Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) Webinar Series

July 24, 2014, 1-2:30 p.m. (EDT)

"Hearing and Vision Impairment from Combat Trauma"

Welcome and thank you for standing by. All participants are in a listen-only mode for the duration of today's conference, which is being recorded. If you have any objections, you may disconnect at this time. After the presentation we will conduct a question-and-answer session. I'd like to direct you to our host on today's call, who is Dr. Lolita O'Donnell. Dr. O'Donnell, you may proceed.

Thank you, ma'am. Good afternoon and thank you for joining us today for the DCoE, which stands for Defense Centers of Excellent, for psychological health and traumatic brain injury, the 8th of July webinar. My name is Dr. Lolita O'Donnell. I'm the events planning chief for DCoE. I will be your moderator for today's webinar.

Before we begin, let us review some webinar details. Live closed captioning is available through Federal Relay Conference Captioning. Please see the pod beneath the presentation slides. Defense Connect online and Adobe Connect are the technical platforms hosting today's webinar. Should you experience technical difficulties, please visit DCoE.mil/webinars, and click on the troubleshooting link under the monthly webinars heading.

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Our presenter and I will answer content-related questions during the last 30 minute of the webinar. While we encourage you to identify yourselves to other attendees via the chat box, we will leave the chat box open for additional networking opportunities ten minutes after the webinar has concluded. Please refrain from marketing your organization or product.

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Throughout the webinar you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. All questions will be anonymous. Please do not submit technical or content-related questions via the chat pod. The Q&A pod is monitored during the webinar and questions will be forwarded to our presenters for response during the question-and-answer session of the webinar. Participants may also chat amongst each other during the webinar using the chat pod. We will keep the chat function open for ten minutes after the conclusion of the webinar.

I will now move on to today's webinar, "Hearing and Vision Impairment From Combat Trauma." Consequences of blast exposure can lead to a variety of popular otologic and vestibular injuries. Serious combat eye trauma accounts for approximately 15% of all battlefield injuries, and up to 75% of those affected experience short- or long-term visual dysfunction.

Hearing loss and tinnitus prevalence for service members and veterans is increasing 13 to 18% annually and accounts for the top two most common service-connected disabilities among our veterans. The majority of neurosensory disorders resulting from combat trauma are caused by mild traumatic brain injury. Understanding the mechanics of the injury and the associated research guides patient care and treatment recommendations. While there are assistive devices, technologies, training programs, and support group, to assist those with vision or hearing loss, it is also important to provide psychological health support to the injured and their family.

This webinar will examine current research and evidence-based processes to reduce injury risk and to enable prevention and treatment in both clinical and non-clinical settings. During this webinar, participants will learn to do the following: describe hearing imbalance disorders associated with combat trauma, articulate the basic science concepts and neurosensory disorders, incorporate evidence-based practices into approaches supporting care treatment methodologies, summarize the methods and tools known to reduce risk of injury to hearing and vision in a combat setting.

I would now like to introduce our first presenter, Captain Michael Hoffer. Captain Hoffer directs the Spatial Orientation Center at Naval Medical Center in San Diego, that provides the clinical care, performs basic research, translates research finding and educates medical providers on balance and hearing issues.

Captain Hoffer graduated from Stanford University and attended the University of California San Diego School of Medicine. After his internship in general surgery and residency in otolaryngology, head and neck surgery at the University of Pennsylvania, Captain Hoffer completed a fellowship in otology/neurotology at the Ear Research Institute in Sarasota, Florida. Captain Hoffer is double boarded in otolaryngology and neurotology. His research has focused on the basic science, diagnosis, and treatment of vestibular disorders. Captain Hoffer and his colleagues at the Spatial Orientation Center have authored over 50 peer-reviewed articles on neurosensory issues after trauma.

I would also like to present our second presenters, Dr. Carey Balaban. Dr. Balaban is the vice provost for faculty affairs, and he is a professor in the Departments of otolaryngology, neurobiology, communication in science disorders in bioengineering at the University of Pittsburg. He holds a PhD in anatomy from the University Chicago, and a PhD in physiology from the University Tokyo, Japan. He is a Potomac Institute for Policy Studies academic fellow at the Center for Neurotechnology Studies, health policy and preparedness.

Dr. Balaban is active in National Institutes of Health Research activities as the principal investigator, co-principal investigator, and subproject director. He has authored well over 100 journal articles, monographs, and book chapters. Dr. Balaban is the recipient of the National Institute's Research Service Award and the National Institute of Health's Research Career Development Award.

Thank you for joining us, and welcome Captain Hoffer and Dr. Balaban.

Good morning, or afternoon I guess. Can everybody hear me? I'm Michael Hoffer, and I'm going to start off our presentation on hearing and balance disorders in operational environment. The disclosure: These views expressed in this presentation are those of the presenters and do not reflect the official policy of the Military Service, Department of Defense, or the U.S. Government. The presenters have no relevant financial relationships to disclose and do not intend to discuss the off-label investigative or other unapproved uses of commercial products or devices. The slides we are presenting have been approved by military DOD public affairs officers.

In combat or training environments there are a number of threats to hearing imbalance; penetrating head injuries and open head injuries, which we will not discuss further on this call; noise, be it continuous noise or impulse noise; and then traumatic brain injury emerging from blocked or blast trauma, or exposure.

Noise is a ubiquitous hazard that mainly produce hearing loss and ringing in the ear. As you heard earlier, these are two of the most common -- in fact, they are the two most common VA disabilities, and disability claims are well over $1 billion per year for these disorders and climbing at an astonishing rate. The effects of hearing loss include impaired mission accomplishment, loss of key personnel, and, of course, the morbidity to the effected individuals, the family, and their friends who all suffer when someone has hearing loss.

This is a slide that shows the noise that we are exposed to in a number of navy environments. And notice the sort of dashed yellow line below. I think I can point it out with this device here. Oh, it didn't grab. Anyway, there's yellow line here that shows where single protection is, a dotted line here that shows where double protection is. And notice that even with double protection, many of our environments in the Navy are above the protective level.

Going further into actual weapons that we use, notice, again, that a number of the weapons we use, all these down here, exceed the protection that one gets from double hearing protection. So we're in a noisy environment, and a noisy environment that's difficult to protect against.

