Sean Fearns: Good afternoon everyone. Yes, good afternoon. My name is Sean Fearns on behalf of all of us with the DEA Museum and the DEA Community Outreach section here at headquarters, we want to welcome you to this webcast and lecture on cocaine. A particular welcome to those watching live on the internet and those who are actually working on continuing medical education credits through CME Outfitters, we welcome you as well. Today, we have another ripped from the headline topics, the topic is Cocaine. We are going to hear from the DEA Intelligence Division on the resurging production of coca in South America as well as trafficking trends. As well as from an amazing and brilliant panel of experts and researchers on this drug and its effects on the body and the brain.

I will mention now that there will be time at the end for question-and-answer, so please feel free to think about things **[00:01:00]** that you would like to pepper our panel with. Also, for those watching the webcast, if you are watching it live as it happens today, there is a place on the web viewer where you can also submit questions here to the panel in the room. Today our panel is being led by our moderator Dr. Mark Gold. Dr. Mark Gold, if you do not know him simply by reputation, he is an internationally renowned researcher on cocaine and other drugs and addiction in general. Dr. Gold has over a 1,000 peer reviewed articles and texts over his lifetime and we are going to say to-date because he still continues to do a lot of work. He has been recognized with the McGovern Award from the American Society of Addiction Medicine. He served as the University of Florida distinguished professor and chair, the of Disney chair, and he has been an adjunct professor of Washington University School of Medicine in St. Louis, Missouri, and **[00:02:00]** as chairman of RiverMend Health Scientific Advisory Board. It is important to note Dr. Gold's ground-breaking work 30 years ago -- 30 years plus on cocaine which I am sure will come up during our panel.

Dr. Gold will introduce our panelists and have them give presentations and then we'll leave time at the end for Q&A. Please join me in welcoming Dr. Mark Gold.

Dr. Mark Gold: Thank you Sean, it's nice to be here at DEA and this is a particularly interesting and timely topic. The last time that I was here as a moderator, I think we had Ted Cicero talking about his new paper on how prescription opioids were a major problem and morphing in to the heroin epidemic. I hope that the panel today **[00:03:00]** can raise awareness and help us understand this emerging problem as well. Thanks for my introduction.

Of all the articles, the number one most cited article in my career was on cocaine and is on the cocaine dopamine connection, and how cocaine rather than just simply being thought of as a drug that causes dopamine increases over time, causes decreases and depletion. That's very interesting for me because it changed my way of thinking about cocaine. It changed our way as a field of thinking about addiction. Cocaine, remember at that time, was considered not addicting. Cocaine was considered safe. **[00:04:00]**

There was one news magazine that had cocaine the champagne of drugs. Cocaine by being proven to be addicting changed the definition of addiction to something more like pathological attachment than simply having an acute abstinence or withdrawal syndrome. All of that made it possible by the way for us today to consider sugar, gambling, and other behavioral addictions which have less abstinence syndromes and much more in the way of fatal attraction.

We have a great panel. Leah Bloomenstein is our speaker here from DEA and she is currently DEA Domestic Intelligence, Current Intelligence on Cocaine. She will have a lot to add to the little I know from going to **[00:05:00]** Cartagena and reading the newspaper and the Washington Post they had this person who stuffed cocaine into their pants and was identified going through customs. In Cartagena, we saw coca production and changes in production. We even talked about submarine smuggling full of cocaine into the United States. Hopefully, her talk will look at that as well as changes in overall production and how that translates into more use and more problems.

Second expert speaker is Jean Lud Cadet who came to New York City from Haiti in 1970. I have known him since the time he was an intern. He is a career researcher. **[00:06:00]** He has authored numerous important papers and collaborated with many other experts as well. He has written work that not normally thought of which is use consequence from the brain point of view that just because you stopped taking a drug, does that mean that your brain is the same as it was if you had never taken a drug. Really very, very critical and important work. He is the Chief of Molecular Neuropsychiatry, the research branch and Chief of Molecular section at NIDA and just a great role model and mentor. Even though he won't have time to give his full talk on methamphetamine, methamphetamine is happening as well, feel free to ask him questions since he is the world class expert on **[00:07:00]** methamphetamine in the brain. Sean and I worked together on this cover for biological psychiatry related to methamphetamine showing how it was similar in many ways to a concussion.

Tom Kosten is our last speaker and has really pioneered the whole idea of medically assisted, medication assisted and immunological approaches to treatment for a large number of different drug problems and addictions. He as you can tell is exceptionally well trained and equally easy to talk to. He's got a lot of good advice which he has shared with the field many times. When we talk about cocaine and the possibilities of a cocaine epidemic, **[00:08:00]** we can't really compare it to the opioid epidemic because where is the Narcan or naloxone for cocaine overdose? Where is the MAT treatment for cocaine addiction? We have none of the tools and he is working on that. Both Tom Kosten and I came from Yale and there the famous historian David Musto, now deceased, taught about the American disease. You can see some of this in the

museum and think this through, but Musto if he was here would remind us that almost every opioid epidemic ends with a psycho stimulant epidemic.

Whether it is cocaine or methamphetamine, he wouldn't have a horse in that race, but he would say one begets another. This is just a, I put this in the slide deck, so everybody would have access **[00:09:00]** to the most recent data but again life expectancy has dropped as opioid deaths have surged and that's a crisis that everyone is paying attention to. Deaths in the United States in 2014, the biggest changes how cocaine has moved up the death, cocaine related deaths, and if you adjust that and look at trends, you will see the most recent data showing that synthetic opioids other than methadone have had this huge spike since 2013 and cocaine since 2015 is in a similar spike. Age-adjusted involving cocaine you can see this much more clearly but it is beyond question.

Looking at the Florida data, **[00:10:00]** cocaine is now an almost half of the fentanyl related deaths reported by coroners. Co-use of cocaine laced with fentanyl and this is just the most recent data and gives you a URL which you can click on and get the most current data from the state of Florida. Thank you to Dr. Bruce Goldberger for access to these data and for continuing to update this. Even seized cocaine contains fentanyl and carfentanil, tranquilizer that we use at the University Veterinary Hospital to knock animals down. Cocaine related overdose deaths that are in this peer reviewed paper would summarize them very recently **[00:11:00]** because cocaine related overdose deaths increased significantly between 2000 and 2006, between 2006 and 2010 with changes in supply. Public health and public safety responses should be comprehensive and important and keep in mind the role of opioids. Prevention is the only treatment that's a 100% safe and effective; education and prevention.

Overdoses can be accidental, and they can also be due to other drugs that are in the drug being purchased because these are not pharmaceutical purchases, they are street drugs and they contain lots of adulterants. The large majority 87% of cocaine bricks contain levamisole or levamisole mixtures and that was identified in DEA Threat Assessment. All of this has combined to move unintentional injuries which include drug overdoses and suicide **[00:12:00]** if you add them together are part of the -- what we see in the reduced life expectancies. Lastly, keep in mind that while some overdoses are accidental, and others are accidental poisonings, others are poisonings, some may be suicide attempts. Even passive suicide attempts kind of like Russian roulette and this is ongoing work but important to keep in mind.

Drugs change the brain. Drugs like opioids and cocaine change the brain in a way where a person can be depressed for a very good reason. They can be depressed about where their life has gone but also feel physically depressed and look depressed. Many people forget that the animal models used to discover new anti-depressants are post psycho stimulant **[00:13:00]** withdrawal models. Meaning animals self-administer psycho stimulants, you stop it and in that post

state the psycho motor retarded depression is very similar to naturally occurring depression. We shouldn't be surprised that depressions occur. I am not going to introduce any of the other speakers other than to say my time is up and I appreciate Leah Bloomenstein speaking next.

