vehicle accident or a sports injury. And then they compared that to blast exposure. And what they did was after they had subjected the animals to the injury, they isolated RNA from the brains of these animals and they performed essentially whole transcriptome analysis on these animals. And what they found was that, in fact, there was a common set of genes that were either up regulated or down regulated in both models. But what they found was, in addition, was that most of the genes that they were seeing that either went up or down, went in different directions if you compared the physical model of head trauma to the blast model of head trauma. And furthermore, when they did a functional analysis pathway of this, what they found was that genes that were either up regulated or down regulated in Alzheimer’s Disease were regulated in similar directions by the non-blast TBI, while they saw the opposite was going on following the blast exposure. So in other words, the genes that were going up in the Alzheimer’s Disease go up with non-blast TBI, but they go down in the context of blast TBI, again suggesting that there is some sort of difference between these two types of injuries.

And finally, in thinking about where this field is going in the future and what I think you are probably going to see in the future, is I think you are going to see more and more interest in really trying to understand the pathophysiology of blast. And one of the areas where I think you are going to be seeing a lot of interest is in the role of blast on the vasculature. And in fact, some evidence that is emerging to suggest that there seems to be some sort of a selective vulnerability of the vasculature to blast. So these again are some electron micrographs from some studies that we were involved in. And if you just look at this panel up here on the left, this is what a normal vessel looks like. And the rest of these vessels are from tissues from animals that were exposed to blast and then were sacrificed 24 hours after the exposure. And you see this kind of nice normal round vessel up here in the left. And I think if you look at these vessels down here in the panel in the lower right hand corner, even if you are not an electron microscopist, I think you can see that this vessel really does not look normal. These vessels just look unusual. They look misshapen. They look irregular. But the remarkable thing about these figures is that if you look at the surrounding brain tissue, the surrounding neuropil, it all looks normal. And what we are seeing is that there seems to be very early on in this disorder some sort of a selective effect that is really impacting the vasculature before it impacts anything else. This has led us to think that maybe part of what is going on here is we have an initial vascular injury, which then itself sets off a cascade of injuries which might include inflammation and other factors. And perhaps the behavioral effects some of these other changes in neurons are actually downstream of this initial insult that is occurring in the vasculature itself. And I think you are going to be seeing more of a story developing in this area as we go forward in the future.

So just to finish then, I just want to acknowledge the people who have been involved in doing, the researchers at various sites, either at NMRC or the Icahn School of Medicine at Mount Sinai. If you are interested in any additional reading, I particularly recommend the reviews by Dr. DePalma , which are quite excellent places to start. The review that we wrote expands on the PTSD theme. The Cernak review is a little more technically oriented. If you are interested in the whole relationship of this entity, Shell Shock is a fascinating history unto itself. I would recommend the Jones article. And then just finally, if anybody wants to get in contact with me, the easiest way to do that is probably through the VA Outlook and again, I am at the Bronx VA in New York.

Unidentified Female: Excellent. Thank you so much, Dr. Elder. That was a very informative presentation. We do have time for questions now from the audience. I know a lot of our audience joined us after the top of the hour so I would like to remind you to submit any questions or comments for Dr. Elder simply use the question block. That is located on the go-to web on our dashboard on the right hand side of your screen. To expand that, just click the plus sign next to the word questions and you will see the box open up where you can submit any questions or comments you may have. Our first question: What peer reviewed publications on the breachers can be recommended? Are there any?

Dr. Gregory Elder: The only published study that I am aware of is there was a study that came out either late last year or earlier this year that was done on studies of some breachers in New Zealand. And they are looking at biomarkers and finding that actually you could see some effects of the period of time in their training. If you want to send me an email, I can find you that reference. There has been a fair amount of work on imaging that has been done by James Stone, who is at the University of Virginia that he has presented in abstract form but has not yet published.

Unidentified Female: Thank you for that reply. Our next question: Does DSM-5 overemphasize the cognitive aspects of TBI? Does this need revision?

Dr. Gregory Elder: Well, I would say that in terms of distinguishing the central question that I sort of was trying to go out of here of trying to distinguish TBI from PTSD. I think you would have to say that in the context of mild TBI that the cognitive symptoms usually overlap very heavily. And I think that you are right that it may well need some revision in terms of how one divides again the mild TBI postconcussion from the more chronic mental health issues.

Unidentified Female: Thank you for that reply. And the next question: Do athletes suffering from concussion display PTSD symptoms?

Dr. Gregory Elder: No. They remarkably do not typically. And the usual explanation is that athletes who have suffered a mild TBI are typically highly motivated to return to their sport, to go back to their endeavors, but the answer is no. They really do not get PTSD.

Unidentified Female: Interesting. Thank you. What are the treatment implications if you differentiate between PTSD and mTBI in diagnosis?

Dr. Gregory Elder: Well, I think that the treatment implications would be of course in PTSD the treatment now is really geared toward the behavioral therapy and really geared towards treating at least as I think of it as sort of the underlying neural mechanisms that have created this cycle that leads to PTSD. I think how it would change if you thought of mild TBI or blast related TBI in a more organic model, then you would begin to say well, what are the causes that are then leading to the behavioral syndrome? And as I laid out before, I think that we do have some evidence that probably something that effects the vasculature early on is part of the initial picture. There certainly seems to be some type of an inflammatory response in the brain that becomes chronic that is associated with this. If you believe that those factors are then driving the downstream neural effect, then if you are going to be successful in treatment, you are probably going to have to do something that is going to target the inflammation, that is going to target the effects on the vasculature or you may not be able to reverse the behavioral effects.

Unidentified Female: Thank you for that reply. The next question: Are the effects of multiple mTBIs cumulative? Is each successive mTBI lead to greater and more prolonged deficits?