Here's what happens when you have hear thing loss. This is from an ARL study done in late '80s actually. But notice for tank crews there's a 25% increase risk if one of the members has a hearing loss for being off target or being, unfortunately, a better target yourself. If we drop from a H1 hearing level to an H2 hearing level, our ability to hear footsteps goes from 100 feet down to 5.5 feet. So, obviously, dramatic reductions in mission effectiveness with just a little bit of hearing loss.

So what can we do about hearing loss? Well, of course, prevention is the best option. Close screening and hearing conservation programs are in place in all branches of the military, and they help a little bit. Human factor engineering is something the military has invested significantly to make things less noisy or protect people better, and, of course, improve mechanical protection, which is underway in all services for protection that can give us more protection against that noise.

But there are new approaches. There are newer audiology/otolaryngology techniques that may tell us when people are at risk for hearing loss down the road, pharmaceutical protection to prevent hearing loss or reverse hearing loss, and then genetic studies to determine at-risk populations. So these are new things we can do that might help us to reduce the amount of hearing loss our troops are suffering.

So lessons for the provider, those who are out there in the audience, hearing loss is a significant disability, not just the price of doing business. Hearing loss must be evaluated by audiologists and otolaryngologist if it occurs, and hearing loss is an operational risk and a safety risk. Solutions include a assistive listening devices for people who have hearing loss, hearing aids for people who have hearing loss, and in some places surgeries, and then we've developed -- not we, but the science has developed a number of implantable devices that may be of use in individuals who have hearing loss.

Now to move on to mild traumatic brain injury. Mild traumatic brain injury has been called the injury of modern warfare. Body armor allows individuals to survive more injuries. Personal protective gear can protect against other injuries, but not that effective against the head. And our enemy's weapon of choice are often improvised explosive devices that lead to back injury and mild traumatic brain injury. The frequency, blast accounts for 80 to 90% of all battle injuries.

The Rand Corporation suggested that about 19% of all those you deploy will come back with mild traumatic brain injury. Now, remember, about 50 to 80% of all those who deploy are in support roles, so that 19 to 20% represents virtually everyone who is a combat intense environment. The mild traumatic brain injury accounts for a million ER visits per year in the civilian population, and over 5 million Americans suffer from the effects of mild traumatic brain injury at any given time, and this is increasingly common VA disability.

The VA DOD definition for TBI is shown there. I won't read it out for you, but notice that there's a structural or other injury, some period of loss or decreased level of consciousness, and then effects afterwards. So you suffer an injury, you have a little bit of decreased consciousness or out of it, and then you have an effect, then you then you have mild traumatic brain injury as described by the DOD and -- VA or DOD, and that's not dramatically than the civilian definition. And there is a disruption.

There are several ways that we get mild traumatic brain injury. One of them is the old blunt thing that many of us learned about in our training, whatever training that was. There was a coup injury where we hit our head, and then a countrecoup where the brain rebounds and hits inside the skull about 180 degrees from where we hit, so as you see from diagram there -- let's see if I can get the thing going -- you have a coop injury and then the countrecoup.

Then, of course the blast injury. This, shown here, is a Friedlander wave. The Friedlander wave is the positive, and then negative impact you get when you have a blast. The Friedlander wave, anyone that's ever felt a blast knows that what happens is you get a inward and outward sort of air passage through your body. That's what the blast is.

So there's primary -- there's a number of categories of blast injury. I won't belabor the point too much, but the primary blast injuries, that shock wave I just showed, and then there's shrapnel fragments that occur, then the individual can be thrown and impact objects, and then there's actually a heat electromagnetic pulse or detonation of toxins in the area. So one little blast can produce a lot of things. So we've done studies -- and this is published in the blue reference

down at the bottom -- determining the difference in presenting symptoms of blast-induced mild traumatic brain injury and the function of time and what the diagnostic and management implications were.

So we had three groups of individuals. We had a group that I saw in Iraq within 72 hours of their injury, a sub-acute group who was seen here at Navy Medical Center San Diego at this period of time, and a chronic group at this period of time. All had mild traumatic brain injury as defined by that DOD definition we showed earlier. This is a sunny day in Iraq. It was sunny until the sand storm came in, and then it became not so sunny. Here is our little device in our area in Iraq that we evaluated patients. Those in Iraq got a history and physical, a gate test, and a hearing test. Those that at Navy Medical Center San Diego got a host of standard investigations.

So our two groups include 81 individuals that I saw in a three-month period in Iraq. Our sub-acute group of 25 and our chronic group of 42, that was a one-month collection, a one-month collection, at Navy Medical Center San Diego, a lot of people that had pure blast injury. That tells you how many people we were seeing at the height of the war to get, you know, 67 in one month that were pure blast.

And here's what happened. Notice that dizziness is the most common disorder at any time point. It's far and away the most common acutely. It's tied with headache sub-acutely, and it's the most common disorder, barely over headache, chronically. So dizziness is number one, and headache is number two, and hearing loss, interesting enough, starts at about a third but grows to a half over time. Actual spinning vertigo is low initially and grows to about a third over time. This dizziness over here is more an unsteadiness phenomenon. PTSD starts out very low and grows over time.

So we were able to actually look at the patterns of balance disorders in sub-acute and chronic blast exposure and noticed that there's positional dizziness, which is very similar, the same as benign disorder vertigo that we see without trauma. There's a post-blast exercise induced dizziness, where soon after beginning exertion of exercise individuals get dizzy, and then there's post-blast dizziness where they have a constant feeling of unsteadiness when standing and walking. They'll come and they'll say, "Doc, I have a constant headache. I constantly feel off balance." And then a subset of these individuals will also say, "In addition to that, I get episodes where the room spins." That's the difference between these two.

And this is a slide -- it's a little bit complicated. But the important thing to understand is that if you look at this slide here, everyone who is at .7 or better, all the individuals got better. And some in the dark circles are chronic, so we were seeing them anywhere from a month to a year after injury. In the light circles, they were sub-acute. They were being seen the first month after injury. So notice that some in both groups get better.

But if you talk about those who don't get better, who have scores below .7, notice down here are all the chronic people, so the chronic people are doing worse over time, and the sub-acutes over here, suggesting that if you get better great, but if you don't get better, you're going to get worse over time. That's shown also when we look at rotary chair testing. Notice the sub-acute individuals have either no abnormalities or half of them have abnormalities. The chronic individuals, the majority of them have abnormalities on chair testing. Saying that, again, over time, these are not the same people, these are different groups, but suggesting that over time you get worse if you're not treated. So dizziness and headache are the dominants we're seeing after mild traumatic brain injury. Balance disorders can be classified, and objective (indiscernible) tests tend to worsen over time.