Leah Bloomenstein: All right, thank you. As Dr. Gold mentioned my name is Leah-Perle Bloomenstein and I am an Intelligence Research Specialist for the Drug Enforcement Administration in our domestic strategic unit. **[00:14:00]** We have an analyst in our section that follows most of the major drugs of abuse and my area is cocaine. We review DEA cases throughout the year and speak with the state and local law enforcement agencies, attend conferences, speak with other agencies including those in the intelligence and health and treatment communities, and review academic research in order to stay on top of the nation's current drug trafficking trends. Today, I am going to give you a quick overview at the current national level cocaine trends. I am going to begin by discussing coca cultivation and cocaine production trends and how they affect domestic availability. Then I am going to look at how cocaine enters United States and move into price and purity information and end with national-level survey, use, treatment, and death data and take a brief look at the emerging trend that Dr. Gold mentioned about synthetic opioids and cocaine. **[00:15:00]**

Columbian sourced cocaine continues to dominate the US market. According to DEA's cocaine signature program, over 90% of samples analyzed in 2016 were from Columbia. In 2017, over 94% of samples analyzed were from Columbia and only 2% were from Peru. Therefore, production estimates for Peru are less significant for the US cocaine market than cocaine production estimates from Columbia. Potential pure cocaine production in Columbia has reached the highest levels ever recorded. Production increased 35% between 2015 and 2016. During the same time frame Columbia's coca cultivation increased 18% to in part to decreases in both aerial and manual eradication as well as counter measures by coca farmers to build block manual eradication and shift coca fields to areas where **[00:16:00]** cultivation is already prohibited such as in national parks and areas near the border with Ecuador.

Production potential, the amount of cocaine that can be produced from the cultivation of coca is the single most important cocaine metric produced by the US government. Keep in mind that potential pure cocaine production estimates make comparisons between different source countries and here its easier. While export quality cocaine production estimates are indicative of average purity at which cocaine departs the source zone. Export quality purity in Columbia average to about 73% to 87% in the last 10 years. As this graph demonstrate recent trends in export quality cocaine are worrisome. In 2016, Columbian potential export quality cocaine production was at the highest level recorded in the last 9 years **[00:17:00]** 28% higher in 2015 and of 87% in the last two years.

Potential cocaine production is likely to increase further through to 2018 even if cultivation levels remain constant due to the maturation of previously lower yielding coca planted in 2015. Columbian territorial seizures were the amount of cocaine that seized within the borders of Columbia also jumped approximately 30% between 2015 and 2016 from about 249 metric tons to 323 metric tons. The highest levels observed in a decade. In 2017, there were approximately 647 metric tons seized in Columbia, a new record high, which is about a 100% increase in the amount of cocaine seized.

Due to a greater supply of cocaine Northbound cocaine movement from South America increased **[00:18:00]** from 2015 to 2016. In 2016, at least 82% of the documented cocaine departing South America transited through the Eastern Pacific with smaller amounts transshipped directly through the western and central eastern Caribbean. These increases were driven primarily by increases in coca cultivation in Columbia and coca production in the Indian region and increases in documented cocaine flow through the Eastern Pacific vector. Increased flow was also documented in the Caribbean Corridor although the Caribbean Corridor's overall share of flow was less in 2015 than in 2016. Though not all the cocaine passing through Mexico and Central American Corridor is destined for the United States, some of it stays in the region or goes to Africa or Europe. **[00:19:00]**

Cocaine entering the United States via the South West border initially flows through here. Cocaine entering the Caribbean corridor destined for the United States typically passes through the Dominican Republic or Puerto Rico first. The majority of cocaine destined for the United States is transshipped through the southwest border via Mexico. From there cocaine is moved to major hub cities near and along the south west border via the interstate highway system to cities in Arizona, California and Texas and then along to other states in the mid-west and east coast and Florida. Cocaine is primarily traffic through legitimate ports of entry as opposed to in between border checkpoints. The primary mode of conveyance or how it gets into the country is through private vehicles.

Cocaine seizures along the southwest border increased **[00:20:00]** from fiscal year 2016 to 2017 by 23% to over 12,572 kilograms which is the most cocaine seized along the southwest border since at least 2012. This marks the third consecutive year that seizures have risen along the southwest border following two years of decreasing seizures in 2013 and 2014. The total number of seizures also rose from 801 seizures in 2016 to 960 seizures in 2017 as to the average weight of each seizure. This is most likely due to an increase in Colombian cocaine production and higher domestic demand. Maritime transit zone seizures and disruptions also increased nearly 6% in the last year. Previously, it was assumed that as Colombian cocaine production rose, average retail purity should rise and the price of cocaine in the United States should fall **[00:21:00].** While Colombian cocaine production and average annual cocaine purity in the United States has had a moderately strong correlation, analysis of

the last 15 years of price and purity data in the United States reveals a weak correlation between domestic prices and cocaine production. This likely means that other factors including competition within drug markets and changes in the local user population have a greater influence on domestic prices. Retail purity for cocaine in the United States has remained relatively stable since 2012 increasing about 24% from 45% purity to 56% purity over the last four years which is well below the 10-year high of 61% average purity observed a decade ago. This is all despite significant fluctuations in Colombian cocaine production since 2009. The average annual expected price **[00:22:00]** per pure gram of cocaine rose in the last 10 years from about $116 to $174 although it too has remained surprisingly consistent since 2012.

Now that I've talked about production, cultivation and seizure estimates, I want to switch gears a little and talk about some survey data. I first want to talk about the National Drug Threat Survey or NDTS which is produced annually by DEA to solicit information from a nationally representative sample of state local and tribal law enforcement agencies. This survey collects data of law enforcement's perception of topics such as the greatest drug threat, availability levels, drug related crime and changes in demand. In 2017, DEA significantly increased the number of agencies surveyed to get a better understanding of the current drug threats facing the United States. As a result, we received 5,155 responses **[00:23:00]** to the 2017 NDTS from across the country and in 2017 DEA also combined crack cocaine and powder cocaine into one single response labeled cocaine powder or crack to better capture and understand the current cocaine threat facing the country.

This map is based on the 2017 NDTS. The number of respondents who identified cocaine as the greatest drug threat in their area has been steadily decreasing since 2009. Law enforcement's perception of the cocaine threat has likely been impacted by the growing opioid crisis in the Midwest and eastern US as well as the prevalent methamphetamine threat in the western US. In 2017, only 3.2% of NDTS respondents identified either powdered or crack cocaine as the greatest drug threat in their area which was the second lowest rate amongst major drugs surveyed **[00:24:00]**. However, 22% of NDTS respondents identified cocaine as highly available in their areas and 12% indicated an increase in either availability or demand indicating that the cocaine threat is growing in several areas primarily concentrated in eastern US and in the Caribbean.

Cocaine exhibits submitted nationally to the National Forensic Laboratory System remain stable from 2015 to 2016 after increasing slightly from 2014 and steadily decreasing from 2008 to 2014. Nationally, 14% of all drugs in NFLS were identified as cocaine and it was the third most frequently identified drug after cannabis and methamphetamine. Laboratories representing the south and northeast reported the highest levels of cocaine. Population estimates for national use rates come from the national survey on drug use and health or

NSDUH. Approximately **[00:25:00]** 70,000 households participate in this survey annually. The number of current US cocaine users meaning they'd used the drug in the last 30 days remained stable from 2015 to 2016 and correspond to about 0.7% of the US population. Of the current 2016 user population, there was a subset of users that identified themselves as crack cocaine users which equals about 0.2% of the US population all aged 12 or older. Neither of the total cocaine user population or the crack sub-user population experienced statistically significant increase from 2015 to 2016.