Dr. Gregory Elder: And the answer very clearly from the sports medicine is that yes it does. And that as people have more mild TBIs, they become more susceptible to TBI. They are at the potential of accumulating more deficits. I think that is pretty clear and that is why if you read in some of the criterions in sports medicine literature, they even begin thinking about magic numbers and things like that. And it has a significance in the military and again that if you think about this in applying to the military of people who have had multiple TBIs, at what point do you begin to say that they are becoming so significantly at risk to being returned to their endeavors that we have to really be concerned about that.

Unidentified Female: Thank you for that reply. Did not the Goldstein blast tube create significant head oscillation as they were in the tube?

Dr. Gregory Elder: So there is some controversy about the Goldstein study. And the way that Goldstein did his studies, yes, that has been the principal criticism was that they did not restrain the head. So your blasting an animal that is anesthetized and he shows in the paper that there is a substantial oscillation of the head that takes place. And what he showed in his paper, furthermore, was that if he restrained the head that essentially the effects on the tau pathology that he saw went away, so even his interpretation is that the effect of blast in producing tau pathology is really on this oscillation. It is really on these effects that may not be directly related to the primary blast wave itself. So the answer is yes, they were significant.

Unidentified Female: Thank you. The next question: Many veterans do not receive treatment until years after the mTBI. Can the vets still successfully be treated?

Dr. Gregory Elder: Of course, we try to treat everyone. I would have to say from my experiences that if you see the folks who come in. They are several years out. They are just not getting better. Their symptoms are complicated by the PTSD and the depression. They become much more difficult to treat. I think that is unfortunately the case and that we seem to see a lot of folks who have these established symptoms and once they become well-established, unfortunately, we do not have great treatment for them.

Unidentified Female: Thank you. The next starts with a comment and ends with a question. The blood vessel impairment seems to be an early finding according to the studies presented. How does the surrounding tissue change over time since the blood vessel anomalies would affect the surrounding tissue?

Dr. Gregory Elder: So again, remember I would first of all say that we are looking at a rat model in which we are trying to mimic a mild TBI. And mild TBI of course historically is not really associated with pathology. And what we see in these animals is that over time, we really do not see major histopathologies now. And I think probably what happens in the blood vessels over time is that it seems that there is to some extent a partial repair process so that it is not like that it becomes an injury to the tissue. It is not like producing a stroke or some vocal area of ischemia. But these vessels probably remain chronically leaky and that probably effects the underlying, the \_\_\_\_\_ [00:50:09], the other elements that are floating around in the tissue. But the short answer to the question is no, we do not really see a huge chronic pathology in these animals.

Unidentified Female: Thank you for that reply. Is there a clear dividing line between the number of blast wave exposures and possible damage to the axons and tissue?

Dr. Gregory Elder: No, I do not think anyone has defined a number. It probably, in addition to number, it probably also depends on the severity of the insult, how bad the insult is in combination with the number of insults. There certainly is the impression that multiple repetitive traumas just like you see in sports leads to more problems than single incidents. But nobody really has a magic number.

Unidentified Female: Thank you. Should we also count blast exposures without clear alteration of consciousness when evaluating for TBI?

Dr. Gregory Elder: Well, I think that is a very interesting question and that to many extent is kind of the new frontier. And it is in one of the elements of how blast is kind of a little bit different because you can be exposed to a primary blast wave yet not have an event that we would label as being a TBI. And I think that, in fact, that is what you see for example in the breachers. That they are exposed to multiple blast waves but at pressures that are below that which would produce a clinical event. And there is some evidence that with chronic exposure in these guys that they do develop some chronic cognitive problems. And as I said, I think this really is kind of the new frontier in what we do not know of how much blast exposure beneath the level of something that would produce a clinical event is meaningful. And my suspicion is that it probably is meaningful and it even sort of raises the bigger question if you now extend blast exposure into the subclinical realm, well then maybe TBI is not even the right model for blast exposure. Maybe you have to think about it more broadly in terms of these subclinical exposures as well. And to a certain extent you are actually even seeing that in just the regular TBI literature. I mean, there is stuff coming out now on hockey players that have been studied over the course of a season and changes that occur in their MRIs, even though they have not had TBIs. So I think that yes, the subclinical exposure is real and is of concern.

Unidentified Female: Thank you for that reply. We do have some more questions. I believe that you mentioned animals in the Goldstein tube were anesthetized. Did you know what happens if they were not?

Dr. Gregory Elder: It is very difficult to do animal studies without anesthesia. There have been a few of them that have been done but they are kind of heroic efforts to get the animals habituated to just sit in the tube to begin with. Institutional animal care committees look very closely at these kinds of studies. They are very few people who are even thinking about doing studies on unanesthetized animals. It is kind of the state of the field.

Unidentified Female: Thank you. I am going to ask our attendees to hold on just a sec. I am about to put up our feedback survey. But Dr. Elder, I would like to give you the opportunity to make any concluding comments if you would like.

Dr. Gregory Elder: I just want to thank you again for the opportunity to present and I hope that folks found this useful.

Unidentified Female: Wonderful. Well we really appreciate you lending your expertise to the field. That was a great presentation and, of course, I do want to thank the attendees for joining us today. As I mentioned, you are going to see a feedback survey in just a moment. Please do take just a second to fill that out. We do pay close attention to what you write in and it helps us decide which sessions and topics to support and also helps us to improve our program. So thank you again to Dr. Gregory Elder. Thank you to Dr. Ralph DePalma for organizing this talk. And please do keep an eye on our monthly announcements for the next TBI presentation. So for our attendees, as you exit out of today’s meeting, please wait just a second while the feedback survey populates on your screen. Thanks once again everybody and have a great day.