So what can you do about mild traumatic brain injury? Personal protective gear is helpful if it can be put on the head, of course, human factors, engineering to make blasts less effective, and there are pharmaceutical measures that have been published on. The important issues include go/no-go criteria for operational missions. Someone suffers an MTBI in theater when can they go back out, be on the wire; levels of peer determinations, where people need to be treated in theater at row one, at row two, at row three; and, again, issue of multiple TBIs over short or even long periods of time, how does that affect our fighting forces.

So these are the care issues and the comorbidities that are also issues. It's a real injury. It's associated with many comorbidities. And let's see, now I think I'm turning the presentation over to Dr. Balaban.

All right, I'll start here. We might slip my picture in, I will make myself live so you can see me. What I will speak about, what I'll be talking about a little bit here today are some of the basic science studies that tells us a bit about what is happening to individuals with noises, hearing loss to these exposures briefly, and then with mild traumatic brain injury, particularly blast-related mild traumatic brain injury.

With noises-induced hearing loss there can be several kinds of injury, either acute or prolonged. So acutely, mechanical injury from the noise can occur to the inner ear hair cells and to the vasculature. Of course, this impacts hearing. Secondarily, to damage which is not particularly severe mechanical injury, one can get oxidative stress, and you've probably heard much in the literature about how antioxidants can protect against -- may be able to protect against hearing loss long term. We'll look at a few mechanism that might be involved in that. Thirdly, injury could affect endolymph and perilymph in the eustasis inside the ear, that is a balance between two fluids in the ear. In some cases one could get small ruptures of the membrane, and that can affect hearing.

And finally, just to remind everyone of something very important, these hearing injuries we accumulate over life will also interact with toxins, either drugs that we take normally, that could be the glycosides or some anticancer agents like cisplatin, or, in fact, with organic solvents and a variety of exposures in military operational environments. And this is just giving a broad overview and picture so that we can just look at some of these features.

Now when we think about what's going on inside the ear, we have a variety of different players. We have the sensors or the hair cells, we have the cells that make up the nerve, the auditory nerve entering in, which are from ganglion cells, and we also have vascular elements inside. The ear is a very complicated organ itself, more than just neural elements. So when they're exposed to various challenges, compounds that might be physiological toxic, mechanical trauma, or oxidative stress, these mechanisms can contribute together in that complex environment to producing ringing in the ears, or even a sensitivity to sound, or vertigo. And what we'll see, the theme will play off on continually here, looking at both the exposures for hearing loss and for mild traumatic brain injury is the body is an adaptive system. It gets injured, it tries to repair itself. There can be effects that improve the situation, but there can also be secondary biologic effects that produce symptoms and may make one vulnerable to long-term effects.

Now when we take a look at the noise-induced hearing loss in ototoxicity there's been a lot of attention paid -- of course you've all heard about this -- to reactive oxygen species, and reactive species are generated in a number of different challenges. Aminoglycosides, which are antibiotics commonly used, are one source, and they're often used for studies in animal models.

There have been protective effects of antioxidant treatments against aminoglycoside loss, as well as noise-induced hearing loss in animal models. What this does is focuses our attention on cellular responses to oxidative stress and how this may be a way to design new interventions to help interrupt some of the long-term changes that can produce such profound hearing loss in so many of our war fighters of the time.

Now aminoglycosides have been used because they provide us -- in animal studies who often see that they're used as model to look at these cellular responses. And a few of the mechanisms that we've seen for this, these are some. I won't go through all of these. This is taken from a review paper that we published a number of years ago. But simply stated here, there are a few -- can you see the arrow? If you take a look at the top figure on the plasmalemma, okay, this is the membrane of the cell, so the receptors, a variety of different receptors for neurotransmitters, as well as IN channels are inserted in this particular area. And one of them that's been very interesting inside the inner ear is the so-called capsaicin or pepper receptor fits in. And, in fact, that ends up being regulated in many cases of toxic exposures. We have calcium channels, we've shown here, a particular kind of track receptor that responds to some growth factors. And these are just several of the actors that play in response to injury and recovery.

Inside the cell, many of these exposures, whether they're damage or other exposures, lead to generation of reactive oxygen, reactive nitrogen species, and also the calcium signaling that's trying to help make the cell survive. These reactive nitrogen oxygen species can act in two places. They can damage DNA, and the DNA then has to be repaired, and by the way, the common anticancer drugs, cisplatin, is ototoxic, primarily through DNA. It binds covalently with DNA and then has to be repaired. On the other hand, it can also affect in the mitochondria of the cells, shown here, the presence of reactive oxygen species. And one of the things we see responding to that are some of the enzymes that break down oxygen species like superoxide dismutase 2. You'll see some of this when we look at the blast-related injury.

But one of the more interesting things that have come up in recent years is they will also affect a series of proteins that adjust ATP production inside the cell. It's called "mitochondrial uncoupling protein," and these generate heat, and it may very well be that some of the cellular heat generated by these mechanisms contributes as well to the injury. As you can see, there are many complicated pathways here, and many possible places for intervention. And part of our challenge right now is understanding doubting which of the potential drugs that we have and options that we have may be the proper places for intervention and alleviation of some of the long-term symptoms that we see developing.

Now we speak about traumatic brain injury. We also have the problem, traumatic brain injury is really just a description. You saw from the definition. So we have a known exposure. We have signs and symptoms. We might want to look for biomarkers. The real challenge that we face now, looking at chronic TBI, chronic symptoms of TBI, is understanding it etiologically. Go beyond the description of the person got a conk on the head of a blast exposure and they have the following symptoms to what's going on in the brain, what's going on in blood vessels in the brain? What is the longitudinal, the long-term disease process? And once we understand these trajectories, how can we design meaningful interventions to prevent the deleterious long-term effects that we might see?

Now what I'll review very briefly here is we'll go very quickly through some of the major results from animal work, and the best way, since we can't study these mechanisms in our patients, we have to do correlative animal studies. There are two ways that these are done; open field blast

exposure with explosives, and I'll show some data from that, versus a shock tube, which creates a Friedlander wave, like Dr. Hoffer showed earlier. And the studies that I'll speak about here have explored a fairly great range. They've gone all the way down from 2.9 PSI, which is a fairly low peak overpressure exposure, right up to 17 or 18. And to give you an idea, the eardrum ruptures at about a 15 PSI blast over pressure.