In 2016, past year initiates are those who began using cocaine for the first time in the last 365 days continued to show signs of further growth. The number of past year cocaine initiates **[00:26:00]** increased 12% in the last year to just over 1.1 million. Based on a strong historical correlation between past year initiates and Colombian cocaine production, it's expected that the number of past year cocaine initiates will continue to rise in 2018. Annually the substance abuse and mental health services administration collects admissions data from publicly funded treatment facilities in the US. This data is referred to as the treatment episode data set or TEDS. The most current TEDS data set is from 2015 which creates a lag time for trend analysis, but it is important historical data to review. Cocaine treatment admissions continue to decline from 14% of all treatment admissions in 2005 to only 5% in 2015. Crack cocaine referred to in the TEDS data as smoked cocaine represented 72% of all cocaine related treatment admissions in 2015.

[00:27:00] So, I finally want to end with a few slides regarding cocaine related overdose deaths. The CDC reported cocaine related overdose deaths rose for the fourth straight year to over 10,375 deaths. This was about a 53% increase over 2015 based on a strong historical correlation between the US cocaine poisoning deaths and Colombian potential cocaine production. It is expected that this will continue to rise to 2018 as well. This map shows the age adjusted rates of cocaine overdose deaths per 100,000 population. The states with the highest reported rates of overdose deaths in 2016 were Washington DC, Rhode Island, Ohio, Massachusetts, and West Virginia. Overall as you can see there were higher in the eastern US versus the western US. In three states Florida, South Carolina and South Dakota, cocaine was reported as having **[00:28:00]** higher drug related overdose tests compared to heroin and other psychostimulants such as methamphetamine.

The continued mixture of cocaine with fentanyl and fentanyl related compounds is an emerging threat in a number of markets particularly concentrated on the east coast which is also experiencing both the resurgence of cocaine and as well as other opioid related deaths. While cocaine and opioids are sometimes intentionally mixed, DEA and other law enforcement reporting indicates that currently the majority of fentanyl and cocaine mixtures are encountered unintentionally and further increasing the risk for overdose and death. Indicative of the growing overlap between these two drugs, the states with the highest rates

of cocaine overdose deaths, Washington DC **[00:29:00]** and Rhode Island. We're also in the top 10 for overdose deaths regarding cocaine and an opioid and synthetic opioids. Thank you.

[Applause]

Jean Lud Cadet: First, I would like to thank Dr. Gold and the DEA administration for inviting me to come and talk here. This is my first time here and I really enjoyed my tour of the museum. I actually took some pictures that I'm going to show all the people in my lab. It's really fascinating pictures. This is my real title. My goal has a tendency to change my titles whenever we go somewhere to talk together, but I put it from a medical perspective and pushes it from a medical I don't know perspective **[00:30:00]**.

Because a CME being given, I wanted to -- is there a pointer, oh this works as a pointer. What I wanted to do is cover, the number of medical issue and neuroscience issue in my talk. We'll talk about dopamine system to remind the audience how cocaine works. We'll talk about the interaction between cocaine and the dopamine system. We'll talk about cocaine use disorders in neuropsychiatry. I'm actually trained in both neurology and psychiatry. We'll talk about the cocaine use disorder and cognitive finding, with one of the first investigators showing some cognitive abnormalities and structural changes in the brain of cocaine users. We'll also talk about cocaine and neuroimaging findings and the basic mechanism as to why some of these changes are seen **[00:31:00]** in the brain of patients. Also, we'll talk a little bit about some summary and suggestions.

For the dopamine system in the brain there are a lot of neurotransmitter systems. Dopamine is classified as a monoamine, and it's also a catecholamine. The other monoamine is serotonin, but that's an indolamine. Serotonin actually plays an important role in cocaine addiction. Dr. Gold talked about depression, and I think from my perspective, the reason why cocaine patients become depressed, is because of depletion of not only dopamine but of serotonin. Under neuropeptide some of them have become rather important as far as addiction to cocaine is concerned. Oxytocin is the main one and CRH is related to the stress withdrawal **[00:32:00]**. The stress that you see with withdrawal from cocaine.

This is dopamine and there are, for the physician and other people in the group there are four dopamine neurons, four sets of dopamine neurons in the brain. There's the Mesostriatal Dopamine System where the cell bodies go from the substantia nigra to the striatum. That's a dopamine system that's affected in Parkinson's patients. With methamphetamine we won't talk too much about methamphetamine. With methamphetamine reviews you see a really significant abnormality is in that system.

The Mesolimbic Dopamine System is with the cell bodies in the ventral tegmental area that's important for addiction and probably depression. The Mesocortical Dopamine System, the cell bodies in the VTA that project to the **[00:33:00]** nucleus accumbens, but they also have branches that go to the frontal cortex and that's probably why patients have a number of problems with cortical function. Then you have the neurohormonal system which cell body in the hypothalamus and they project to the pituitary.

Cocaine, historically, we had a really nice review of cocaine in terms of where it's being found and where it's being produced but to remind your cocaine is an ester of benzoic acid and methylecgonine. It is a schedule II, I think it's the schedule II, medication used primarily for topical anesthesia. Cocaine is a local anesthetic with vasoconstrictor properties and because it also blocks norepinephrine re-uptake. As far as cocaine in dopamine system **[00:34:00]**, as you know dopamine gets made in the dopamine neurons and it gets packaged in vesicles and can get released in the synaptic cleft. Cocaine works under that, which is the protein that takes dopamine back into the terminal. When cocaine blocks the terminal, it makes the level of dopamine much higher in the synaptic cleft and the dopamine can interact with dopamine receptors. This slide shows the effects of cocaine, so you can give cocaine and you can see a big increase in the level of dopamine. This other slide, this shows its been more schematically you have a lot of dopamine. **[00:35:00]** When the dopamine is really high, if you remember, there are five dopamine receptors, then there will be more dopamine to interact with the dopamine receptors.

Now the dopamine hypothesis basically comes from the idea then that cocaine can block the dopamine transporter and can increase the level of dopamine and that's why we think that people take those drugs. Methamphetamine blocks the uptake site also, but mostly works as a releaser. When there isn't enough cocaine onboard, then people can go through this binge and crashes where they become very depressed as Dr. Gold mentioned earlier. This slide shows you what we think happened and this is really based on a lot of the work by Gold in 1985 papers **[00:36:00]** indeed a classic, as he and C.A. Dackis we know all three of us knew each other at the time. You take cocaine, there's an increase in dopamine level that leads, because it stimulates the receptor, the receptor gets down regulated, there is look -- when you don't have cocaine onboard, maybe the dopamine returns to normal level, maybe not, but when they, what we know is that there is a decrease in dopamine receptors in the brain of cocaine abusers. Dr. [inaudible 00:36:34] and other investigators have shown that repeatedly that in the brain of cocaine abusers there is a decrease in dopamine receptors. Because you don't have enough dopamine or don't have enough receptors, then people crave the drug, that might be one of the reason why they relapse with taking drugs.

[00:37:00] Just to remind you again, those are the dopamine system with their projections and because cocaine is interacting with the dopamine system, you

could predict based on the effects of dopamine in the brain, what might happen, in the patients who take the drug acutely. Acute, you have to flush. People take the drug because they become euphoric, they are excitable, and they are hypervigilant. Then they also get agitated, but if they take too much, they can become paranoid and psychotic. Dr. Gold and I just published a paper on METH-induced psychosis, but I think we should do one on cocaine-induced psychosis, but chronically in terms of the neurological side effects, patients have a problem bruxism, **[00:38:00]** they can have problems with their hand, chorea, they become dystonic. They can have myoclonus, and with a high dose they can have seizures and strokes and obviously they can die.

The most important aspect I think of chronic use of cocaine is the cognitive dysfunction that we have reported in some patients who abuse cocaine as you can see here. They can have problems with verbal memory, problem with attention, this is very important because somebody is working, and they have poor attention, it is very difficult for them to **[00:39:00]** function at work. The other -- I highlighted some of the issues, problem with spatial memory, difficulty making decisions, and the executive function is -- that's the paper that we published together with [Inaudible 00:39:25] in 1999 and we showed problem with executive functions, psychomotor speed, they had problem with manual dexterity, and visual perception. The idea that cocaine can cause this cognitive abnormality is really very important. In the past that wasn't stressed enough, and Dr. Gold mentioned that back in late 70s, early 80s. Most people, including some scientists were saying cocaine wasn't addictive because it didn't cause the withdrawal symptoms **[00:40:00]** that you see, for example, with heroin. Chronic abusers of drugs, even those who are not using drugs very heavily actually have been shown to have some cognitive deficits.

A paper was published in 1999 and a number of people have now replicated a lot of papers. That paper actually is a classic too in terms of quotation. Everybody who has looked has shown that cocaine abusers have executive function abnormalities. From reviewing the literature, we just published a paper, reviewing the cognitive function in drugs in general, not just cocaine. What we came up with, with cocaine, is that the chronic heavy use of the drug **[00:41:00]** is associated with persistent cognitive deficits. People use higher dosages of cocaine, have more neurobehavioral impairment, and these abnormalities might be direct effects of the drug.

In terms of neuroimaging finding, we published some papers on the neuroimaging effects of cocaine. We published a paper showing that there is cortical atrophy in people who abuse the drug and Dr. Goldstein has shown, now repeatedly that also that she finds abnormality in executive function in those patients and that those were related to abnormality in metabolism in the dorsal - frontal cortex **[00:42:00]** and anterior cingulate cortex. The other one that was of interest to me is the fact that if you look at the last one, so it's not only the higher cortical areas that are affected with cocaine abuse, you have decreased

activation in the thalamus, which is the sub cortical area, and then you have abnormalities in the brain stem and mid brain, so in the some patients where you can also see abnormalities in the frontal and parietal cortex.

Now there's some imaging data and if you look at the last two, I highlighted those in blue. Again, they have abnormality - decision making. The patients show abnormalities in learning and memory and also again have abnormality in **[00:43:00]** neuroimaging. All of this, points to the fact that the drugs are not benign. Back in the 80s when I was a resident at Columbia University, people were talking about why cocaine is such a big issue. No, it's not benign. These drugs are not benign, and it seemed to impact the frontal cortex, and also sub cortical areas of a patient's brain. Now, this is a paper -- this really just came out last year, this is a paper from the National Institute on Drug Abuse by a group led by Dr. Elliot Stein and they did fMRI and also did some neuropsychological testing and in this paper, what this shown is that the **[00:44:00]** abnormalities in the left insular, in the right insular, so the patients have smaller insular than the control group, and that was also associated with this cognitive connectivity dysfunction. We all have a certain degree of connectivity with different brain regions connecting to other brain regions and in that patient population they saw abnormalities in those brain regions as you can see here.

Replicating the earlier studies that we published, one of the thing looking at structure is that in their functional imaging study, they also show a negative dose response curve. The higher dose of cocaine that somebody is taking, the more abnormalities they have **[00:45:00]** in terms of their connectivity in the frontal cortex. Remember, decision making, a lot of the cognitive dysfunction that we reported are related to frontal lobe abnormalities. The basic mechanisms are listed here for the psychiatric manifestation that's probably related to the blocking of the reuptake of monoamines and by monoamines we mean not only dopamine but norepinephrine and epinephrine. For the stroke – cocaine causes vasoconstriction because of a stimulation of adrenergic receptors and that could lead to ischemia, but some patients actually have hemorrhagic strokes because they have AVM (arteriovenous malformation) and key is the hemorrhagic stroke related to saccular aneurysms **[00:46:00]**, vascular malformation and cell death. Now, the reasons why we think there might be cell death in the brain of cocaine abusers is because when dopamine level is high, it can get oxidized to make free radicals. Okay, and this is shown here, so there's high level of dopamine, it goes through formation of 6-hydroxydopamine, 6-hydroxydopamine can make superoxide radical, which is really toxic and that could really damage cells in the brain. We've studied methamphetamine and I have shown that very clearly, but we haven't really spent a lot of time trying to figure out how and where cocaine causes cell death. There's a real need for post mortem studies of brains of patients who have abused cocaine to carry those studies.

This slide **[00:47:00]** tells you what we think is going on in the brain of people who take drugs, psychostimulant, so they take the drug and there are toxic

vascular and hypoxic abnormalities in their brain that can lead to neuronal loss and astrocytosis and microgliosis and those cells when they get activated, they can release substances in the brain that are really toxic. Now, the drugs in terms of vascular if they cause changes in the cerebral blood flow, that can damage the brain also. That's why in imaging study we are seeing both white matter and gray matter abnormalities in the brain of cocaine abusers. Yes, just a moment. Okay.

[00:48:00] That also explains some of the hypo and hyper connectivity problems that have been reported. If you see these brain changes, then that can lead to functional abnormalities as experienced by those patient's cognitive deficits. On the basis of what I've just reviewed for you, we think it's important that treatment programs take into account the cognitive deficit, the functional and structural abnormalities that are associated with prolonged use of cocaine when they're planning long-term care of their patients. The other thing that we really believe in is that in addition to developing treatment drug, we need to give patients cognitive enhancers in order to have them function **[00:49:00]** daily.

This is my last slide. We have this idea that drugs, when people take them, their individual factors that can either lead to resilience or susceptibility to becoming addicted and those are related, and we've published papers with Dr. Gold showing that that are changes in gene expression and environment where people live might also have an impact and those can lead to epigenetic alteration. We've spent a lot of time trying to figure out why is it that after people having taken drugs for a long period of time, why are they still addicted from my perspective and we are spending a lot of time on looking at epigenetic basis for this. We think this goes on in every person, but the results are not always the same. Some people might become resilient, others addicted **[00:50:00]** and for some it might be easier to become abstinent based on what's going on with the drug. Thank you very much.

Thomas R. Kosten: Well thank you for inviting me and what I'll try to do is with, through a couple of things in terms of how we're thinking about treatment and new ideas that look at pharmacogenetics, which means genetic factors that may influence medication treatment and start to match them up and then the vaccines that we've been working on to treat cocaine addiction for the last, sorry to say 25 years. Just a couple of disclosures that there are -- these are all off label uses. There's nothing that's approved and that I have consulted with a variety of pharmaceutical companies **[00:51:00]** over the years. On the cocaine pharmacotherapies, I'd like to say something about disulfiram and doxazosin and these are both agents that reduce noradrenergic activity. Doxazosin is actually used as an antihypertensive and the pharmacogenetics, we'll focus on the noradrenergic system, which has often been kind of ignored in the sense that dopamine has always been a large focus and for a good reason, of course, as Mark had indicated, Dr. Gold had indicated. Then on the cocaine vaccines, we'll

say a little bit about the original work that was done where we did have partial clinical success with a cholera-based vaccine.