And so many of these studies reported some various forms of vascular, as well as parenchymal issue injury in brains that are extracted prior to histopathological effects. So most of the time in these studies they'll fix the tissue, remove the brain, and then they will go ahead and take a look and study this pathologically. You'll see one approach that we've taken is a little different, is we actually section the whole head, so we'll see all the tissues and see too, and I'll present some of those data in a moment.

Now when we're speaking about the blast injury, we're really speaking to these studies of a pure shock-wave effect. These animals are not thrown, they're not exposed to secondary, tertiary quaternary injuries. They're restrained. So what I'll show you are some examples of microvascular injuries. There's suspicion of higher pressures. There's sheer injury to vestibular end organ, explaining some of the balance deficits. We see evidence of oxidative cellular stress. There's evidence from a number of studies, we get release of excitatory transmitters, much in the same way you would in a minor stroke, ischemic event, and one can get direct activation of episodic pathways leading to cell death, again, depending on the exposure. Now this diagram is something we put together several years ago, which shows how we can think about the effects of low-level blast over pressure.

If you take a look at the left box, blast over pressure impinges directly on tissue in the cranial cavity. That could be the ear, the eye, and the brain. And it basically compresses and decompresses the tissue there as the shock wave goes through. What I'll show you is evidence that at very low levels one gets injury to small veins, small hemorrhage, as well as small thrombus formation. The brain and the other tissues then attempt to respond to this, and so the tissue injury responses will include inflammation and repair responses for the veins, as well as the surrounding barrier between the veins and the neural tissues. Neuroplasticity begins to work to try to get to a functional recovery, but the inflammation and repair can also cause generation of reactive oxidative species, and, in fact, release of excitotoxicity amino acids and toxicity. These can have secondary effects cell death, and, in fact, cell death and direct tissue damage will give you permanent functional loss. So this is a way to think about the complex processes that are going on in vascular and neural tissues in the head [indiscernible] themselves.

Now this is taken from one of our papers that studied open field blast exposure with our colleague, Chagi Pick, the senior author on this paper from Tel-Aviv University. And in central Israel, the figure below in A shows you a number of anesthetized mice being restrained in a field, and the label of the capital D is a pressure sensor that's right near them. If you look over in the right-hand figure, in figure B, what you can see is two of these groups of animals, labeled B and C, were placed at a distance from a shake TNT charge made by some explosives experts in Israel at A. And so when you detonate the charge you can expose, at these different distances, animals to different levels of shockwave exposure in a realistic environment.

Now these figures show some of the results from the paper in terms of behavioral performance of the animals, animals exposed to either a 2.5 at seven meters from the blast, or 5.5 PSI at four meters from the blast shockwave produced from through real explosive detonation. The discrimination index shows you how the animals respond to exploring a new visual object. Normal animals or sham animals will do great deal of exploration, shown by the discrimination

index. As you see, the exploration is greatly blunted at both 7 days and 30 days after blast in animals exposed to even very low levels of blast.
On the right side is a memory test in a [indiscernible], and again, you can see that both 7 days and 30 days after blast, the function is blunted, particularly at the higher blast level.

Now when we take a look inside the brain, the figure 6 show it is blood brain/barrier permeability index. And what we saw here, very surprisingly, is with the lowest level blast, that is a 2.5 PSI blast, animals were seven meters from the blast, we saw at 30 days after, a chronic change in permeability that wasn't suspected. When we look shorter term at functional and isotropy, both long and shorter terms, shown below, we see that there's areas in the brain where there are changes indicative of there being more water or change to permeability there. When we took the section -- the whole heads from some of these animals and sectioned them and stained histologically for some markers of oxidative stress, what we found is that one of the mitochondrial enzymes, manganese superoxide dismutase 2, was greatly elevated in areas showing fractional isotropy changes.

And this is just showing -- the sections on the left show sections through the hypothalamic region of these animals. The middle picture -- I'll grab that arrow here some place. See, the middle picture shows -- thank you -- the middle picture shows, in this area, that there's very little from a control animal superoxide dismutase activity, and look at how much this oxidative stress handling enzyme went up 72 hours after blast explosion in the animals. So this is taken -- the evidence was the same areas that were showing the signs of functional changes, we saw changes in protein expression.

And if you take a look in fiber tracts after the blast, there is an inflammatory related and vascular remodeling related receptor, a chemokine receptor, CXC receptor 3 that is built up, and you can see, if we take a look at some of the fiber tracks, in the tracks taking fibers to and from the cortex for cerebra, you see surrounding all these blood vessels the high expression. We see it in the fornix. We also see in it in the optic tracks, all the tracks on the outside of the brain where there's not on the control side. And these insets show you bone marrow from the skulls of each of these animals to show that the lymphocytes that normally stain, they look the same in both of them.

So there's a real change in terms of this inflammatory and remodeling receptor being expressed, and we found this of great interest, because high levels of this receptor are associated with some autoimmune disorders, such as thyroid disease, and, in fact, development of multiple sclerosis. Advance here. Here we go.

The other thing that we saw, when we kept all the membranes around the brain intact, is that many of the veins around the brain were showing hemorrhage in the subarachnoid space. Here is one from a 13 PSI exposure in a rat taken. This is 24 hours after. Here we're looking near the hippocampus at caroidal vessels. We see vessels that were damage, evidence of injured membranes and closed membranes on veins, as well as in other animals we could see hemorrhage or thrombus formation right in this area near the hippocampus, which can account for perhaps some of the memory -- may contribute to some of the memory and other sorts of features that we see in individuals after low-level blast.

When we continued looking through at different periods of time, we found that small veins in the subarachnoid space around the outside of the brain showed, at all times we looked at, evidence of hemorrhage. These are red blood cells, goes 24 hours after near the vascular artery. Here we see 42 days after, presence of some proinflammatory cells near it. 21 days after, we see these

little circulating almost like little balls. The red blood cells goes from inflammatory cells in cerebral spinal fluid.

We're seeing this hemorrhage that occurs in this privileged compartment can't be removed and probably is providing like an arachnoiditis for some kind of long-term irritative sign that is contributing to long-term effects. We also found now, for those of us working in the ear, in the inner ear. This is a section taken through the ear. Here is the organ of corti. Here is a space filled with Perilymph. Here is the tympanic membrane. You can see signs of hemorrhage from the vestibulocochlear vein actually, right where in enters into the petrosal sinus in all of these animals. There's evidence of hemorrhage and blood cells in them. In fact, 3 out of 15 rats had a lower levels, and in 9 out of 17, slightly higher-level exposures. We found evidence of hemorrhage in the inner ear, which can contribute, of course, to hearing signs and symptoms.