We now have a new one that's based on tetanus toxoid and the new adjuvant, which is called the Entolimod, which is based on flagella that's in a bacteria and what we get with these new vaccines is about six-fold greater antibody levels and that's the key to success. You have to get high **[00:52:00]** antibody levels. What about, disulfiram and doxazosin like both reduced norepinephrine. They do it by different mechanisms. Disulfiram inhibits the enzyme that produces -- changes dopamine into norepinephrine, so it inhibits that enzyme, so what you do is get a lot more dopamine and a lot less norepinephrine, and there's a pharmacogenetics of that that's applied to both doxazosin and with doxazosin, there's a alterations, genetic variants in the adrenergic receptor, the receptor that norepinephrine stimulates, it is the Alpha one receptor. If we block this receptor, we can block the acute effects of cocaine and doxazosin is the drug that we've done that with and we have data indicating that doxazosin in fact reduces cocaine use and with particular patients, reduces a quite a bit with these genetic variants.

Disulfiram is Antabuse. **[00:53:00]** This is a drug that's been used for treating alcohol for a long time. They've been actually more than seven now outpatient clinical trials done with this. What you can see here is that disulfiram is producing more cocaine-free urines than placebo does. No, obviously it's not a cure. The other major problem with disulfiram is that it does make you sick when you drink alcohol and many of these patients use cocaine and alcohol and it's a drug that costs about twenty-five cents, so no drug company is going to try to develop this as a treatment for cocaine, although many of us use this treatment for cocaine at relatively low dosages, so it doesn't produce those Antabuse like reactions in people. This is just briefly to say what I've said already, which is you have norepinephrine neurons and disulfiram is an enzyme inhibitor. It's a very broad enzyme inhibitor. It inhibits all the enzymes that are copper dependent and ends up dopamine beta-hydroxylase **[00:54:00]** as a copper dependent enzyme, so that inhibits the transformation of dopamine to norepinephrine, which will increase dopamine, decrease norepinephrine and the neurons that are ordinarily excreting or neurotransmitting using norepinephrine will now be excreting or neurotransmitting using dopamine.

Why that makes a difference is when you're in withdrawal from drugs, you get high levels of norepinephrine. When you want to feel like you're enjoying the drugs, you get high levels of dopamine and most of these patients are all greatly dopamine deficient. We're fixing up an abnormality with this, which is this dopamine deficiency and reducing an abnormality gets induced when they stop using the drugs that is reducing the norepinephrine. What about doxazosin? Doxazosin is and what we found is that it works. Now, how did it work? One of the things we think that's most important is reducing noradrenergic activity. We said why not just block those noradrenergic receptors **[00:55:00]** directly, which

is what we did with doxazosin. It's a long acting drug. It's got a half-life of 22 hours, which means taking it once a day is good enough. We looked at four milligrams doxazosin and we gave it to people and the high that they get from giving them in a human laboratory 20 to 40 milligrams of intravenous cocaine is actually blocked by the doxazosin.

With an 8 mg dose, which is twice the dose we then used that in outpatient studies and we've had two clinical trials, both of which show that doxazosin was significantly reducing their cocaine use compared to a placebo. In this study what we found is the same genetic variant in this receptor, in this adrenergic receptor, weakens the acute cocaine reinforcement that is if you have this variant, you get a much less of a stimulation from cocaine when you take it. **[00:56:00]** Also, if you have that same variant in an outpatient study with cocaine, with cocaine abusers that is, those are the people where this medication works the best if you have this variant. In other words, you're getting less reinforcement from the cocaine just based on genetics and then if you block that reinforcement looks like it is in fact norepinephrine dependent and so that's what pharmacogenetics is about finding a genetic variant. In this case, this genetic variant occurs in about 40% of people, so it's not a rare variant. It's relatively common.

This is simply the laboratory study that we did. What you can see is that on the left is the area under the curve of basically how much of a high do they get. With the 40 milligrams you can see the red bars indicate how much you're knocking down the high at the 40-milligram dose of cocaine. At the 20-milligram dose of cocaine, you can see you knocked that high down more than 50%, which is very impressive.

Of course **[00:57:00]** with the placebo cocaine, you don't show any difference, which is nice so you're not getting bad side effects from doxazosin, but a 50% reduction is a substantial reduction. If you then just want to look at it over time what's shown on the right is the change in the kind of high that someone would get if you had doxazosin onboard. The placebo is how much of a high you'd get with just the cocaine being given at 40 milligrams. The red line there is what happens if you have doxazosin there first and with the doxazosin there you can see it's blocking the cocaine effect about 50%, so this is independent of genetics right now. If you start looking at the genetics, what you see is the people who have this adrenergic, this variant in the genetic receptor that those people are the ones that have the dotted line below when we give them cocaine. The upper one is the ones that don't have this genetic variant and you can see they get quite a big high from cocaine, so if you have this variant, **[00:58:00]** you're already, you might say less susceptible to cocaine use, but all you have to do is increase the amount of cocaine use, which is exactly what they do. They just double the amount of cocaine they use, so it's not a big secret how to in fact overcome genetic variation. You just take more.

What about the clinical trials? When we looked at the clinical trials, this is two different clinical trials that were done. One on the left you can see that the people who got placebo had very little reduction in their cocaine use or improvement in cocaine-free urines. Whereas those who got the doxazosin on the right, you can see they had a very big improvement big, big difference between the placebo and the active treatment. This was a relatively small study in 35 people. We then did another one and almost 90 people. Now, the thing that's a little puzzling about this is when you look at this slide, you can see that the placebo people at the baseline seem to be having a little bit more cocaine use than the people who in fact were randomized to get the doxazosin **[00:59:00]** so we did have to control for that baseline, but what you can see is that the cocaine positive urines and the people who get the placebo are clearly going up. Whereas the people who got the doxazosin their cocaine use is clearly going down.

So encouraging. What happened when we looked at the pharmacogenetics in the same trial? We took the people, the 89 people and we said, okay, about 40% of them have this variant, that means 60% of them don't and if you look at the people that have the variant, what you're finding is again, again a peculiar finding, but the ones who get this cc variant, they in fact have a significant reduction in their cocaine use when they get the doxazosin and the placebo group, which are the squares along the left side of your slide, they're not changing at all. What's odd is the right side. You are seeing some reduction in cocaine use with the doxazosin **[01:00:00]** but the people that have the placebo, when we put them on a placebo and say, okay, we're now in a treatment study that we're helping you. They said, no, you're not. I mean basically their cocaine use is going up, so there's something that's making them a much higher risk group which ties in with those of the people with less -- lot less cocaine and get a much bigger high. You might say they're much higher risk so that if we can block some of these people that have to double up on their cocaine use, we can actually make an impact on them. These are obviously not curative medications, so we're making the problem better, but we're not curing them, you got to have a little motivation to want to stop too. This is all along the lines of personalized medicine. This is what is the hot topic in medicine right now. It's pharmacogenetics using doxazosin. It's a variant in the adrenergic receptor that again about 40% of us carry this variant. The cocaine-free urines are clearly increasing with the doxazosin **[01:01:00]** by about 10% decrease while with the placebo, there's about a 10% increase. There's a net superiority of about 20% for doxazosin in unselected patients.