Now when we move over and we're looking in more detail in more recent years, using mass spectrum imaging methods -- this paper is one paper that we did on this -- at changes that might be recurring at more detailed level inside cells after blast injury. And this is collaborative work done with Amina Woods, who is a staff investigator at the National Institute on Drug Abuse, and an entire team of others, including Captain Hoffer, and including Dr. Barry Hoffer, who is formerly the director of intramural research at NIDA, National Institute on Drug Abuse.

So when we do mass spectrometric imaging, we can actually measure about -- now we're measuring several hundred lipids in a 1/20th of a millimeter diameter 50 nanometer deep laser burn in tissue. So these images are all made up of thousands of samples taken across the section, and we've measured one of the lipids here, which is a mono cell ganglioside GM2. And, in fact, this is the one that's dysregulated in Tay-Sachs disease. And one of the striking findings here is, if you look at a controlled section through the thalamus and hippocampus, you see that there is very little in the control, but look what happens after a very low-level blast. This was a 5.5, and here a 2.2 PSI blast, open field blast to the mouse with our Israeli colleagues. You see that you get an up regulation in the hippocampus, and this is in something called the "parafascicular nucleus." These are areas involved, by the way, circuit in epilepsy generation or epileptic-like generation. See how it's progressed. It's the same, hippocampal -[indiscernible] in 24 hours. It begins to resolve at 72 hours. At the lower blast level we see much less evidence of this.

We also can find the precursor. One of the more interesting things that happens here is that the precursor for all of these cell membrane lipids goes way down, so after blast, you see that the ceramides, which is a precursor for many of the cell membrane constituents, drop and then begin to cover. And we've been showing that there's a great deal of change in membrane structure afterwards, which may account -- which may be used for remodeling. It may also be accounting for some of the acute symptoms and the symptom complex changing over time.

So what I hope we've shown you very briefly here is a way that we're trying to move from, saying, oh, we have blast-related mild TBI and trying to classify it by symptoms, by a few signs and biomarkers, and trying to understand what processes might be going on inside the tissue. And, in fact, really, inside the individual that might be leaded to this so we can plan interventions. And very basically what we've seen -- what we can say here is we know that even low-level blast overpressures seem to be producing venous injury, and these small bleeds that we're picking up in the animals are too small to pick up with any imaging techniques now, but it looks as if one has presence, in both the ear and fluid surrounding the brain, tissue, small hematomas, as well as thrombus formation of the vessels, leading to inflammation and repair responses, which are associated with reactive oxygen species generation and can lead to either

recovery or contribute to permanent loss. So part of the challenge that we face here is figuring out which interventions should we make.

Now one of the key things that this indicates actually, is that if you have early venous injury you will have permeability changes between the blood and the brain in the areas where that injury occurred. This could be a very -- this is likely to be a very important clue in getting drug deliveries to the correct place. So if we would give a drug with low side effects, such as n-acetyl cysteine being an example, early dosing will lead to its delivery where the barrier is light, and there where the barrier is leaky, and, therefore, to deliver it to the correct areas where it is needed. And these are some of the kinds of insights that are coming along from this type of work that are leading us to think of proper interventions and principles for treatment.
And with that, we concludes our presentation.

Thank you for your presentation. , Dr. Balaban and Captain Hoffer. We appreciate you highlighting hearing imbalance disorders resulting from combat injuries, from combat trauma, and also discussing some of the pathology of blast injury.

It is now time for us to present our final presenter, Dr. Robert Mazzoli. Dr. Mazzoli is a the director of Education Training, Simulation, and Readiness at the DOD VA Vision Center of Excellence. Dr. Mazzoli's Army career spans 34 years of active service in both the signal and medical Corps. Key rolls include consultant in ophthalmology to the surgeon general of the Army and chief and chairman ophthalmology at Madigan Army Medical Center. Dr. Mazzoli graduated from West Point and the Uniform Service University of the Health Sciences. After an internship, his optomic training was received at Brooke Army Medical Center in the Wills Eye Hospital in Philadelphia, Pennsylvania.

His academic interests include surgical simulation in education, telemedicine, and advanced technologies, military optomic readiness, and regenerative medicine. Highlights of Dr. Mazzoli's numerous academic achievements and awards include over 40 publications and book chapters, and examiners for both the American Board of Ophthalmology and the American Society of Ophthalmic, Plastic and Reconstructive Surgery, or ASOPRS. He is a fellow of the American Academy of ophthalmology, the AFOPRS, the American college of surgeons, the Society for Simulation in Health Care, the Association for Research and Vision in Ophthalmology, and the Wills Eye Hospital Society. Welcome, Dr. Mazzoli.

Thank you very much, and thanks for the opportunity to talk about ocular and combat eye injuries, and thanks for your attendance today. Let me just get this. Thanks. I have no conflicts or financial relationships to disclose, and there are very few clinical photographs. These are my opinions and do not reflect any of the Department of Defense or Veterans Affairs.

Today being the 24th of July, I'm struck by the proximity to the 28th of July being the 100th anniversary of the actual first declaration of war in World War I a hundred years ago. And to look at combat eye injury as something of a historic perspective, we can take a look at the rate of eye injuries across, say, from the Civil War previously to now, where the -- from the Civil War in the pre-modern era through wars across the 20th Century from what's then 1%, about just over a half a percent rate of injuries in the civil war to current war, where we are currently rating around 10 to 15% of eye injuries. That's obviously a rolling number. But in the early days to the war we were above 20 to 25% of combat injuries. I want you to take a look at the difference between the Civil Wartime and the World War I and World War II as we cross into the 20th Century, this quadrupling, we'll talk about that here in just a second.

Why is it that we have the increase in eye injuries? Well, combat is very much a visual activity. If you can't see you can't fight. And, understandably, people who are in that combat zone are reluctant to put anything in front of their eyes that is going to interfere with their vision, or that they perceive would interfere with their vision. Taken in the face of improved body armor and better protection for the head, the torso, and other areas that previously would have been fatal, that leaves the eye increasingly vulnerable to injury in modern combat. In fact, given the very small size of the eye relative to the total body surface area, about .1% per eye, less than 4% of the total face. The rate of eye injury is surprisingly high given the very small surface area represented by the eye. On top of that, we have better survival rates. Across every war that we have fought the survival rate has gotten better and better. Currently, with the current war, we're at about 95% survival rate. A lot of that has to do with increasing the medical capability and medical care, as well as a parallel improvement in body armor.

Again, if we look historically in terms of the causes of eye injury, if you look back into the medieval timeframe of injuries, again, you could do anything you wanted to protect your body, but, again, your eyes needed to be unimpaired, and consequently, even though your head may be totally encased in a helmet of steel, the eye slits still had to be open. Very famously, King Henry of France, back in 1559, at the end of a tournament, a jousting tournament, decided to have one last joust. He challenged the captain of his guard to the final joust, the captain's lance hit the king's armor, the lance shattered, and a large piece of the captain's lance entered exactly in the visor slit, impaled through the king's eye and into his brain, and about three to five days later the king died of overwhelming sepsis, despite being treated and attended by Ambroise Pare and Visalius. Now, interestingly, that injury and the death of the king was predicted by Nostradamus a little while prior to that.

Even if you think that that's a once in a lifetime sort of event, that how could that ever happen, a similar casually did occur in this reenactment in England, but in 2007 during a jousting reenactment in England, the very same accident occurred where a lance splintered, the splinter entered the visor slit, and the person died a few days later.

If we jump forward to Civil War, which is really the last of the non-modern combats. Eye and head injury were very often lethal. The explosive of the time, both in terms of rifle, as well as in artillery, was black powder, black powder being a low-energy explosive. You heard Dr. Hoffer and Dr. Balaban talk about Friedlander physics. We'll talk a little bit about that as well. Black powder is a slow burn, slow deflagration. It's a very fiery explosion, but it's a low energy explosion, and it does not follow the Friedlander physics.

The other armaments of the time were an artillery shell, called the "Shrapnel Shell," designed by Major Henry Shrapnel, a British artillery officer back the 1780s. It essentially is very much like our modern fireworks, where the shell is fired from an artillery cannon. It ignites a fuse inside the hollow shell. The hollow shell itself is actually filled with musket balls, surrounding by another charge of black powder. The fuse burns down, and, eventually, the cannonball explodes in midair, firing off these musket balls much like a shotgun shell would. And it's that exploding shell that Francis Scott Key talked about in the War of 1812, as bombs bursting in air was the shrapnel shells.

The pivotal change in terms of small arms in the Civil War, of course, was the develop of Minie Ball and the rifle -- the rifle gun. But all of these in World War I -- or in the Civil War, rather, were relatively large fragments, and if you were to take a fragment through the eye, it very often went through the brain and became lethal. As we turned into World War I and we turned the time into

the 20th Century, the big change was in terms of the explosive and the development of Cordite, which truly is a high-energy explosive and that does follow Friedlander physics.

The artillery munitions at the time, again, there was the Shrapnel Shell, which was employed initially against the advancing infantry, but as the infantry advanced in the early stages of the war, they were mowed down by the machine gun, and very, very quickly, they retreated into the trench warfare and stagnation. The Shrapnel Shell was then adapted to indirect fire, and, as you can see, the number of shell holes that are close to the trench lines, as the targeting got better, it became -- the artillery came closer and closer to the trench lines, the Shrapnel shell would still explode and it would shower down over the top the trench, and it was that that actually brought in the reintroduction of the metal helmet that you see here, the bellboy helmet.

Additionally, there was the development of the trench mortar to try actually, again, get very close to the trench lines. There were other armament introductions of the small hand grenade, obviously the introduction of armored tanks. But the difference between Civil War shrapnel pieces and fragments and World War I is that these injury now -- these fragments were now small very high speeds and they were survivable.

The conglomerations of -- the constellation of a head injury, a neck injury, and an eye injury very quickly became known as the "trinity," and that was a constellation of injuries that was revalidated in World War II, and is revalidated in this current war and has been seen as one of the hallmarks of modern war. Obviously, World War I also introduced the specter of gas warfare.

If you take a look at the injuries that we are seeing in the current war, there is a very familiar familiarity, because, again, the basic munition is the high explosive. And, again, you're talking about close proximity high explosives. Because the explosive itself is either fertilizer or conventional powder charges, it does follow the Friedlander physics, which we talked a little bit earlier. These blast waves, if they are in the open field, they follow Friedlander physics, but very often, if you're in an urban environment, those waves are reflected and refracted. They are additive, they are subtractive, and so the actual blast wave as it hits any particular individual is very complex.

The munitions that we talk about being seen primarily is the IED, but, again, that's primarily artillery or landmines that have been left over, the car bombs, the suicide vests, or the fertilizer, but a common explosive is that is all a high explosive -- a high explosive charge. The shrapnel and fragmentation, again, is very small. They're small fragments. And, again, the cluster of head and eye injuries that we talk about in the trinity that we discovered in World War I, again, that's been revalidated to over 30% incidence. And, again, over the top of that we have, of course, the conventional injuries that we see.

Dr. Hoffer and Dr. Balaban talked about the blast wave and the Friedlander physics. Here's a demonstration of the blast wave at least, and it's the shock front that causes the very high instantaneous increase in overpressure that will -- this shockwave will actually travel supersonically, and it's very difficult to defeat. Dr. Hoffer talked about the different types of injuries, whether they were primary, secondary blast injuries that come from the blast wind; that is what starts to send the shrapnel and the debris.

Tertiary blast injuries are from, as Dr. Hoffer said, translocation, either the blast wind picking the person up and throwing him against an object, or picking up an object and throwing it against

the person. Quaternary injuries involve burns, building collapse, and crush injuries, and there are even quinary injuries that go along with inhaled toxins or chronic toxin exposure.

This is the Friedlander wave, the idealized Friedlander wave. You can see the instantaneous increase in overpressure, which is followed by this negative sucking pressure. And it's this sucking pressure which gives you the classic atomic blast, atomic bomb house where initially the house goes this way and then it gets sucked back the other way.

In terms of eye injury, the primary blast can affect the eyes very significantly. We've known about that since World War I when Colonel de Schweinitz commented that a lack of outward signs was not necessarily an indication that the inside of the eye was uninvolved, and moreover, extensively involved.