If we then take this genetic variant and the receptor and then we look at the difference, it's about a threefold more cocaine-free urines if you have the genetic variant that is a 10% versus 30% or 30% versus 10%. Having this variant is in fact very useful. Again, it's not uncommon, it's a fairly common variant. It's also associated, as I said, with a two and a half fold, reduced craving, liking and high that you get from cocaine when you take it in human laboratory. The pieces fit

together. I'm now in the closing seconds now. Hopefully a few minutes talk about the anti-cocaine vaccine. Excuse me. We've had 25 years of developing them and **[01:02:00]** while our last vaccine failed in phase three studies, it actually didn't totally fail, but our investors felt it failed enough that they said goodbye and they took all their money. We now have a new and a much better vaccine. How do they work? They work fairly straightforwardly. The antibodies that we produce from these vaccines. What you're seeing on the left is you take – say you smoke the cocaine, it goes into your lungs, then there is a straight line goes right up to your brain. That's what you're looking at there on the left is cocaine getting into your brain, activating the dopamine systems, and you feeling wonderful. When we have produced the antibodies in people, the drug never gets into your brain. The antibodies bind the drug of abuse and we can make them to -- basically every drug of abuse except alcohol binds the cocaine and keeps it from getting into the brain.

It just continues to float around in the bloodstream until it gets metabolized and it can get metabolized in the liver, it can get metabolized by excretion in the kidney **[01:03:00]** or can get metabolized by an enzyme in the bloodstream. It's called cholinesterase, and that's a whole other study that I can tell you about if I had another 10 minutes or so that we've come up with an enzyme that in fact breaks it down about 10,000 times faster than the native cholinesterase does and it was derived from bacteria and we're working on some gene. They're essentially gene insertion studies using viruses that we're hoping to get going with Mayo Clinic within the next year.

You had an original cocaine vaccine. We did two outpatient randomized placebo-controlled studies. One of them had about 115 people. The other one had 300 people in it. The 300 was a multisite national study. It had a carrier that was based on cholera toxin. The way that these vaccines work is you don't make antibodies to natural drugs, they are way too small, so what you do is you attach the drug to some carrier that you do produce antibodies to and **[01:04:00]** when your body then makes the antibodies to say, in this case cholera toxin, it's also making antibodies to your drug of abuse because your drug of abuse is attached to the cholera toxin. We have roughly, usually anywhere from 30 to 35 of our drugs of abuse attached to the outside of this big protein. All right, so they were vaccinated five times with a standard dose of this vaccine with the cocaine attached to it, over a 12-week period and we had a target blocking antibody level. We wanted to produce a 43 micrograms per milliliter. At that dose we knew that it would bind to about 80% of the standard 40 milligram dose of cocaine that somebody might want to use to override our blockade. 43, you say well what does that mean? Well, that means about a half a percentage of all the IGG or immune protein that's in your body.

Now, the theoretical limit is two percent. Your body **[01:05:00]** simply won't produce more than two percent of one particular antibody. It just says I have to be ready for other things besides this one stupid thing that you want me to have

a response to. We're working on a big response. What do we get? This was the first study. What you can see is if we looked at that target of 43, we got roughly a third of the people made it above that target. That's what's shown in the little picture there on the left. What you can see is that some people, almost a third of them hardly produced any antibodies at all and then the others were in the middle and they rise over the course of about the 12 weeks of the repeated four vaccinations that they got, they were about vaccinations a couple of weeks apart. Then as it goes up, it then comes back down again. What does that mean? They don't stay up there forever, but you do in fact have to give boosters about every two to three months to get the levels back up. How did it look in the study? This is the proportion **[01:06:00]** of cocaine-free urines.

What you can see is the placebo is the green. That is, they had no antibodies at all against the cocaine. The red is if you had low-level antibodies, which is about 60% of the people. The other was a high. They went over the 43. That was our target and what you can see is they got two and a half times more cocaine-free urines than the people who in fact got the placebo. This is a fairly large effect size and we were delighted to see it. Our investors were also delighted, NIDA was delighted, and everybody gave us some money to keep going, which we did. We then did a second big trial. We've done lots of little ones in between. This is the 300-patient study. We did improve the vaccine a little bit for this study. We got the mean antibody levels up to basically 59 at week 16 and even at week nine, we were already above our 43 that we're hoping for but there was a big range. **[01:07:00]** The range went from 10 to over 200 micrograms. We had in fact approached the theoretical limit of how much we could make. We again looked at the 42 as our cutoff of, so we had a placebo, the low antibody ones, and what we got was better treatment retention, 90% versus 80% actually excellent treatment retention in this. One thing that's really impressive about a vaccine is if you give a vaccine to a cocaine abuser, first off, they all think they got the active vaccine. They then also are convinced that it's a magic bullet, so they actually hang around for a while. They had to hang around for six months for this particular study.

Those who got more than two weeks of abstinence and this was the other was threefold greater in those who had the high antibody levels than either the low or the placebo group. That was encouraging also, and that the percentage rise in cocaine-free urines versus the baseline was 48% of them had a rise in this for the high antibody group and only 8% in the low antibody or **[01:08:00]** placebo group. It's pretty clear if you don't get the antibodies up, it's not going to work, but we didn't find any simple correlation of how higher antibody was with cocaine-free urine. We did find a correlation to some of the other studies where if we got it up to levels that really were around 2% of your IGG, you basically stopped using cocaine. Which is probably not altogether surprising. Interestingly, they didn't switch to amphetamine which was nice. We made a new cocaine vaccine. This has been the last 10 years of my life. A new carrier tetanus toxoid rather than cholera we found that those we've got a two-fold increase in antibodies just

by changing the carrier. New adjuvants, we were just using alums, basically aluminum, and we had this new one called the Entolimod. It's derived from the flagella. It's the little tail protein on the gram-negative bacteria, which if you give that protein to people, you'll basically kill them.

You can give them, but we've modified it slightly, so we don't kill them **[01:09:00]** but we do in fact entice their immune system to be a lot more active. The net effect of both improvements was about a six-fold increase in these antibody levels, which is more than we had hoped for. Anyone here an immunologist? Good, okay then I can say anything I want about this particular slide. There's a lot of things that happened and the Entolimod which is that little thing that's kind of up there is stimulating a lot of different receptors, but in particular it stimulates a tow like receptor five that is important for antibody production, which is going on inside this b cell and we've got the alum which we give, which is stimulating other parts of the cell. The net result is we make a whole lot more antibodies. Okay. If you understand that much from the slide, you're golden. You figured it out.

What did we find that this is the animal studies we've done. **[01:10:00]** What we did find is that if you give cocaine to animals, they run around a lot. We gave the animals 10 milligrams per kilogram of cocaine. If I gave that to any of you in the audience, you'd simply die. This is a big dose of cocaine. What you can see is that if you give this with no vaccine, you get this little stuff on the top, which is the animals run around like crazy, like they're going to die or something. If you then didn't give them anything, of course nothing much happens, but if you then give them the vaccine that is, they're vaccinated first, this new vaccine, and you then still give them the 10 milligrams per kilogram of cocaine, you actually block that locomotor activity quite substantially so that you're blocking essentially effects of the cocaine that we were delighted with.

We did show that there was an association in the animals that is the higher the antibody levels, **[01:11:00]** the more you block the cocaine effects on these various behavioral tests. That's all that this slide shows, and it accounts for about half of the variants and how much you reduce their activity is accounted for not by variations across the animals as much as variations in how much antibody you've produced and that's the kind of thing you'd like to see.

Can someone smoke enough to overcome the vaccine titer? Our evidence so far suggests probably not, but you know, they're never going to stop and so there will be creative people. What can I say in summary, the pharmacogenetic matching of patients to these noradrenergic blockers really promises to substantially enhance the efficacy of these pharmacotherapies such as doxazosin. We are actually making more progress in this than in many other psychiatric disorders. The vaccine with Entolimod does, it is generated six-fold more antibodies or anti-cocaine vaccines then we were **[01:12:00]** ever able to produce before than any other group has been able to produce.

The new vaccine is much better than the old cholera-based vaccine and we've gotten it through the first step of the FDA, so we are in phase one studies now, and it's a no blocked cocaine induced behaviors and the preliminary studies have shown excellent human safety in this early Entolimod combination vaccine studies. We are hoping the FDA will let us continue to go on and that between NIDA and our investors we will get the million bucks, so it takes to make enough vaccine to do the rest of the studies. You can't be a cheapskate and be in this business by the way. We've also got a fentanyl vaccine based on this, which we think ought to be accelerated and a methamphetamine vaccine also the same basis. With that, I would just like to thank a number of my co-investigators and collaborators at a variety of places including NIDA who has remained **[01:13:00]** faithful to me in spite of a few failures here and there. With that, thank you.

Sean Fearns: Collect your credit. We're ready for questions and to receive your CME credits, you have to complete the post-test and evaluation online and here's your link. While our panel is coming up onto the stage, just a quick reminder to those in the audience that have a question, if you could wait for a microphone to come to you so that not only do our panelists here your question, but also those watching the webcast. Those of you who are watching the webcast, there is an opportunity for you to enter in a question and then we have a member of our staff here who is going to pass them through to our moderator, Dr. Mark Gold. As you all get started, let me just ask Dr. Cadet if you could clarify **[01:14:00]** something you mentioned when you were talking about the various scientific effects of cocaine on the brain. Describe or define what executive function means to those of us who are not familiar with that.

Dr. Jean Lud Cadet: On a daily basis when whatever we're doing, whether it's task at work, so our frontal lobe is involved in really helping us make this decision. The decisions that we make, impact what we do. In cocaine abusers we've noticed, so typically I should say take a conglomeration of multiple tasks. In cocaine abusers what we see is that we have a problem with decision making. We have problems with memory function and **[01:15:00]** all of these -- and attention so all of these fall under the purview of executive function.

Dr. Mark Gold: If you have any questions in the audience, please find the microphone so that way it gets on the web.

Female: Good afternoon. Thank you so much for these presentations. I have a few questions for Leah and for Dr. Kosten. First Leah, it's about – first, one of your last statements where you were talking about combinations of fentanyl and cocaine, you mentioned that law enforcement agencies have agreed that your words were, the mixtures were encountered unintentionally. Did you mean on the user side or on the trafficking side? Are you meaning to say that those mixtures are made unintentionally or that they are **[01:16:00]** marketed as such on the street unintentionally?

Leah-Perle Bloomenstein: Primarily on the user side, we are contending that it's unintentional. As for the trafficking side, that's not really an assessment. We can make it this time, but yes, on the user side, yeah, we think that most users don't know that when they use cocaine that there might be fentanyl or other synthetic opioids in it. The cocaine users primarily just want to use cocaine. When there is fentanyl and other synthetic opioids, that is unintentional on the user side.

Female: Okay. Thank you. I'm still hoping that at some point we can figure out why those get mixed up. My next question is you proposed some CDC poisoning death data. Do we have that data separated by mixtures in the sense of what proportion of those **[01:17:00]** deaths are actually caused by fentanyl?

Leah-Perle Bloomenstein: Yeah, the CDC does have different breakdowns by different drugs and they are available online. The category for fentanyl is synthetic opioids other than methadone, and it does include other drugs besides fentanyl. The CDC does contend most of the drug-related overdose deaths in that category are from fentanyl, but it does include other synthetic opioids like Tramadol. For 2016, that number was about 19,400 and online the CDC does have a public access website where you can investigate cocaine and synthetic opioid deaths or cocaine and methadone or cocaine and methamphetamine deaths.

Female: Right. I think I was just trying to confirm whether the **[01:18:00]** cocaine data you presented was clear of opioids or –

Leah-Perle Bloomenstein: No, it was also in combination.

Female: Okay, okay.

Leah-Perle Bloomenstein: Yeah.

Female: Thank you. You propose two consecutive pieces of information that are conflicting and really concerning to everyone I think the fact that the TEDS – the treatment admissions have fallen dramatically at the same time as the use and availability are increasing dramatically. Do you know what that would be influenced by?

Leah-Perle Bloomenstein: The TEDS data set is only about in reference to publicly funded admission. It doesn't include private facilities and it's possible that there's a large number of individuals who use cocaine who are attending privately funded healthcare facilities or **[01:19:00]** we also can believe that there's a portion of cocaine users who consider themselves perhaps to be more casual users and maybe don't seek out treatment as like that. I mean, yes, they are conflicting and the TEDS data sets that has shown a decrease in admissions for a number -- for the last decade, but the use – I mean it has been going up

and yeah, they're just conflicting data sets. We do contend that use is going up and there is availability and we just don't have necessarily all of the data sets in order to be able to capture all of the treatment facilities that would be able to perhaps fill in those gaps because there is no reporting system for private facilities that may explain some of the gaps between **[01:20:00]** treatment and use.

Female: Okay, thank you. Another piece -- another pair of contradicting info, I guess –

Dr. Thomas Kosten: Can I just for perhaps help you with that from the clinical perspective of seeing patients. There's about a five-year delay in when you start using cocaine and when you seek treatment. I mean people don't want to get treatment to an early stage that they want to get high and so what you're seeing now is the epidemic is growing. They're going to show up with about a five-year time lag, so that's the first thing. The second thing is that cocaine price on the street at least from Houston is dropped quite a bit as has amphetamine and so there's a swimmingly large supply of it and when it's cheap, you also don't get treatment because you could just get all the cocaine you want. You don't have to worry about stopping it so there is a supply and demand issue that's going on in this and the recruitment of new customers **[01:21:00]**. I think the thing that's been a little driving people to treatment a little bit now is that they are cutting the cocaine with fentanyl. The reason that they're cutting and at least what the dealers tell me is that they're cutting it because then they can cut the quality of the cocaine and yet the users will get a much bigger high from it because they get the fentanyl boost to the cocaine. It's quite deliberate on their part. The problem is that they don't have pharmacies that mix the cocaine and fentanyl together in a nice even mixture so that some people get a fair amount of cocaine and not much fentanyl in it, and the next buyer gets a fair amount of fentanyl and not that much cocaine in it and user number one says, that was a pretty good high, user number two dies, same dealer. There's a lot of mess in this, but I think it's driven **[01:22:00]** by the dealer and this difference with the TEDS data is two factors. First is a lag time. The second is treatment programs in a lot of places the public ones have been deprived of funds that they can't admit it. We have got waiting lists in Houston for every kind of drug treatment imaginable, and so people just come in the ER and they're out the door. There's no place to send them.

Female: Thank you. Before they take the microphone away from you all, I will ask you a question if you don’t mind Dr. Kosten. You were talking about doxazosin and disulfiram and the lack of interest of drug companies in developing them.

Dr. Thomas Kosten: Yeah, that's true. Disulfiram costs about twenty-five cents, doxazosin costs maybe fifty cents, so the profit margin that they see in developing these medications is none **[01:23:00]**. I mean we went to the

manufacturer for the Antabuse, for example, disulfiram. We gave them all the data to file a new drug application and they said we'd have to be – they would be out of their mind to do that because if the new drug application got approved and they said, okay, now we're going to sell disulfiram for $5 a pill, somebody else would make a generic version of it the next day and sell it for fifty cents a pill. I mean you have to understand patent life and all the other crazy things going. We don't stand a chance with disulfiram although there's a metabolite. With doxazosin, we do stand a chance because they're constantly developing new types of adrenergic one blockers for cardiology, not for us in addiction, and one of those that still has gotten like 10 years of patent life on it. I'm hopeful that we might be able to interest a company in it, so far, their interest has been muted, I guess is the nicest way to say it.