There are concussive injuries. There are contusive injuries, including hyphaema, which is just bleeding in the anterior chamber, or hemorrhage inside the eye otherwise, damage to the photoreceptors that we call "commotion retinae," a variety of damage to the retina, visual field block, decreased intraocular pressure, rupture of the eye, what we are calling "delamination" of the internal layers of the eye such as retinal detachment, choroidal rupture, a condition that we call "proliferative vitreoretinopathy" these days. In World War I it was referred to as "proliferating chorioretinitis cycle dialysis," which can led to long-term glaucoma, traumatic optic neuropathy, transitory astigmatism. All of these we are seeing today were well-documented in World War I.

What we did not document very well in World War I are angle recession, which can lead to chronic glaucoma and vision loss, and corneal endothelial cell loss. The reason we didn’t document those in World War I is that we did not have slit lamp biomicroscope available back then; we do now. And so, again, this shows the limitations of our diagnostic capability that we get better as that improves.

The secondary, tertiary, quaternary blast injuries we saw, again, in World War I. We're seeing them again now. And those are a variety of lacerations, penetrations, perforations, and crush injuries to the eye and the surrounding tissues. We see avulsions of both the eyelid, the eye soft tissues, as well as avulsion of the optic nerve away from the back of the eye. We obviously see burns as part of the blast, but not just from the blast.

We continue to see burns in terms of aviation accidents and secondary fires. The debris that is blown as part of a shrapnel wave can contain a variety of contaminants, both in this war as it did in the trench wars, dirt, bone, animal parts, et cetera. Fracture, again, we see. And, again, we see the traumatic brain injury. Obviously it's well-known in World War I. We called that "shell shock," not just from the psychological aspects but from the physical manifestations of shell shock as well. Very often, again, as is well known, you are left only with symptoms at this point, probably because our diagnostics are still limited.

In terms of visual manifestations of TBI, we see, not uncommonly, accommodative dysfunction of not being able to read very well, and for some reason, we don’t understand it very well, light sensitivity and photophobia. But, again, the majority of all of these were well-documented in World War I. We are seeing them now again.

To talk a little bit about presentation, Dr. Hoffer mentioned that prevention is better than treatment, and that goes for the eye as well. Eye protection obviously is not a novel or a new or a modern concept. If you think about long ago in a galaxy far, far away, the Star Wars Stormtroopers probably had it right in terms of their helmet. Here, again, shows even into

ancient times you can do anything you want to protect the remainder of the head, but the eyes remain exposed.

But even in 1916, again, during World War I, we were recognizing that upwards of 50% of all eye wounds would probably be amenable to some sort of protection if we were smart enough to try and develop that. Dr. Morax and Moreau in France did try to develop a type of eye shield for the World War I helmets, but, again, the difficulty is that those protective efforts decrease the vision and/or decrease the visual field and did not catch on.

Our current eye protection is made out of polycarbonate, which means that they look like sunglasses and, therefore, you can see through it. Rather than leaving your eye exposed, we can actually truly protect the eye, at least against the antiballistic fragments. This is the same person, proving that eye protection works. You can see the negative shadow of where all of this shrapnel is peppering the soldier's face, but his eyes are unscathed. Again, we can see that it can take a pretty good licking and keep on ticking.

The current eye protection is made of polycarbonate. Again, it works primarily for very small fragments as an antiballistic measure. There are designs that are both spectacles and goggles. We even have some for our working dogs; they are called "Doggles." This is Major Butch, a working dog. And they're a commercial design, which means that the government, you can buy them over-the-counter, you can buy them for work, you can buy them for home. You can go out to the PX or the sports store and buy the same model of eye protection right now over the counter, which also means that we can keep up with the changing commercial design. What we don’t know is how good are the goggles and the spectacles, how good is the eye protection against the blast wave, and that is a subject of ongoing research.

In conclusion, I do want to say that eye injuries are common in combat. They're not new. They're not novel, but they are increasing. They're common for a variety of reasons, particularly in a high-explosive environment, whether that environment is on battlefield, whether it's an ancient battlefield or a modern battlefield, or even an urban battlefield, such as the Oklahoma City bombing in the Murrah Building that was a fertilizer explosion. The explosion in West Texas was a fertilizer explosion. Those are all high explosive powders, and consequently the spectrum of eye injury that we should see in the day of modern high explosives ought not be a surprise to us.

The spectrum of eye injuries will run the gamut, from the visible anatomic injuries that we talked about to the subclinical anatomic injuries that you have to look very, very carefully for. Patients may actually have 20/20 vision and not have any visual symptoms but still have true anatomic damage. And on the invisible side there are the TBI vision-related injuries where everything looks fine, and these are the people that come in and say, "Doc, I can't read." These are 20/20 people who have difficulty reading or reading for a long period of time.

As Dr. Hoffer and everybody is continuing to reemphasize, protection is always best, but, nevertheless, the spectrum of eye injuries is always going to be there. They will always occur. And so please be aware of them, especially in conjunction with head injuries. Again, over 30% of head injuries will have a concomitant eye injury. So please be ready to refer. Thank you.

Thank you for your presentation, Dr. Mazzoli. If you have any questions for Dr. Mazzoli, please submit them now via the question pod located on the screen. Your questions will remain anonymous and will be referred to anonymously if answered during the Q&A session. I would like to go ahead and start with a question for Dr. Hoffer.

Okay.

Yeah. You mentioned mild TBI prevention: personal protective gear, human factor engineering, and pharmaceutical measures. Can you elaborate on pharmaceutical measures, how about factor engineering as well? Thank you.

Pharmaceutical measures that have been studied really have actually been for traumatic brain injury treatment in the early period of time. So, Dr. Balaban alluded to our published article in "PLOS" in January of 2014, documenting that an antioxidant, if given shortly after blast injury, can dramatically reduce the symptoms at seven days. So, and that's a relatively -- not relatively -- that's a very safe medicine that's got a 40- to 50-year use period in the United States hospitals. The medicine is called "NAC," "N-acetyl cysteine" and it's the active ingredient in Mucomyst, which, again, has been used for 40 years.

Human factor engineering involves creating vehicles for creating actually, believe it or not, working suits. Dr. Mazzoli mentioned, you know, the Star Wars, but suits like that that actually prevent the blast from impinging on the body. And there's been a lot of work done, dramatic work done on the vehicles; not as much work done on the Star Wars suit. But, believe it or not, there are some renditions out there somewhere.

Thank you, Dr. Hoffer. We do have a question now from Dr. Robert Labuta [ph], and it's directed towards Dr. Mazzoli. Dr. Mazzoli, would you please comment on the specific effects of chlorine gas on the eyes from some recent IEDs?