Female: I mean the federal government **[01:24:00]** has an agency devoted basically to this, right, medication development for addiction. Does NIDA push or help in anyway the development of this type of medication on substances that are not of huge lucrative use or [inaudible 01:24:17]?

Dr. Thomas Kosten: NIDA has funded most of these studies and some private donors have also, but NIDA is not a pharmaceutical company, and they don't -- they've gotten a little bit involved I think with AIDS medications for example. Should they do the same thing with substance abuse? Well considering substance abuse is about 10 times bigger problem than AIDS, one would think so.

Female: It's more in their line of –

Dr. Thomas Kosten: No but I don't make policy and I have for a period thought about visiting with ONDCP, but then realized that I would be stupid to do that. I have too big a mouth.

Female: Thank you **[01:25:00]**. All right. We do have a question from a web viewer. Why are toxic adulterants like levamisole added to cocaine and heroin and are they dangerous?

Dr. Mark Gold: Well, he's a neurologist, but clearly, they're dangerous. They're widely available, they’re filler, they’re what defines a toxic adulterant. Would you say?

Leah-Perle Bloomenstein: Yeah, I agree. They're primarily used for fillers, stretch the profits, increase the effects of the drug.

Dr. Mark Gold: Thank you.

Female: Anybody else in the audience have questions? Then I'll come back to the web questions in a minute. **[01:26:00]**

Male: Thank you guys for your time. My question is for Dr. Kosten, have you guys noticed, or have you guys studied any of the metabolic stress or effects on the organ systems that are processing out the cocaine that's been bound by your [inaudible 01:26:19] product?

Dr. Thomas Kosten: The nice thing about cocaine and just so I repeat the question, so people know is what about the metabolism of cocaine is to stress, damage those enzymes? Well, to a certain extent, yes. I mean if you write your liver out by drinking lots of alcohol, that's generally not good for metabolizing cocaine. Cocaine itself has some liver toxicity, but it's somewhat limited compared to alcohol. It's alcohol and cocaine that would be the killer. The enzyme though that immediately metabolizes cocaine is this cholinesterase enzyme that's in your bloodstream and what **[01:27:00]** the discovery has been is going into basically bacteria and finding versions of this enzyme that can then be humanized so that you can give that bacterial enzymes directly to people, you'll get an allergic response to it, but you can humanize them and then give that enzyme to people and what you will find is that they in fact metabolize the cocaine much, much faster. That's –

Male: Is that for overdose?

Dr. Thomas Kosten: It might well be used for overdose except that supportive care for overdoses generally work just fine and while enzymes can seem like they're fast, they're in fact not that fast and so what happens if you – and again, we've done this Steve [inaudible 01:27:42] and I did this in animals. If you give a lousy vaccine so that it doesn't produce much antibodies, the animals easily override that. If you give -- that is by self-administration or whatever. If you give them the enzyme all by itself, it ends up even when you give a fairly large amount of it, the animals **[01:28:00]** still overcome it because the cocaine gets into your brain faster than the enzyme can metabolize it. On the other hand, if you give them even a crummy vaccine, previous what I had, and you give that with this enhanced enzyme, you cannot infuse cocaine into the animals fast enough to get any effects. You can go 100 times over the toxic level and nothing happens. It's pretty clear that that combination and that's what we're working on now, a better vaccine because while this may seem paradoxical, you have to prove to the FDA that each thing individually is effective.

We have to show that the vaccine is effective before we can say we're going to add the enzyme to it. There's already been an attempt to look at the enzyme by itself in humans and there was a study done by TIVA and they found that the enzyme was not statistically significantly better than not giving the enzyme. We **[01:29:00]** could have told them that before they invested the $10 million, but they did and found it didn't work, but it's going to have to be sequential, and the way that we want to do the enzyme now is rather than infusing the enzyme because that only lasts about a week or two. We can in fact give the DNA to

make the enzyme, put it in a viral cartridge essentially, and when we inject that into animals and we haven't done it with people yet but have been done for other kinds of cancer therapies, it integrates into your liver and for the life of that liver cell will continue to make that enzyme and the life of liver cell is about two and a half years.

So about every two and a half years, you'd have to get another injection of this virus with the DNA, but that way you then have a long acting high activity enzyme and we would vaccinate people probably about every know the initial three or four vaccinations and then about every three months, and that combination would essentially be you couldn't overcome **[01:30:00]**. It'd be a complete blocker.

Sean Fearns: Last question, and I'm going to direct it to you Dr. Gold and if other members of the panel want to comment. This is a lecture hosted by the DEA Museum, so we're going to talk a little history for a second. I'm going to channel a little in your David Musto as well and say someone argued, here we go again with another potential cocaine epidemic when this country battled through one not 40 years ago. What lessons could we take from the cocaine and crack cocaine epidemics of the 80s and early 90s they could apply today?

Dr. Mark Gold: We're really fortunate to have all of these experts here at the DEA and to just go through how each of them dealt with this question, Leah's work said supply is up, production is up, importation is up, prices **[01:31:00]** surely to follow, but access to high quality cocaine is increasing from the East Coast and expected throughout the United States to almost the previous levels and there's no sign that increases are leveling off. Dr. Cadet's work showed quite clearly that cocaine use causes changes that are structural in nature and can often times not be reversed and cause changes in how the person functions in addition medically and neurologically, in addition to psychiatrically and psychologically. Dr. Kosten's work is to emphasize how important education and prevention is because he's still working where **[01:32:00]** he hasn't invented a vaccine that we could use tomorrow. As he said for overdoses, cocaine overdoses are treated symptomatically meaning, IVs packing in eyes, treating cardiac complications and so forth, but that's not the same as having Narcan on every street corner. We're in a position now where the focus on cocaine has been made, brought to everyone's attention because of the rise in overdose deaths whether that truly represents the crisis and changes going on, we'll only know as Dr. Kosten said somewhere down the line, maybe five years down the line **[01:33:00]**. There's plenty of time to help educate people as to cocaine, it's dangerous acutely, chronically and give people, who want to stop a chance to stop and support treatment. I'll emphasize what Dr. Kosten said as well about cocaine treatment admissions. Many of us find cocaine using patients in other treatments so they might be cocaine, might come up as cocaine positive urines in an opioid treatment program, they could be in many other settings.

Again, it's a lag indicator. By the time, we have a crisis in cocaine admissions, we'll have a whole new drug epidemic, but I think the DEA and the Museum **[01:34:00]** by focusing on the shift from prescription opioids with Ted Cicero's work to heroin helped us understand that we highlighted in a subsequent museum event this switching dangers with that and including with fentanyls, and now we would just bring to everyone's attention that cocaine already is number two on the death list and rising fast and supply is flooding the United States and cocaine stimulates its own taking. Yes, it's important to keep in mind that psychostimulant epidemics right up Dr. Cadet's ally methamphetamine and cocaine generally follow these kind of opioid epidemics.

Sean Fearns: I want to take a moment and thank our most excellent panel for being with us this afternoon and **[01:35:00]** speaking. I want to thank the staff of the DEA Museum, Diane Martin in particular for putting the event together. A quick plug that the next lecture for the DEA Museum is set for May 30th and the topic is going to be the new emerging synthetic drugs. Please take a moment to thank our panel and they will be available here to answer your questions.

[Applause]