Yeah. The gas of any kind of is worrisome. It's a specter that we've, of course, been concerned about for a while because it's all out there, whether it's actually a nerve agent or a blood agent or any of the other agents, or even just something that would be an irritant. Chlorine is -- specifically, chlorine can cause an ocular irritation, and the treatment to that would essentially be irrigation at this point. Fortunately, we're not seeing, at least not that I'm aware of, other more potent agents like mustard, which we know is out there as well.

The threat that I see, the fear that I see is that we start looking -- or that we start find finding combination agents. If you get an irritant like chlorine or even pepper gas, that it gets everybody into a protective posture, which makes fighting more difficult, or that it is a combination -- that they are used in combination with things that are more devastating, like the nerve agents.

Thank you so much. There is a question directed to Dr. Balaban. Dr. Balaban, you noted the math model blast examples. Can you elaborate on how this research can be used to drive changes in treatment?

Certainly. Well one of the things that this actually drove was, as Dr. Hoffer mentioned, for the N-acetyl cysteine study, the selection of that drug was impacted by the rodent work. N-acetyl cysteine has been known to be an effective anti-inflammatory and anti-oxidative agent for quite a while. As he mentioned, it's been used safely for a long time in the clinic. But it had been -- it was thought it wouldn’t be so effective against stroke or other similar cases because it doesn’t cross the blood-brain barrier well. Because we saw the sites of injury early in the animals at that time, we reasoned that it would be delivered to the correct site and it would be more effective if given early, and those, in fact, panned out. So it gives us that sort of idea.

Secondly, it shows us that treatment modalities are going to be sensitive to time after injury. So, for example, if we are looking early like that, we can take advantage of the fact the drug doesn't have to be particularly permeable to the blood-brain barrier, that it will go out where the blood-brain barrier is leaky and therefore gets delivered to the correct site. Later on we see that there's a sequence of inflammatory changes. This is in very mild brain injury where there isn't any interstitial neural damage. So we can think about delivering drugs that can affect the vasculature and that vasculature interface where we see the changes pro-inflammatory changes inside those animal models.

Third, it points out some of the vulnerable sites. And a number of us have done engineering model studies looking at the finite element model studies looking at how the brain case and contents surrounding it can be affected by a shockwave. And we have a paper under review now that we did where we focused carefully on the peak-to-peak kinds of stresses seen in the areas. And, in fact, the peak-to-peak stresses in humans were all seen in the supratentorial compartment that is right down near where we saw all the vessel damage in the animals. So they can give us new principles to think about in terms of how to design better helmets or protective gear for -- protective equipment for our war fighters against these sorts of vascular injuries.

These kinds of lessons are sort of heuristic guidelines for rational therapy development, and the more we look at it the more we'll find. Now, for the lipids there are a variety -- people have thought about lipid therapies for a long time. And, again, the changes that we're seeing as we dig deeper down into this give us ideas for interventions that we can make and when to make those correct interventions.

Thank you so much, sir. Unfortunately, at this point we can only take two more questions. So let me go ahead and -- this is a good question to our Centers of Excellence speakers. What is the referral process for the division Center of Excellence for suspected TBI-related symptoms? Who wants to take that on? Dr. Mazzoli?

Sure. There's an awful lot of work with both DCoE and NICoE and the rehab side to evaluate patients for vision-related injuries. The initial requirement would be to make sure that there's not an anatomic injury. But other than that the referral would go through, primarily, DCoE, NICoE, and the eye clinics. We can help -- if you want to write to me about a specific patient and a specific issue, our contact information can be made available.

With regards -- this is Dr. Hoffer. With regards to the Hearing Center of Excellence, we also have a center, you know, office that can coordinate. But we have a spoke-and-hub model, so you can access the Hearing Center of Excellence through any of the major medical centers in the military and the major VAs. So you can certainly go on the website and get a central access or go to your nearest major VA or DoD center and get assessed that way.

Thank you so much. This is our last question before we end the webinar. Dr. Mazzoli, there have been a lot of studies done in regards to eye protection. In the case of this person asking the question, his [indiscernible] has actually ruptured. Have there been any studies done in regards to eye protection?

In terms of -- yeah, in terms of blast injury, yeah, there's been -- that has been an area where we have been trying to focus more attention and try to examine both the blast physics of the transmission of the blast wave through the eye in the orbit, as well as the anatomic injuries that

come from that. There are a couple groups that are looking specifically at that, both in terms of the blast wave transmission and damage models.

There's a very elegant group in San Antonio that is doing some cadaver eye models. They're also trying to develop a computational mathematical model for predictive modeling of the blast wave transmission and tissue damage. There are a variety of other laboratories that are being funded by a variety of federal and defense research programs that are looking at traumatic optic neuropathy and interventional measures for mitigating and improving the traumatic optic neuropathy and retinopathy, just as in the hearing center research.

In terms of the blast physics, we're partnered as well with the folks at Aberdeen, similar to the open field explosion studies that Dr. Balaban was talking about. We're also partnering with the folks at Aberdeen, with the folks at Natick Labs, soldier protective labs, and PEO Soldier, those are the people that own the body protection, the eye protection. In essence, we're trying to investigate and learn more about the blast wave. Those are great issues. We're aware of them and we're trying to learn as much as we can about them.

Excellent. Thank you again to our presenters, Captain Michael Hoffer, Dr. Carey Balaban, and Dr. Robert Mazzoli. We will archive today's presentation in the monthly webinars section of the DCoE website.

After the webinar please visit http://continuingeducation.dcri.duke.edu/ to complete the online CE post-test and evaluation, and to download your CE certificate or certificate of attendance. To help us improve future webinars we also encourage you to complete the feedback tool that will open in a separate browser on your computer.

To access the presentation and resource list for this webinar, visit the DCoE website at dcoe.mil/webinars. We will post a downloadable audio podcast and edited transcript of the closed-captioned text to that link. The chat function will remain open for an additional ten minutes after the conclusion of the webinar for attendees to network and chat.

The next DCoE traumatic brain injury webinar topic is "Breaking the Code: ICD9 Diagnosis Coding for Traumatic Brain Injury." This is scheduled for August 14, from 1:00 to 2:30 p.m. Eastern Time. The next DCoE psychological health webinar topic is "Empowering Patient Engagement in Care" and is scheduled for August 28th from 1:00 to 2:30 P.M. Eastern Time. Thank you again for attending and have a great day.

Thank you.

This concludes today's conference. Participants may disconnect at this time. Speakers, please stand by.